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# Astrocytes in multiple sclerosis and experimental autoimmune encephalomyelitis: Star-shaped cells illuminating the darkness of CNS autoimmunity

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ABSTRACT

Neuropathology in the human autoimmune disease multiple sclerosis (MS) is considered to be mediated by autoreactive leukocytes, such as T cells, B cells, and macrophages. However, the inflammation and tissue damage in MS and its animal model experimental autoimmune encephalomyelitis (EAE) is also critically regulated by astrocytes, the most abundant cell population in the central nervous system (CNS). Under physiological conditions, astrocytes are integral to the development and function of the CNS, whereas in CNS autoimmunity, astrocytes influence the pathogenesis, progression, and recovery of the diseases. In this review, we summarize recent advances in astrocytic functions in the context of MS and EAE, which are categorized into two opposite aspects, one being detrimental and the other beneficial. Inhibition of the detrimental functions and/or enhancement of the beneficial functions of astrocytes might be favorable for the treatment of MS.

## 1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), in which the myelin sheath of neurons is attacked by the immune system and compromised. More than 2.3 million people are affected globally and most are diagnosed between 20 and 50 years of age (Markowitz, 2013). Patients show a variety of physical and cognitive disabilities (Compston and Coles, 2008). Currently, this disease cannot be cured by the existing therapeutic methods, which can only alleviate the symptoms and slow the progression to some extent. So far, four types of MS have been identified, i.e., relapsing-remitting (RR), primary progressive (PP), secondary progressive (SP), and clinically isolated syndrome (CIS) (Bose, 2017). Relapsing-remitting MS (RRMS) is the most common type, accounting for more than 80% of MS cases (Meyer-Moock et al., 2014), and is defined as episodes of new or worsening symptoms followed by periods of recovery. Many RRMS will further develop into secondary progressive MS (SPMS) (Meyer-Moock et al., 2014), a stage that shows no remission but only gradual progression and the available treatments have only slight efficacy towards SPMS.

The etiology of MS is still unclear and MS is generally considered to be an autoimmune disease in which immune cells attack the myelin sheath around axons in the CNS, causing demyelination and formation of lesions. MS lesions can be classified into (i) acute lesion with numerous inflammatory cells and astroglial hypertrophy, (ii) chronic active lesion with edged demyelination, and (iii) chronic lesion with fewer leukocytes but profound demyelination, axonal loss, and astrogliosis (Han et al., 2008). So far, studies about the pathogenesis and treatment of MS have been extensively performed on its animal models, notably experimental autoimmune encephalomyelitis (EAE), which

*Abbreviations:* BBB, blood-brain barrier; BMP4, bone morphogenetic protein 4; CIS, clinically isolated syndrome; CLDNs, claudins; CNS, central nervous system; Cxs, connexins; EAE, experimental autoimmune encephalomyelitis; ECs, endothelial cells; FGF-2, fibroblast growth factor-2; GFAP, glial fibrillary acidic protein; LIF, leukemia inhibitory factor; MHC, major histocompatibility complex; MMPs, matrix metalloproteinases; MS, multiple sclerosis; NF-κB, nuclear factor-κB; NO, nitric oxide; NPCs, neural precursor cells; Nrf2, nuclear factor E2-related factor 2; OPCs, oligodendrocytes progenitor cells; PPMS, primary progressive multiple sclerosis; RBC, red blood cells; RRMS, relapsing-remitting multiple sclerosis; Shh, sonic hedgehog; SPMS, secondary progressive multiple sclerosis; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF-A, vascular endothelial growth factor-A

