Journal of Neuroimmunology 274 (2014) 1–13

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

Neuroimmune regulation of microglial activity involved in neuroinflammation and neurodegenerative diseases

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ARTICLE INFO

Article history:
Received 13 March 2014
Received in revised form 27 June 2014
Accepted 16 July 2014

Keywords:
Neuroinflammation
Neurodegenerative disorders
Microglia
T-cells
Neo-antigens
Blood–brain barrier

ABSTRACT

Neuroinflammation constitutes a fundamental process involved in the progression of several neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis. Microglial cells play a central role in neuroinflammation, promoting neuroprotective or neurotoxic microenvironments, thus controlling neuronal fate. Acquisition of different microglial functions is regulated by intercellular interactions with neurons, astrocytes, the blood–brain barrier, and T-cells infiltrating the central nervous system. In this study, an overview of the regulation of microglial function mediated by different intercellular communications is summarised and discussed. Afterward, we focus in T-cell-mediated regulation of neuroinflammation involved in neurodegenerative disorders.

Contents

Abbreviations: α-syn, α-synuclein; Aβ, β-amyloid peptide; AD, Alzheimer's disease; ALCAM, activated leukocyte cell adhesion molecule; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APCs, antigen-presenting cells; BBB, blood–brain barrier; CCL*n*, C–C chemokine ligand *n*; CCR*n*, C–C chemokine receptor *n*; CD*n*, cluster of differentiation *n*; CNS, central nervous system; CSF, cerebrospinal fluid; CTLA4, cytotoxic T-lymphocyte antigen 4; CXCL*n*, C–X–C chemokine ligand *n*; CXCR*n*, C–X–C chemokine receptor *n*; DCs, dendritic cells; GATA3, GATA binding protein 3; GFAP, Glial Fibrillary Acidic Protein; GM-CSF, granulocyte macrophage-colony stimulating factor; HLA, human leukocyte antigen; HMGB1, high mobility group box 1; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon γ; IL-*n*, interleukin *n*; iNOS, inducible Nitric Oxide Synthase; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MHC, Major Histocompatibility Complex; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; mSOD1, mutant SOD1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA, N-methyl-D-aspartate; NO, nitric oxide; PD, Parkinson's disease; P2Y6, purine-receptor 6; RNS, reactive nitrogen species; ROS, reactive oxygen species; SN*pc*, *substantia nigra pars compacta*; SOD1, superoxide dismutase 1; TCR, T-cell receptor; Th*n*, T helper *n*; TLRs, Toll like receptors; TLR*n*, Toll like receptor *n*; TGF-β, transforming growth factor β; TNF-α, tumour necrosis factor α; TNFR1, TNF-α receptor 1; VCAM-1, vascular cell adhesion molecule 1.

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http://dx.doi.org/10.1016/j.jneuroim.2014.07.012
0165-5728/

1. Introduction

The immune system plays a fundamental role in the regulation of inflammation, a process that may be beneficial in promoting protection against pathogens and tumours and reparation of damaged tissues, but also can be detrimental when it is induced chronically (Takeuchi and Akira, 2010). Neuroinflammation, the inflammation of the central nervous system (CNS), is recognised as a prominent hallmark of many different pathological conditions (Glass et al., 2010). In this regard, several lines of evidence strongly suggest that neuroinflammation is a pivotal process involved in the progression of neuronal degeneration, a common feature observed in several neurodegenerative disorders (Glass et al., 2010; Lucin and Wyss-Coray, 2009).

A common feature in the physiopathology of most neurodegenerative disorders is the presence of protein aggregates in the CNS (Lucin and Wyss-Coray, 2009). Several lines of evidence have shown that these protein aggregates associated with neurodegenerative diseases are recognised by danger-signal sensors called Toll-like receptors (TLRs) expressed in microglial cells, promoting thus their activation. Importantly, depending on the integration of regulatory signals, microglial cells may undergo two different kinds of activation, acquiring a neurotoxic phenotype or a neuroprotective phenotype, which have been called M1-like and M2-like phenotypes respectively by their analogy with phenotypes in peripheral macrophages. Whereas M1-like microglia generate a detrimental microenvironment for neurons by producing inflammatory cytokines and reactive oxygen species (ROS), M2-like microglia secrete neurotrophic factors and anti-inflammatory mediators, thus inducing a supportive microenvironment for neurons (Kettenmann et al., 2011).

Microglial activation, which plays a central role in neuroinflammation and consequent neurodegeneration, may be regulated by several intercellular interactions involving cell-surface molecules and soluble mediators, such as cytokines, ROS and neurotransmitters. Intercellular interactions which regulate microglial activation involve cross-talks of microglia with neurons, with the blood–brain barrier (BBB), with astrocytes and with T-cells which infiltrate the CNS parenchyma. Of note, emerging evidence has shown a fundamental role of T-cells in the regulation of neuroinflammation associated with neurodegenerative disorders and thereby in neuronal fate. An overview of the different interactions regulating microglial function is summarised and discussed in this review. Afterward, we focus in the discussion of the current evidence about T-cell-mediated regulation of neuroinflammation and consequent neurodegeneration involved in neurodegenerative disorders. Finally, we analyse the current data suggesting that the aggregation and covalent modifications of CNS constituents result in the generation of neo-antigens for T-cells, thus giving rise to the hypothesis that autoimmune response against CNS antigens constitutes a major component in the physiopathology of neurodegenerative disorders.

2. Overview of microglial function

Neuroinflammation corresponds to inflammatory processes occurring in the CNS, which is observed in several pathological conditions such as stroke, infections, and neurodegenerative disorders (Glass et al., 2010). This process is characterised by the activation of microglial cells, consequent changes in the permeability of the BBB followed by the infiltration of peripheral immune cells into the CNS parenchyma, secretion of inflammatory cytokines and finally, neuronal damage and death. The current data have indicated that this process involves several cellular types, including microglia, astrocytes, neurons, endothelial cells and cells of the adaptive immune system, such as T-cells (Glass et al., 2010; Goverman, 2009; Lucin and Wyss-Coray, 2009). Because of their central role in neuroinflammation, microglial cells have attracted the attention of several studies addressing cellular and molecular mechanisms involved in neurodegenerative disorders. In this regard, microglial activation seems to be a highly regulated biological process which is not yet fully understood. Despite microglial cells behaving similarly to peripheral macrophages, they also show some important differences. For instance, the disruption of the BBB is sensed by microglia, which become activated by serum proteins (Ransohoff and Perry, 2009). Another important difference is that unlike macrophages, which are constantly replaced by new myeloid progenitors, microglial cells are not continuously recycled in the brain; nevertheless they proliferate upon activation (Kettenmann et al., 2011; Ransohoff and Perry, 2009). In the healthy brain, microglial cells display a "homeostatic" phenotype, which continually monitor the surrounding environment (Nimmerjahn et al., 2005). In this regard, they express surface molecules and secrete soluble factors which influence astrocytes and neuron function (Kettenmann et al., 2011), promote the clearance of cellular debris and aggregated proteins (S. Lee et al., 2010) and play an active role in synaptic pruning (Paolicelli et al., 2011) — all activities which support brain homeostasis. However, when exposed to infections or injuries, microglial cells exhibit responses similar of that of peripheral macrophages. In this regard, in response to lipopolysaccharide (LPS), TNF-α and/or IFN-γ, macrophages become classically activated and acquire an M1 phenotype, which express several pro-inflammatory cytokines and enzymes that promote a sustained tissue inflammation. In contrast, "alternative activation" in response to IL-4, IL-13, glucocorticoids, TGF-β and/or IL-10, macrophages differentiate into the anti-inflammatory M2 phenotype, which is associated with the resolution of inflammation and tissue reparation (Shechter et al., 2013; Sica and Mantovani, 2012). Similarly, in response to CNS injury or infection, homeostatic microglial cells exposed to LPS and IFN-γ become activated and undergo phenotypic changes acquiring M1-like features, including amoeboid shape, production of high amounts of pro-inflammatory cytokines, high mobility, strong phagocytic capacity and up-regulation of some molecular markers such as CD86, inducible Nitric Oxide Synthase (iNOS) and CD16/32 (Bedi et al., 2013; Burguillos et al., 2011; Ransohoff and Perry, 2009). In contrast, in response to anti-inflammatory cytokines, such as IL-4 and IL-10, microglial cells acquire an M2-like phenotype characterised by thin cell bodies, branched processes, and up-regulation of specific molecular markers, for instance macrophage mannose receptor 1 (CD206) and Arginase-1 (Nimmerjahn et al., 2005; Ransohoff and Perry, 2009). Thus, normally, after a CNS injury or infection, there is an initial inflammatory response mediated by M1-like microglia. This early activation plays a beneficial role, involving microbicide activity against most microorganisms and phagocytic activity necessary for the clearance of cellular debris, which is required for subsequent reparation of lesions. After early activation, M1-like microglia can acquire two different fates in the recovery phase. The beneficial fate is when, during late stages, M2-like microglia participate in attenuating inflammation induced by M1-like microglia and, concomitantly, produce neurotrophic factors, thus promoting tissue reparation (Shechter et al., 2013). The second option, the detrimental fate, is when M1-microglia undergo uncontrolled activation or over-activation, thus triggering chronic inflammation which results in the production of neurotoxic factors and leads to neuronal loss over time (Burguillos et al., 2011). In this case, microglial cells become a prominent source of inflammatory mediators such as TNF-α, IL-6, IL-1β, IL-1α, nitric oxide (NO), hydrogen peroxide, superoxide anion, chemokines such as RANTES and MCP-1, proteolytic enzymes

and glutamate (Barger and Basile, 2001; Block et al., 2007; Dickson et al., 1993; Hegg et al., 2000; Kettenmann et al., 2011; Qiu et al., 1997; Reynolds et al., 2009) — all of which are capable of inducing neuronal damage in different and complementary ways. In the next section, we discuss molecular mechanisms by which microglia acquire M1-like phenotype in the context of neurodegenerative disorders and then we analyse the neurotoxic molecular signals produced by M1-like microglia.

3. Molecular regulation of microglia in neuroinflammation

Inflammatory responses to infectious agents are initiated by the stimulation of receptors for pathogen-associated-molecular-patterns, such as TLRs. Importantly, it has been described that these receptors not only recognise molecules such as LPS, flagellin or double-stranded RNA (Sica and Mantovani, 2012), but they also can be stimulated by some endogenous aggregated and oxidised proteins (Kim et al., 2013; Reed-Geaghan et al., 2009). The TLRs' stimulation involves the recruitment of intracellular adapter proteins MyD88 and TRIF, and consequent activation of kinases including IκB kinases and MAP kinases. Whereas the phosphorylation of IκB results in nuclear translocation of NF-κB, MAP kinase activation leads to the activation of AP-1 transcription factor. The concerted action of these signalling pathways together results in a strong induction of pro-inflammatory cytokines, including type I IFNs (Takeuchi and Akira, 2010). Many TLRs (TLR1–TLR9) and their co-receptors have been found in microglial cells (see a review in Kettenmann et al., 2011). Amongst these TLRs, TLR4 and TLR2 expressed in microglial cells have been specifically associated with both neuroinflammation and clearance of aggregated proteins involved in neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Kim et al., 2013; Reed-Geaghan et al., 2009). With regard to AD, it has been shown that, by stimulating TLR4, aggregated amyloid-β (Aβ) stimulates microglial cells to produce strong levels of pro-inflammatory factors such as NO, IL-6 and TNF-α (Walter et al., 2007). Consistent with these findings, increased accumulation of diffuse and fibrillar Aβ deposits have been found in the brain of mice bearing a non-functional version of TLR4 in a mouse model of AD (Tahara et al., 2006). Moreover, TLR4-stimulation induced by intra-hippocampal injections of LPS in wild-type mice reduces aggregated-Aβ load, which is accompanied by moderate microglial activation (DiCarlo et al., 2001). Interestingly, TLR4 polymorphism has been associated with a risk of AD, although it does not exist in similar studies on PD (Balistreri et al., 2009). Addressing the involvement of TLR4 in PD, it has been shown that TLR4 expression is up-regulated in the brain of mice undergoing PD (Panaro et al., 2008). Importantly, Noelker et al., have shown that TLR4 deficiency results in a decreased susceptibility to induce microglial activation and neurodegeneration in a mouse model of PD (Noelker et al., 2013). In agreement with these studies, mice treated with chronic administration of low-dose systemic LPS develop neuroinflammation in the midbrain, where microglia acquire an activated M1-like phenotype, resulting thus in enhanced loss of dopaminergic neurons of the nigrostriatal pathway and in consequent locomotor dysfunction (Frank-Cannon et al., 2008). Thus, these findings indicate that TLR4 contributes to chronic microglia activation, and consequent neuroinflammation and neurodegeneration. Glial TLR2 has also been involved in PD and AD. For instance, aggregated-Aβ induces TLR2-mediated microglial activation (Reed-Geaghan et al., 2009). Similarly, oligomeric α-synuclein (α-syn) activates an inflammatory response in microglial cells by stimulating TLR2 (Kim et al., 2013). Moreover, TLR2 up-regulation has been described in the brain of both AD and PD animal models (Letiembre et al., 2009). Importantly, some studies carried out with AD animal models have shown that TLR2 deficiency results in an attenuated microglial activation and microglial-mediated phagocytosis, augmented deposition of aggregated-Aβ and exacerbated cognitive damage (Reed-Geaghan et al., 2009; Richard et al., 2008). Thus, in contrast to the role of TLR4, it seems that TLR2 stimulation represents a beneficial contribution against neurodegenerative processes involved in AD. There are also some data about the involvement of other TLRs in neuroinflammation associated with these neurodegenerative disorders. For instance, it has been shown that the stimulation of microglial TLR9 attenuates Aβ-mediated neurotoxicity *in vitro* and in models of AD *in vivo* (Doi et al., 2009). All of these studies underline the important role of TLRs expressed on microglia in regulating acquisition of the M1-like phenotype and chronic inflammation, which lead to neurotoxicity in neurodegenerative disorders.

How does chronic inflammation mediated by M1-like microglia promotes neuronal death? The best described pathway by which microglia exerts neuronal damage involves the generation of toxic species of nitrogen and oxygen. In this regard, the activation and translocation of NADPH oxidase to the microglial cell surface results in a high production of anion superoxide (Qian et al., 2007). In the same direction, the up-regulation of iNOS in M1-like microglia results in the synthesis of high levels of NO (Dawson et al., 1993). Subsequently, both superoxide and NO exert direct oxidative damage and neurotoxicity. In addition to reactive species of nitrogen and oxygen, inflammatory cytokine produced by M1-like microglia, such as TNF-α, can directly induce neuronal death mediated by the stimulation of their corresponding receptors (Ferrari et al., 2006; Gordon et al., 2012; Reale et al., 2009). Furthermore, activated microglia can release large amounts of glutamate which can induce neurotoxic action mediated by ionotropic glutamate receptors expressed in neurons (Takeuchi et al., 2006). With regard to neurotoxicity mediated by inflammatory cytokines, microglial cells are the main source of TNF-α in the injured brain, a cytokine which can directly promote neuron death by stimulating TNF receptor 1 (TNFR1). Experiments carried out *in vitro* and *in vivo* have demonstrated that TNF-α promotes the neurodegeneration of dopaminergic neurons in the *substantia nigra pars compacta* (SN*pc*) in PD (McCoy et al., 2006). Indeed, systemic administration of LPS, which leads to a chronic production of TNF-α by microglia, results in the loss of dopaminergic neurons in the SN*pc* in mice. Accordingly, systemic administration of LPS has been used as a PD model in mice (Qin et al., 2007). Importantly, these findings are consistent with elevated levels of TNF-α in the brain and cerebrospinal fluid (CSF) described in PD patients (Boka et al., 1994). Furthermore, studies addressing the functional relevance of TNF-α mediated signalling in neurodegenerative processes have shown that the deficiency of TNFR1 results in attenuated neurodegeneration of dopaminergic neurons of the SN*pc* in a mouse model of PD (Sriram et al., 2002). Moreover, TNFR1 deficiency results in decreased brain depositions of aggregated-Aβ, thus preventing the behavioural impairment in a mouse model of AD (He et al., 2007). Thus, the evidence indicates that brain TNF-α, which is produced mainly by microglia, plays a fundamental role in neurodegenerative processes involved in PD and AD (McAlpine et al., 2009). Another important mediator of neurotoxicity produced by microglia is the excitatory neurotransmitter glutamate (Pacheco et al., 2007; Takeuchi et al., 2006). High extracellular glutamate concentrations in the CNS promote excitotoxicity, which has been involved in various pathological conditions, including acute CNS trauma such as brain or axonal injury (Alessandri and Bullock, 1998), ischaemia (Lipton, 1999), and epilepsy (Fountain, 2000), as well as in chronic neurodegenerative disorders such as PD, AD and amyotrophic lateral sclerosis (ALS) (Choi, 1988). When the CNS is injured, glutamate buffering cells, astrocytes, are lost and the damaged site is repopulated by M1-like activated microglia (Schwartz et al., 2003). Although neurons, astrocytes and homeostatic microglia can release moderate levels of glutamate, M1-like activated microglia can release toxic amounts of glutamate through a mechanism which involves connexin hemichannels and the cystine/glutamate antiporter system (Takeuchi et al., 2005, 2006). Excessive stimulation of the ionotropic glutamate receptor N-methyl-D-aspartate (NMDA) in neurons promotes the deregulation of calcium influx, which leads to cellular death (Choi, 1988). Interestingly, TNF-α stimulates the up-regulation of glutaminase in microglial

cells, which promotes further synthesis and release of glutamate by these cells. Concomitantly, TNF-α inhibits the glutamate uptake mediated by astrocytes. Thus, this inflammatory cytokine produced by microglial cells exacerbates the increase of extracellular glutamate levels, which leads to further neuronal loss (Zou and Crews, 2005; Takeuchi et al., 2006). Moreover, necrotic neurons stimulate TLRs expressed in microglia promoting further up-regulation of glutaminase expression, thus feeding the neurotoxic profile of microglial cells (Pais et al., 2008). In addition, autocrine stimulation of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor and metabotropic glutamate receptors expressed on microglia induces an increase of synthesis and release of TNF-α (Hagino et al., 2004; Kaushal and Schlichter, 2008; Noda et al., 2000). Thereby, the release of glutamate and TNF-α production constitute two synergistic neurotoxic mechanisms which act concertedly. Importantly, neuroinflammatory mechanisms mediated by microglia may be strongly influenced by resident brain cells, including neurons and astrocytes (see Section 4) and by peripheral immune cells infiltrating the CNS parenchyma (see Section 5). Intercellular interactions relevant for the regulation of neuroinflammation are illustrated in Fig. 1 and discussed in the following sections.

4. Neurons and astrocytes, two cellular regulators of neuroinflammation

4.1. Involvement of astrocytes in neuroinflammation and neurodegeneration

Although current evidence has shown microglial cells as the major mediators of inflammation involved in neurodegeneration, astrocytes constitute another local population of cells actively involved in the modulation of CNS immunity and in the regulation of damage/repair of nervous tissue. Regarding homeostatic functions of astrocytes, they exert several effects in the healthy brain to support physiological processes, such as the control and formation of neuronal synapses (Eroglu and Barres, 2010), turnover of neurotransmitters (Haydon and Carmignoto, 2006), control of neuronal energy (Rouach et al., 2008) and regulation of BBB permeability (Abbott et al., 2006). On the other hand, during CNS injury, astrocytes become reactive, migrate to the damaged site and form the glial scar, response denominated reactive astrogliosis (Pekny et al., 2014). Reactive astrogliosis constitutes a neuropathological feature in the SN*pc* of PD patients (Hirsch and Hunot, 2009) and in nervous tissue surrounding Aβ deposits in AD patients (Wyss-Coray et al., 2003). Thereby, these findings support the notion that astrocytes would be active players during neurodegeneration. In this regard, *in vitro* activated astrocytes migrate towards Aβ deposits and degrade them (Wyss-Coray et al., 2003). Moreover, the deletion of Glial Fibrillary Acidic Protein (GFAP) and Vimentin genes in a genetic mice model of AD *in vivo* results in a complete inhibition of astroglial activation as well as a marked increase of Aβ deposits and dystrophic neurites (Kraft et al., 2013). Thus, these results suggest an important beneficial role of activated astrocytes in attenuating the formation of amyloid plaques in AD. In the same direction, neuronal death correlates inversely with the number of activated astrocytes in necropsies of PD patients (Damier et al., 1993). Accordingly, it has been shown that astrocytes play an important neuroprotective role performing the clearance of ROS in the surrounding environment. Thus, neuronal regions displaying lower density of activated astrocytes are more susceptible to oxidative damage (Damier et al., 1993). Therefore, a growing group of studies support a beneficial role for activated astrocytes in neuroinflammation associated with neurodegenerative diseases.

On the other hand, a group of studies has indicated that activated astrocytes display a neurotoxic behaviour similar to that of activated

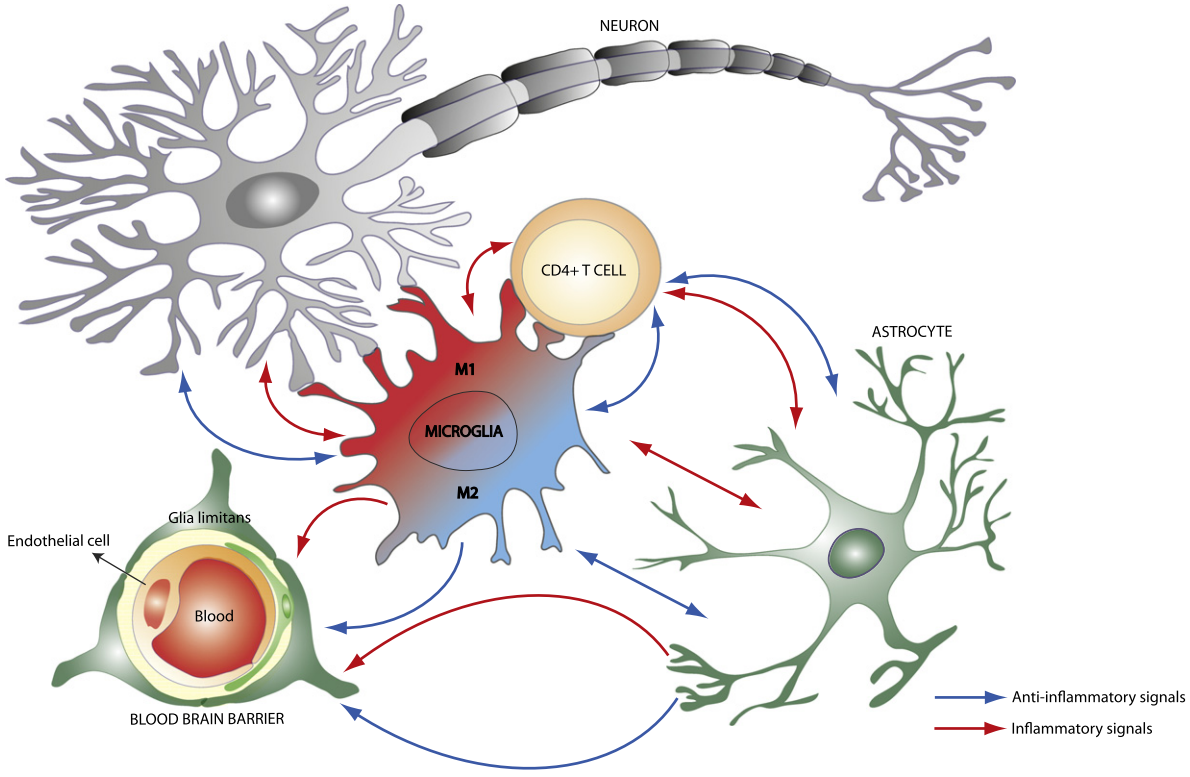


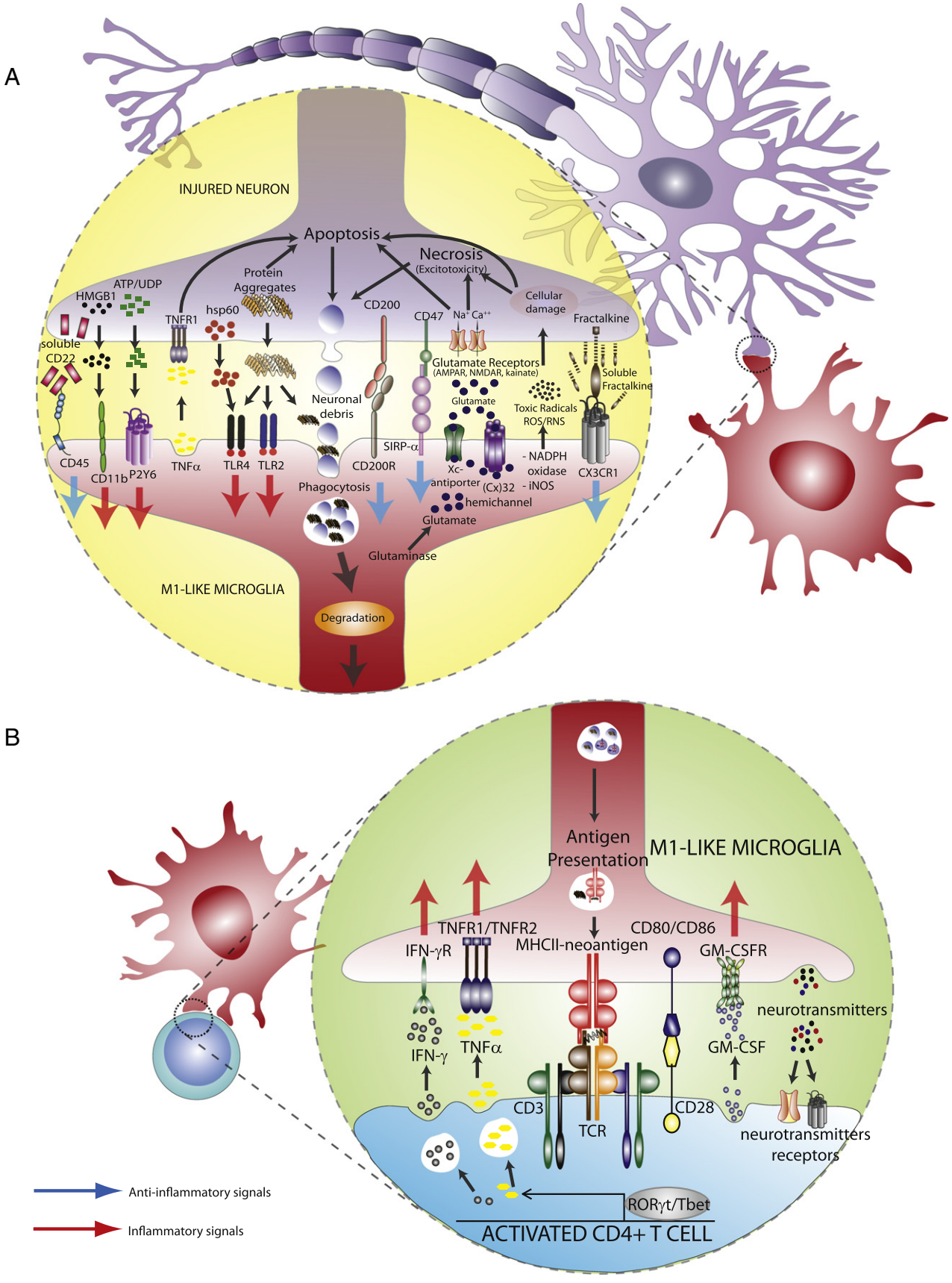
Fig. 1. Microglia as the central actor in neuroinflammation. The scheme illustrates bidirectional inter-cellular interactions between microglia and other cell types in the brain parenchyma, which regulate neurodegeneration. Microglial cells might exert either beneficial or detrimental roles on neuronal survival depending on the phenotype acquired, which is regulated by the integration of several inter-cellular interactions with key cell players illustrated in the scheme. Inflammatory microglia display the M1-like phenotype (red) and stimulate astrocyte activation, neuronal damage, T-cell activation (re-stimulation) and disruption of the BBB, all effects favouring neuroinflammation and subsequent neuronal loss. In contrast, microglia displaying the anti-inflammatory M2-like phenotype (blue) attenuate inflammatory and neurotoxic effects induced by M1-like microglia, supporting neuronal survival, restricting BBB permeability and promoting repairing of damaged tissue. Red arrows indicate pro-inflammatory signals, whilst blue arrows indicate anti-inflammatory signals.

microglia during chronic inflammation of CNS. In this regard, astrocytes express several TLRs, including TLRs1–6 and TLR9, which imply that these cells could respond to infections and to protein aggregates (Carpentier et al., 2005; Farina et al., 2007). Nonetheless, the functional impact of TLR stimulation in astrocytes and its relevance in neuroinflammation have been poorly studied. *In vitro* experiments have recently shown that the stimulation of astrocytes with ligands for TLRs 2, 4, 5 or 6 enhances the production of ROS, IL-1β, IL-6, glutamate and TNF-α, thereby favouring neuronal loss (Ma et al., 2013). Importantly, protein aggregates may induce an inflammatory behaviour in astrocytes. In this regard, the stimulation of astrocytes with aggregated-Aβ induces the production of inflammatory mediators such as IL-1β, TNF-α and ROS (Johnstone et al., 1999). Similarly, in response to aggregated α-syn, astrocytes secrete inflammatory cytokines, such as IL-1β, IL-6 and IL-18 (H.J. Lee et al., 2010). Although receptors involved in this response have not yet been identified, it is likely that it is mediated by TLRs. Notably, experiments using an animal model of spinal cord injury have shown that selective inactivation of NF-κB in astrocytes leads to a strong improvement in locomotor performance (Brambilla et al., 2005). Since the activation of NF-κB is associated with a high expression of pro-inflammatory factors, these results strongly suggest that the inflammatory response mediated by astrocytes has a detrimental role in neuronal survival. An important feature of activated astrocytes is the production of chemokines, including CCL2, CCL5, CCL20, CXCL10, CXCL12, CXCL1, CXCL2 and CX3CL1 (Farina et al., 2007). These chemokines are involved in the recruitment of microglia, monocytes/macrophages, T-cells and dendritic cells (DCs) into the inflamed sites of the CNS, thus favouring the encounter of different cellular actors involved in neuroinflammation. Importantly, most inflammatory mediators produced by astrocytes may act on microglial cells, thus exacerbating chronic microglial activation and thereby favouring neuronal death (Kettenmann et al., 2011). Similarly, inflammatory mediators produced by microglia may exacerbate astrocyte activation. For instance, high levels of TNF-α produced by microglia induce amplification of glutamate release by astrocytes with consequent enhanced neuronal excitotoxicity (Barcia et al., 2011; Bezzi et al., 2001). Since high production of brain TNF-α has been consistently associated with PD and AD, this microglia–astrocyte positive feedback could be a relevant mechanism involved in the physiopathology of these disorders (McAlpine et al., 2009; McCoy et al., 2006). Thus, several studies have indicated a detrimental role of activated astrocytes in chronic neuroinflammation associated with neurodegenerative diseases. Conciliating data have suggested a dual role of activated astrocytes depending on the levels of TNF-α. It has been shown that, whilst high extracellular levels of TNF-α favour the inflammation and neurodegeneration mediated by astrocytes and microglia, low levels of TNF-α secreted mainly by astrocytes autocrinely stimulate the secretion of neurotrophic factors, supporting neuronal survival (Kuno et al., 2006). Of note, when activated, astrocytes express class II MHC (Major Histocompatibility Complex) and costimulatory molecules on the cell surface. Thereby, they can stimulate T-cell activation in the CNS (Nikcevich et al., 1997). Thus, although the microglia are the main mediators of the inflammatory damage of the CNS during neurodegeneration, astrocytes behave similarly to microglia and they both act synergistically, promoting chronic neuroinflammation or favouring neuroprotection. Microglia–astrocyte and other intercellular interactions relevant for neuroinflammation are schematised in Fig. 1.

Another important feature of astrocytes associated with neuroinflammation is related to their role as a cell component of the BBB. Astrocytes form the glia limitans in the BBB and, thereby, they can directly regulate the flow of blood components within the brain parenchyma (Abbott et al., 2006). It is well known that endothelial cells react with inflammatory cytokines affecting the selectivity and permeability of the BBB (Biernacki et al., 2001; Stanimirovic et al., 1997). Thus, because of the direct interaction between astrocyte endfeet and endothelial cells, it is likely that any change in the profile of inflammatory mediators secreted by reactive astrocytes could affect the properties of the BBB (see Fig. 1). Accordingly, an important and exclusive function of astrocytes is their direct control on BBB permeability, which could favour the infiltration of peripheral immune cells within the brain parenchyma during neurodegenerative diseases, as discussed in Section 5.

4.2. Involvement of neuron–microglia interactions in neuroinflammation and neurodegeneration

Although classically the main focus in the study of neuroinflammation has been glial cells, the role of neurons in the inflammatory response associated with neurodegeneration has gained the attention of study during the last decade. Emerging evidence has shown an active bidirectional crosstalk between neurons and microglial cells, which constitutes an important point of regulation for neuroinflammation and neurodegeneration. Whereas M1-like and M2-like microglia exert respectively detrimental and beneficial effects in neuron survival and homeostasis (see Section 1), neurons also can induce effects on microglial physiology turning-on or turning-off an inflammatory response in these cells (Fig. 2A). In this regard, it has been described that after neuronal injury, heat shock protein 60 is released from necrotic or apoptotic neurons, which triggers an oxidative response in microglia by inducing the synthesis of the neurotoxic mediator NO in a TLR4-dependent mechanism (Lehnardt et al., 2008). Another important mechanism turned-on in microglia upon CNS injury is mediated by metabotropic purine-receptor 6 (P2Y6). This receptor is up-regulated in microglia when neurons are damaged. Moreover, upon neuron damage, nucleotides are released to the extracellular compartment. Koizumi et al. have described that the P2Y6 receptor expressed in microglia can function as a sensor of diffusible uridine diphosphate, triggering phagocytosis upon neuronal damage (Koizumi et al., 2007). Another example of communication involved in neurodegeneration going from neurons to microglia is the high mobility group box 1 (HMGB1), a protein released by injured or dying neurons and activated microglia, which acts subsequently on microglial cells, promoting further neurodegeneration in stroke and PD models (Gao et al., 2011; Muhammad et al., 2008). Experiments addressing the molecular target of HMGB1 suggest that this protein binds the CD11b expressed in the cell surface of microglia, stimulating the NF-κB pathway and NADPH oxidase to stimulate the production of multiple inflammatory and neurotoxic factors. Neutralisation of HMGB1 or genetic deficiency of CD11b and NADPH oxidase blocks progressive neurodegeneration (Gao et al., 2011). Thus, these data show a number of mechanisms mediated by neuron–microglia interactions in which activated microglia and damaged neurons form a vicious cycle mediating chronic and progressive neurodegeneration. These findings may constitute a mechanistic basis for chronic PD progression. However, not only pro-inflammatory signals, but also anti-inflammatory signals can be promoted by neurons on microglial behaviour. For instance, the interaction between CD200 expressed on the microglial cell surface and its receptor CD200R expressed on the neuron surface exerts anti-inflammatory effects. Several studies have indicated that CD200–CD200R signalling is critical for restraining microglial activation. The current data indicates that CD200–CD200R interaction triggers the down-regulation of pro-inflammatory mediators and up-regulation of anti-inflammatory mechanisms in microglia (Lue et al., 2010), thus changing the phenotype of these cells from M1-like towards M2-like. The relevance of this interaction has been demonstrated in different neurodegenerative conditions, as the dysfunction of this interaction results in exacerbated degeneration of dopaminergic neurons in a PD model (Zhang et al., 2011), increased neuroinflammation in an AD model (Lyons et al., 2007) and a faster onset of experimental autoimmune encephalomyelitis in a mouse model of multiple sclerosis (MS) (Hoek et al., 2000). In agreement with this, a CD200R agonist has been shown to be beneficial in AD and MS models (Liu et al., 2010; Lyons et al., 2012). Furthermore, decreased expression of CD200 and CD200R has been described in AD patients (Walker et al., 2009). Another anti-inflammatory


A
INJURED NEURON
Apoptosis
Necrosis
(Excitotoxicity)
Protein Aggregates
ATP/UDP
HMGB1
hsp60
TNFR1
CD200
CD47
Na+ Ca++
Cellular damage
Fractalkine
soluble CD22
Glutamate Receptors
(AMPAR, NMDAR, kainate)
Soluble Fractalkine
Glutamate
Toxic Radicals ROS/RNS
Neuronal debris
SIRP-α
CD45
CD11b
P2Y6
TNFα
TLR4
TLR2
CD200R
Xc- antiporter
(Cx)32 hemichannel
- NADPH oxidase - iNOS
CX3CR1
Phagocytosis
Glutamate
Glutaminase
M1-LIKE MICROGLIA
Degradation
B
Antigen Presentation
M1-LIKE MICROGLIA
TNFR1/TNFR2
IFN-γR
MHCII-neoantigen
CD80/CD86
GM-CSFR
neurotransmitters
IFN-γ
TNFα
GM-CSF
CD3
TCR
CD28
neurotransmitters receptors
RORγt/Tbet
ACTIVATED CD4+ T CELL
Anti-inflammatory signals
Inflammatory signals

interaction is mediated by the chemokine CX3CL1 (also called fractalkine). Several studies have addressed the role of CX3CL1 in neuroinflammation. CX3CL1 is expressed by neurons as a transmembrane-anchored protein which can be cleaved to yield a soluble isoform. It has been shown that soluble CX3CL1 acts on its receptor CX3CR1 expressed on microglia inhibiting activated M1-like phenotype, thus turning down neuroinflammatory response and neurodegeneration. The relevance of CX3CL1-mediated anti-inflammatory response has been demonstrated in the attenuation of neurodegeneration in animal models of PD (Morganti et al., 2012; Pabon et al., 2011), ALS (Cardona et al., 2006), as well as AD (Bhaskar et al., 2010). Other anti-inflammatory signals exerted by neurons over microglia are mediated by interactions between CD47 expressed in neurons and its receptor SIRPα (signal-regulatory protein alpha) expressed on microglial cells and macrophages (Gitik et al., 2011; Ohnishi et al., 2005), and CD22 secreted by neurons which acts on its receptor CD45 expressed on microglia and macrophages infiltrated into the CNS (Mott et al., 2004). Anti-inflammatory and inflammatory regulations mediated by interactions between neurons and microglia are summarised in Fig. 2A. Taken together, this data indicates that microglial activation is a tightly regulated process and part of this regulation is exerted directly by neurons. During homeostasis, neurons are actively inducing anti-inflammatory regulation over microglia, however when environmental or genetic factors perturb these neuron-mediated anti-inflammatory signals, microglia can promote neuroinflammation and consequent neurodegeneration.

5. T-cells: the engine of chronic neuroinflammation

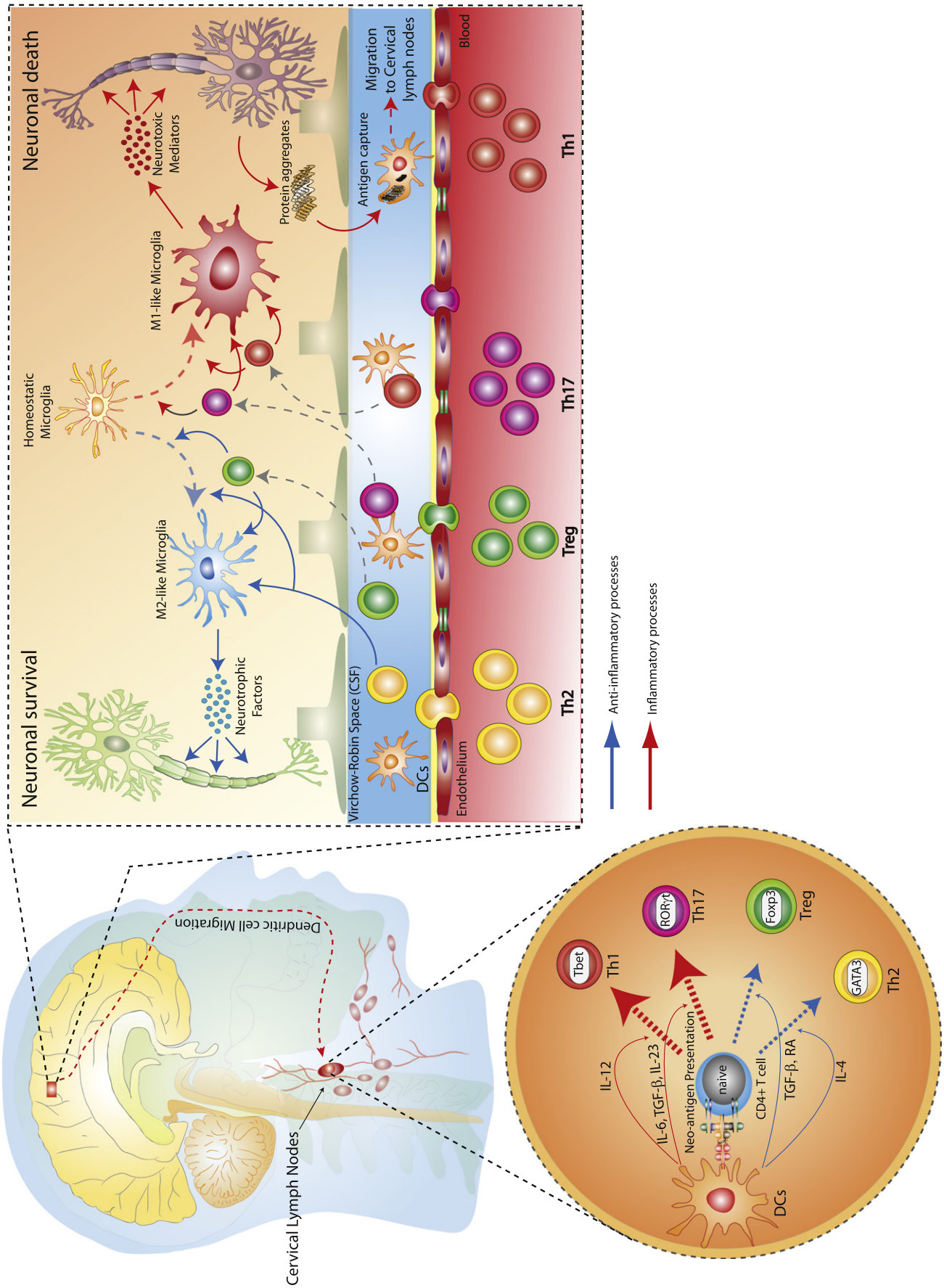
5.1. T-cells play important roles in the CNS during health and neuroinflammatory diseases

Under normal physiological conditions peripheral immune cells cannot infiltrate the CNS parenchyma. However, some peripheral immune cells may infiltrate into the CSF, which is produced by choroid plexus epithelia and flows into the subarachnoid space. Importantly, the CSF drains into the cervical lymph nodes, enabling peripheral immune cells to recognise and respond to CNS antigens in the absence or presence of inflammation (Hatterer et al., 2008; Laman and Weller, 2013). Accordingly, the subarachnoid space and choroid plexus of healthy mice contain substantial numbers of T-cells and are heavily populated by myeloid cells, including DCs (Anandasabapathy et al., 2011; Derecki et al., 2010). Importantly, immune cells found in the subarachnoid space are not only related with surveillance in the CNS. Under normal conditions, CD4+ T-cells expressing T-cell receptors (TCRs) specific for CNS antigens are activated by environmental/psychological stimuli and they positively regulate nervous system processes, such as memory consolidation, hippocampal long-term potentiation, and neurogenesis and they also contribute to psychological stress resilience (Baruch and Schwartz, 2013; Lewitus and Schwartz, 2009; Yirmiya and Goshen, 2011; Ziv et al., 2006). However, upon neuroinflammatory processes initiated by microglial activation, peripheral T-cells infiltrate the CNS parenchyma, where they play a crucial role in the physiopathology of many neurodegenerative diseases (Lucin and Wyss-Coray, 2009). It is possible that encephalitogenic CD4+ T-cells activated during neurodegenerative diseases express TCRs specific to neo-antigens produced from CNS-self antigens modified by oxidative stress, as discussed in Section 6. These neo-antigens would be presented initially by antigen-presenting cells (APCs) which capture these antigens in the CNS parenchyma or CSF and then migrate into the cervical lymph nodes to present them to peripheral naive CD4+ T-cells expressing TCRs specific to these neo-antigens. Subsequently, memory and effector CD4+ T-cells generated could be restimulated *in situ* by APCs residing in the brain parenchyma or in the CSF. This idea is supported by the fact that it is possible to detect class II MHC+ cells in the CSF and in the brain parenchyma in close proximity with CD4+ T-cells (Anandasabapathy et al., 2011; Baruch and Schwartz, 2013; Derecki et al., 2010; Lucin and Wyss-Coray, 2009). The restimulation of auto-reactive CD4+ T-cells with inflammatory phenotypes in the CNS parenchyma would result in a strong production of inflammatory cytokines which act directly or indirectly in microglia and infiltrated macrophages exacerbating their M1 and M1-like inflammatory properties (Fig. 2B). Thus, the infiltration of inflammatory T-cells in the CNS parenchyma after an initial microglia-mediated neuroinflammation results in a positive feedback, spreading and perpetuating neuroinflammatory processes involved in neurodegenerative diseases (Fig. 3).

5.2. BBB disruption: a key step in T-cell-dependent neurodegeneration

An early consequence of neuroinflammation is the dysfunction of the BBB, both processes being observed during the initiation and progression of neurodegenerative disorders (Lucin and Wyss-Coray, 2009; Stolp and Dziegielewska, 2009). An important consequence of BBB dysfunction is the entrance of peripheral immune cells into the CNS parenchyma. T-cells, macrophages, DCs and other immune cells play important roles in neuroinflammatory processes. Brain endothelial cells are the principal components of the BBB and they play a key role in maintaining the homeostasis of the CNS and regulating the infiltration of cellular and molecular components from the periphery. Initially during the inflammatory response to neuronal injury, the oxidative stress and pro-inflammatory cytokines produced by activated microglia, such as TNF-α, promote a strong up-regulation of TLR expression in brain endothelial cells (Cheng et al., 2008; Ozinsky et al., 2000). For instance, TLR2 and TLR6, which can be expressed as a heterodimer in BBB endothelial cells, may be stimulated by diverse pathogens and certain endogenous molecules associated with tissue damage. In this regard, it has been shown that the stimulation of TLR2/6 leads to a down-regulation of tight junctions on the cell surface, thus favouring the cellular transmigration of leukocytes across the BBB (Nagyoszi et al., 2010). Moreover, inflammatory cytokines such as TNF-α and IL-1β act directly on BBB endothelial cells up-regulating the expression of several cell surface molecules which mediate intercellular interactions with leukocytes, thus favouring their recruitment inside the brain. For instance, cell surface intercellular adhesion molecule 1 (ICAM-1) is up-regulated on the cell surface of BBB endothelial cells, which binds lymphocyte function-associated antigen 1 (LFA-1), expressed on the cell surface of several leukocyte populations

Fig. 2. Bidirectional cellular communications between microglia–neuron and microglia–CD4+ T-cells during neuroinflammatory processes. An amplification of neuron–microglia interactions is shown in panel A; homeostatic neurons actively produce anti-inflammatory signals aimed at inhibiting the acquisition of the inflammatory M1-like phenotype by microglial cells. During neurodegenerative disorders or after nervous system injury, cellular mediators associated with damage are released by dying/injured neurons stimulating M1-like microglial activation. Subsequently, M1-like microglia release reactive species of oxygen and nitrogen (ROS and RNS), glutamate and TNF-α. Importantly, an oxidative environment favours further oxidation and aggregation of self-proteins in damaged neurons, which promotes neuronal death and also stimulates TLRs in microglia. Moreover, aggregated proteins and apoptotic bodies are phagocytosed by microglia, which are subsequently degraded and presented to CD4+ T-cells. An amplification of interactions between CD4+ T-cells infiltrated within the cerebral parenchyma and microglia is shown in panel B; neuron-derived antigens are degraded into peptides, which are presented on class II MHC to CD4+ T-cells. Neurotransmitters released by microglia or by neighbouring neurons may regulate the activation and acquisition of CD4+ T-cells phenotype. Re-stimulation of infiltrating inflammatory CD4+ T-cells (bearing TCRs specific to neuron-derived neo-antigens) induces the release of inflammatory cytokines, which further enhances inflammatory features in microglia, potentiating further neuronal damage. Some inflammatory cytokines released by T-cells can also directly act on neurons, promoting further neurodegeneration, but this has been omitted from the figure for simplification. Red arrows indicate pro-inflammatory signals, whilst blue arrows indicate anti-inflammatory signals. For abbreviations and further details, see the text.


Neuronal death
Neuronal survival
Homeostatic Microglia
M1-like Microglia
M2-like Microglia
Neurotoxic Mediators
Neurotrophic Factors
Protein aggregates
Antigen capture
Migration to Cervical lymph nodes
Virchow-Robin Space (CSF)
DCs
Endothelium
Blood
Th1
Th17
Treg
Th2
Anti-inflammatory processes
Inflammatory processes
Dendritic cell Migration
Cervical Lymph Nodes
IL-12
IL-6, TGF-β, IL-23
Neo-antigen Presentation
naive
CD4+ T cell
TGF-β, RA
IL-4
Tbet
Th1
RORγt
Th17
Foxp3
Treg
GATA3
Th2
DCs

(Stanimirovic et al., 1997; Biernacki et al., 2001). The expression of vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells of the BBB favours the entrance of activated lymphocytes into the inflamed CNS by direct interaction with surface α4-integrins (Vajkoczy et al., 2001). The surface-activated leukocyte cell adhesion molecule (ALCAM) induced on endothelial cells during the inflammation of the BBB binds to CD6 expressed on T-cells, allowing their entrance into the brain parenchyma (Cayrol et al., 2008). Interestingly, studies carried out using a mouse model of MS have shown that IL-17 and IL-22 receptors are up-regulated on the surface of BBB endothelial cells, and their stimulation by their respective ligands induces the disruption of tight junctions, thus breaking down the BBB permeability for T-cells producing IL-22 and IL-17 (Kebir et al., 2007). This is a relevant mechanism mediating encephalitogenic T-cell infiltration into the CNS in autoimmune disorders involving CNS antigens, such as MS and PD (Benner et al., 2008; Reynolds et al., 2010). Many chemokines secreted by endothelial cells of the BBB during brain inflammation play also an important role in the recruitment of leukocytes into the CNS as well. For instance, the chemokines CXCL9, CXCL10, CXCL11 (Kivisakk et al., 2002), CCL19, CCL21, and MCP-1 (Engelhardt, 2006) constitute important chemoattractants for the successful recruitment of T-cells through the BBB during neurodegenerative diseases. Similarly, these chemokines can attract other immune cells such as monocytes/macrophages, B cells, natural killer (NK) cells and DCs. Thus, these data indicate that the response of BBB endothelial cells to inflammation is crucial in the regulation of infiltration of peripheral immune cells into the brain parenchyma. Interactions of the BBB with microglia and astrocytes are schematised in Fig. 1.

5.3. Inflammatory and anti-inflammatory T-cells participate in regulating neuroinflammation

Depending of the molecular context in which an antigen is presented by APCs, CD4+ T-cells can acquire different functional phenotypes, each of them specialised in producing different groups of mediators and in recruiting different sets of immune cells, with inflammatory or anti-inflammatory consequences. For instance, the inflammatory phenotype T-helper 1 (Th1), which is governed by the expression of the master transcription factor Tbet, is associated with the production of IFN-γ and often TNF-α, as well. This phenotype strongly stimulates the activation of M1-like microglia and M1 macrophages (Barcia et al., 2011; Sica and Mantovani, 2012), and in addition potentiates the function of CD8+ T-cells and NK cells (Dardalhon et al., 2008). Differentiation of CD4+ T-cells towards the Th1 phenotype is favoured by the high expression of co-stimulatory molecule CD86 on the APCs' surface, IL-12 secreted by APCs and by some neurotransmitters, such as glutamate and acetylcholine (Dardalhon et al., 2008; Pacheco et al., 2010). Another important inflammatory phenotype for CD4+ T-cells is Th17, a programme of differentiation controlled by the master transcription factor RORγt. This inflammatory phenotype is normally favoured by IL-6 and TGF-β acting together and they mainly produce IL-22 and IL-17, two inflammatory cytokines specialised in disrupting BBB integrity (see Section 5) (Kebir et al., 2007). Encephalitogenic Th17 cells are especially important in early stages of neuroinflammatory processes, as they express the chemokine receptor CCR6, which allows them to migrate quickly after T-cell activation towards CCL20, a chemokine which is constitutively produced by the choroid plexus in the brain (Reboldi et al., 2009). Importantly, recent studies have shown that there are two subpopulations of Th17 cells: pathogenic Th17 cells which express RORγt and Tbet at the same time and produce GM-CSF, and non-pathogenic Th17 cells, which express RORγt but not Tbet and do not produce GM-CSF (Codarri et al., 2011; Lee et al., 2012; Yang et al., 2009). GM-CSF produced by encephalitogenic pathogenic Th17 cells acts on peripheral macrophages infiltrated into the brain, strongly promoting the M1 phenotype, thus reinforcing neuroinflammatory processes (Codarri et al., 2011). An essential cytokine required for the acquisition of the pathogenic Th17 phenotype and inhibition of differentiation towards the non-pathogenic Th17 phenotype is IL-23, which can be produced by DCs (Lee et al., 2012). With regard to anti-inflammatory phenotypes of encephalitogenic CD4+ T-cells involved in the regulation of neuroinflammation, there are two main phenotypes, Th2 and regulatory T-cells (Tregs) (Appel, 2009). Tregs are not only pivotal in the maintenance of peripheral immune tolerance, but they are also important in regulating neuroinflammation negatively acting directly on microglial cells and also the attenuating function of inflammatory Th1 and Th17 cells (Dardalhon et al., 2008). The Treg phenotype is controlled by the master transcription factor FoxP3, which can be induced during thymic maturation in CD4+ T-cells (namely natural Tregs) or after thymic maturation in naive CD4+ T-cells exposed to the presence of TGF-β (called inducible Tregs) (Burzyn et al., 2013). The main anti-inflammatory cytokines produced by Tregs are IL-10 and TGF-β through which they can attenuate M1-like microglial activation and Th1/Th17 function (Fontenot et al., 2003; Reynolds et al., 2010). Moreover, these cells may also inhibit inflammatory T-cell function through intercellular interactions mediated by membrane-bound molecules, such as CTLA4, which binds to co-stimulatory molecules expressed in APCs (Wing et al., 2011). In this way, CTLA4 expressed in Tregs, by binding B7 expressed on the surface of microglia or peripheral macrophages and DCs, inhibits co-stimulatory interaction of B7 with CD28, thus attenuating the activation of inflammatory T-cells (Badie et al., 2002). A second phenotype of CD4+ T-cells which can act as an anti-inflammatory in the context of neuroinflammation is Th2 cells. This phenotype, which is induced and maintained by the master transcription factor GATA3, can be induced by the exposition of naive CD4+ T-cells to IL-4 (Dardalhon et al., 2008). Importantly, these cells produce a cytokine milieu constituted mainly by IL-4, IL-5 and IL-13, all of which are important regulators of microglia and peripheral macrophages infiltrated into the CNS parenchyma. In this regard, it has been described that Th2-derived cytokines not only attenuate the M1 and M1-like phenotypes in macrophage/microglia, but they also induce the M2 and M2-like phenotypes respectively in these cells, favouring the production of neurotrophic factors necessary for neurogenesis and tissue reparation after CNS-injury (Appel, 2009;

Fig. 3. CD4+ T-cells as the engine of chronic neuroinflammation involved in neurodegenerative disorders. The scheme illustrates the anatomical and cellular components involved in the adaptive immune response against CNS-constituents mediated by CD4+ T-cells during neurodegenerative disorders. Damaged neurons release aggregated proteins (containing covalent modifications, *i.e.* nitrated-α-synuclein) to extracellular milieu as a consequence of protein oxidation or abnormal protein folding and degradation. Meningeal DCs capture these modified proteins, degrade them and migrate towards the cervical lymph nodes. Upon antigen-presentation within the cervical lymph nodes, they induce the activation of naive CD4+ T-cells (with TCRs specific to CNS-derived neo-antigens presented) and differentiation into inflammatory effector phenotypes, including Th1 and Th17 (left-bottom panel). When meningeal DCs capture CNS-derived antigens in the absence of inflammation, they acquire an immature tolerogenic phenotype and thereby induce an anti-inflammatory phenotype (Tregs/Th2) in CD4+ T-cells specific to CNS-antigens presented in the cervical lymph nodes. Subsequently, those activated CD4+ T-cells cross the permissive BBB and migrate into the CNS where they are re-stimulated by local APCs. Re-stimulation of Th1 and Th17 cells induces a high production of proinflammatory cytokines, which act synergistically, inducing a stronger acquisition of M1-like features by microglia. Thus, Th1 as well as Th17 cells perpetuate the M1-like phenotype in microglia, which actively induces neurodegeneration by producing glutamate, ROS, RNS and TNF-α. Neuronal death and the oxidative environment evoked by activated microglia and infiltrated Th1/Th17 cells favour further formation of aggregated proteins, which are captured by activated microglia, inducing further neo-antigen presentation for infiltrating CD4+ T-cells, thereby perpetuating a neuroinflammation–neurodegeneration cycle in the CNS. On the other hand, the infiltration and participation of Tregs in the CNS stimulates the acquisition of M2-like phenotype by microglia, and attenuates the inflammatory cycle induced by M1-like microglia. Finally, by secreting IL-4, the participation of Th2 cells favours the production of neurotrophic factors through M2-like microglia, supporting neuronal survival. Red arrows indicate pro-inflammatory processes, whilst blue arrows indicate anti-inflammatory processes. Whereas arrows displaying solid lines indicate stimuli/effects, arrows with dotted lines correspond to differentiation/migration. Grey dotted-line arrows indicate CD4+ T-cells infiltrating the CNS parenchyma. For abbreviations and further details, see the text.

Derecki et al., 2010; Shechter et al., 2013). Thus, encephalitogenic Th2 cells may promote a switch from an inflammatory/neurotoxic environment towards an anti-inflammatory/neuroprotective environment. Therefore, this evidence indicates that the precise phenotype acquired by encephalitogenic CD4+ T-cells participating in neuroinflammation is critical for the outcome of neurodegenerative diseases or CNS recovery after injury. A summary of T-cell-microglia intercellular interactions regulating neuroinflammation is represented in Fig. 2B, and an overview of the role of different T-cell phenotypes in neuroinflammation and consequent neurodegeneration is illustrated in Fig. 3.

6. Antigens involved in the adaptive immune response associated with neurodegenerative diseases

6.1. Modified CNS-self antigens are involved in neurodegenerative diseases

The participation of the adaptive immune system infiltrated in the CNS during neurodegenerative diseases implicates the involvement of antigen-specific immune responses. In fact, it has been recently demonstrated that meningeal T-cells which contribute to the acquisition of learning and memory in healthy individuals are autoreactive CD4+ T-cells bearing beneficial phenotypes and TCRs against CNS self-constituents (Baruch and Schwartz, 2013). The concept of autoimmunity involves the loss of tolerance to self-proteins in susceptible individuals in association with specific environmental factors. The loss of tolerance can occur through the modification of self-antigens, generating neo-antigens, such as the case of citrullined self-antigens in rheumatoid arthritis (Goeb et al., 2009; Klareskog et al., 2006; Matsuo et al., 2006). Generation of these citrullined self-antigens due to environmental factors (*i.e.* by smoking) in genetically susceptible individuals (*i.e.* human leukocyte antigen (HLA-DR) polymorphism) results in both humoral and cellular immune responses against these neo-antigens (Goeb et al., 2009; Klareskog et al., 2006; Matsuo et al., 2006). In a similar way, the aggregation and/or oxidation of self-antigens in the CNS could result in the generation of neo-antigens, such as in the case of oxidised α-syn in Lewy bodies (in PD), aggregated Aβ (in AD) and aggregated mSOD1 (in ALS). Regarding this hypothesis, there is strong evidence supporting the formation of neo-antigens in the case of PD. In this regard, PD patients display high immunoreactivity to IgG on dopaminergic neurons, with strong immunostaining of Lewy bodies (Orr et al., 2005). These findings suggest the presence of autoantibodies against antigens present in Lewy bodies, which are probably derived from dopaminergic neurons. Several studies support that aggregated α-syn, the main constituent of Lewy bodies, is one of the proteins recognised by autoantibodies in PD patients (Benner et al., 2008; Papachroni et al., 2007; Spillantini et al., 1997). In fact, it has been shown that 90% of patients with familial PD are positive for autoantibodies against α-syn (Papachroni et al., 2007). The characteristic neuronal stress involved in PD favours the self-assembly of α-syn into oligomeric species (Winner et al., 2011), which are highly toxic and constitute major components of Lewy bodies (Spillantini et al., 1997). Fibrillar aggregates of α-syn are originated by post-translational modifications, such as phosphorylation (Fujiwara et al., 2002), ubiquitination (Shimura et al., 2001) or oxidation/nitration (Tieu et al., 2003). In this regard, reactive oxygen and nitrogen species are pivotal components of the cascade of events leading to neurodegeneration in PD. Of note, peroxynitrite constitutes a potent oxidant generated by the reaction of NO and superoxide anions, and selectively modifies tyrosine residues in self-proteins (Gauba et al., 2011; Tieu et al., 2003). Importantly, tyrosine nitration of α-syn has been described in various synucleinopathies, including PD, a Lewy body variant of AD, multiple system atrophy and dementia with Lewy bodies, indicating a causal association between oxidative stress and neurodegeneration (Giasson et al., 2000). Nitrated α-syn has been found in *post-mortem* samples of the brains of PD patients (Giasson et al., 2000) as well as in animal models of PD (Benner et al., 2008; Yu et al., 2010), where it favours neuronal loss and motor dysfunction (Stone et al., 2012; Yu et al., 2010). Importantly, by stimulating TLRs, nitrated α-syn induces inflammatory microglial activation (see Section 3) and, on the other hand, these covalently-modified forms of α-syn constitute a source of neo-antigen. Thereby, inflammatory cytokines produced by M1-like microglia would promote an immunogenic microenvironment for the presentation of neo-antigens by APCs (Ohmori and Kanayama, 2005), thus triggering an inflammatory T-cell response against cells expressing nitrated α-syn. Supporting this notion, it has been shown that nitrated forms of α-syn drain from the CNS into the cervical lymph nodes in mice undergoing MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced PD, increasing the expression of class II MHC by local APCs (Benner et al., 2008). Accordingly, MPTP-treated mice generate a robust antigen specific T-cell and B-cell response against nitrated α-syn (Benner et al., 2008). Moreover, the transfer of T-cells obtained from mice immunised with α-syn into MPTP-treated mice led to a robust neuroinflammatory response with accelerated dopaminergic cell loss (Benner et al., 2008). Further experiments performed by the same researchers have shown that a T-cell-specific response against nitrated α-syn is mediated by Th17 and Th1 cells (Reynolds et al., 2010). In the same direction, previous reports in mice immunised with class I and class II MHC-restricted peptides demonstrated that the conversion of tyrosine to nitrotyrosine evades central tolerance and elicits a robust inflammatory immune response against nitrated peptides (Birnboim et al., 2003; Hardy et al., 2008). The stimulation of T-cells specific for nitrated self-proteins has been shown to be critical for the generation of auto-reactive antibodies (Benner et al., 2008; Gauba et al., 2011), and it has been associated with autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus (Khan and Ali, 2006; Khan and Siddiqui, 2006).

6.2. Presentation of neo-antigens

Although the CNS lacks a lymphatic system, meningeal DCs accumulate in the CSF (Pashenkov et al., 2002), where they will capture CNS-derived antigens, including neo-antigens generated in neurodegenerative diseases (Ransohoff and Engelhardt, 2012). A recent study has shown that meningeal DCs may be generated from local myeloid precursors, and they exhibit a differentiation and antigen-presenting programme similar to spleen DCs (Anandasabapathy et al., 2011). Thus, these meningeal DCs could take CNS-derived antigens in the CSF and, subsequently, present them in the cervical lymph nodes to peripheral naive T-cells. In this way, auto-reactive naive CD4+ T-cells specific to neo-antigens could be initially activated during neurodegenerative diseases. After initial activation, these effector CD4+ T-cells will cross the permissive and inflamed BBB and will be re-stimulated in the CNS parenchyma by resident APCs, for instance microglia or peripheral monocytes/macrophages or DCs infiltrating the brain. Supporting this notion, a significant correlation between the degree of expression of class II MHC and α-syn deposition in the SN*pc* has been observed in *post-mortem* brain samples of PD patients (Croisier et al., 2005). This observation suggests an enhanced antigenic presentation to CD4+ T-cells in association with an increased deposition of Lewy bodies. With regard to the cell type acting as local APCs, it has been described that microglial cells express class II MHC, CD40 and other co-stimulatory molecules necessary to antigen presentation to T-cells (Ransohoff and Engelhardt, 2012). Accordingly, the processing and presentation of α-syn by microglial cells stimulate the proliferation of CD4+ T-cells and trigger cytokine release (Harms et al., 2013). Similar to microglia, class II MHC and costimulatory molecules are expressed in activated astrocytes, which thus could present antigens to CD4+ T-cells, stimulating their activation in the CNS (Nikcevich et al., 1997). Interestingly, a specific myeloid cell population CD11c+ (typically used as a DC marker) has been described in the juxtavascular parenchyma of the healthy brains (Prodinger et al.,

2011). However, whether this population is capable of presenting antigens remains to be determined. Consistent with this, perivascular macrophages expressing CD11c have been detected in the Virchow–Robin space (Nayak et al., 2012). Taken together, these data indicate that the CNS is populated by a number of myeloid cell populations, although their functional and anatomic significance as APCs during neurodegenerative disorders remains to be determined. The proposed role of CD4+ T-cells, APCs and neoantigens in neurodegenerative diseases is summarised and integrated in Fig. 3.

7. Concluding remarks

Neuroinflammation represents a fundamental component in the physiopathology of neurodegenerative disorders, which is required for the progression of the neurodegenerative process. Differential activation of microglia constitutes a central point of regulation in neuroinflammation, which can yield neurotoxic or neurosupportive environments, being critical for neurons' fate. Evidence has shown the participation of several cellular actors in the regulation of microglial activation, including neurons, astrocytes, the BBB and T-cells. Resident CNS cells, including neurons and astrocytes, actively exert an anti-inflammatory influence on microglial cells upon health. However, when inflammatory processes are triggered by infections or protein aggregates, not only resident nervous cells, but also peripheral immune cells infiltrating the CNS exert several pro-inflammatory mechanisms on microglial cells feeding neuroinflammatory processes. Growing evidence has indicated a pivotal role of CD4+ T-cells in the regulation of neuroinflammation and consequent neurodegeneration in several neurodegenerative diseases. In this regard, encephalitogenic inflammatory CD4+ T-cells such as Th1, Th17 and GM-CSF-producer CD4+ T-cells constitute the engine of chronic neuroinflammation, thus perpetuating neurodegenerative processes. In contrast, encephalitogenic or meningeal Tregs and Th2 cells attenuate inflammatory functions in microglia and promote a neuroprotective microenvironment, even in a healthy CNS, contributing to cognitive tasks. Emerging evidence suggests involvement of antigen-specific T-cell responses against neo-antigens generated by the modification of CNS self-constituents. Thus arises the hypothesis that autoimmune response against CNS antigens constitutes a major component in the physiopathology of neurodegenerative disorders. Accordingly, antigen-specific immunosuppressive-based therapies, such as the use of Tregs or tolerogenic DCs, should be considered for future therapeutic strategies in neurodegenerative disorders.

Acknowledgements

This work was supported by grants 1130271 from FONDECYT, PFB-16 from CONICYT and 2011-0001-R from Universidad San Sebastián. DE holds a graduated fellowship from Universidad Andrés Bello. AM holds a CONICYT graduated fellowship.

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