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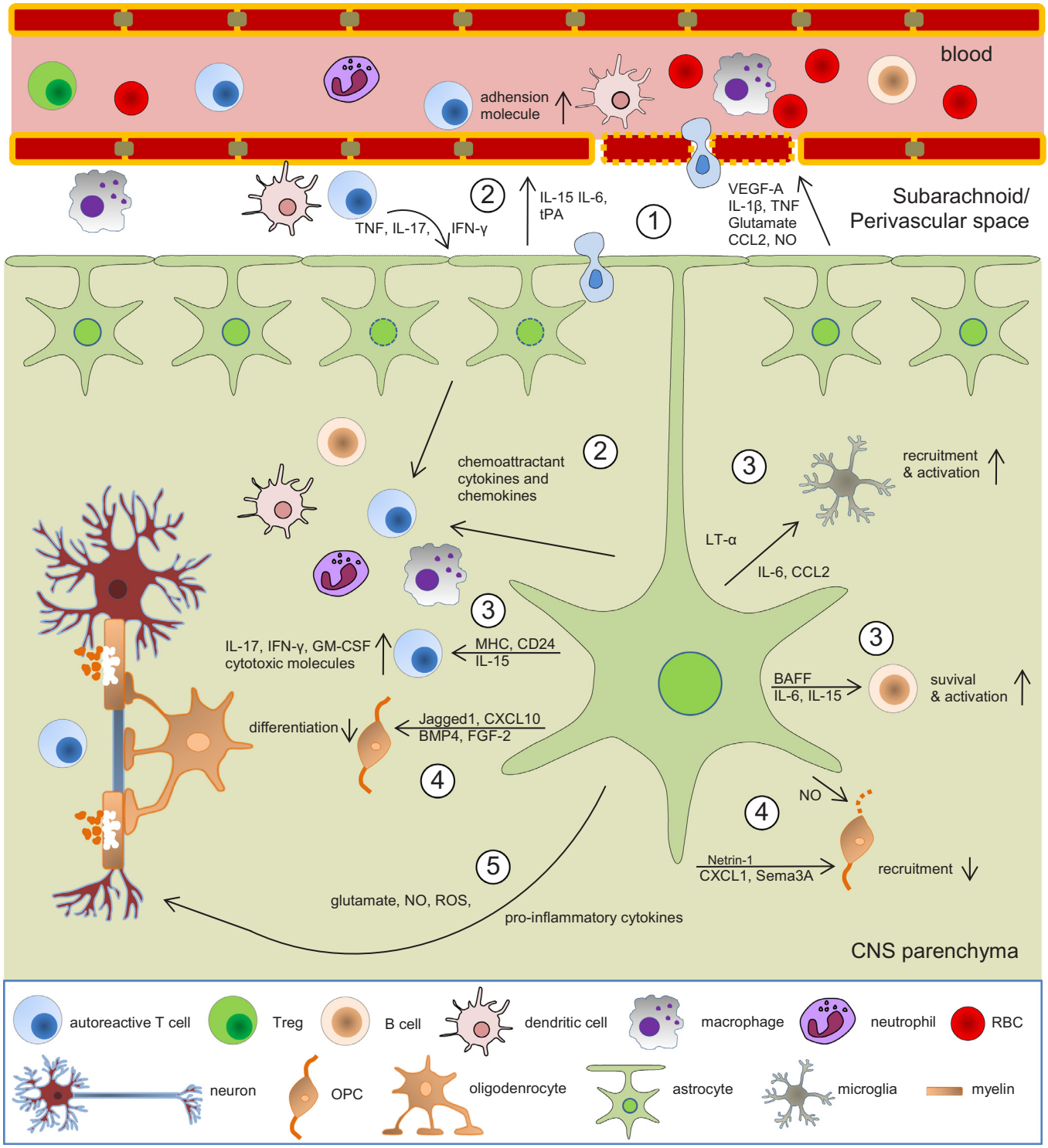


**Fig. 1.** Schematic model of detrimental aspects mediated by astrocytes in EAE and MS. In MS and EAE, astrocytes are activated by multiple stimuli, especially cytokines derived from autoreactive T cells. In turn, reactive astrocytes contribute to disease progression in various ways. The physical barriers composed of the BBB and glia limitans are the first line of defense against immune attacks. Soluble factors released by reactive astrocytes promote apoptosis of ECs and downregulate junction proteins on their surface, causing the breakdown of the BBB. Besides, activated astrocytes lose end feet around small vessels, leading to the disruption of glia limitans. In addition to passively allowing the infiltration of leukocytes, astrocytes also positively recruit leukocytes to the CNS by producing chemoattractant molecules and increasing adhesion molecules on ECs. The recruited leukocytes and CNS-resident microglia are further activated by astrocytes to be more effective in damaging myelin and neurons. In addition to facilitating demyelination, astrocytes inhibit remyelination by inhibiting the recruitment, differentiation and survival of OPCs. Last but not least, astrocytes aggravate the disease by directly causing axonal and neuronal damage.

shares many common pathological features with MS, like neuroinflammation, glial cell activation, axonal loss, and demyelination (Constantinescu et al., 2011). It is of note that MS cannot be entirely recapitulated by EAE and the therapies developed against EAE cannot always be successfully translated to clinical treatment for MS (Constantinescu et al., 2011; Simmons et al., 2013). Despite these drawbacks, studies with EAE have substantially broadened our knowledge about MS.

Astrocytes, or astroglia, were initially identified as star-shaped glial cells and named with the Greek word 'astron', which means star, and 'kytos', which means cell. However, new staining methods have illustrated that the morphology of astrocytes is more complex and region-dependent (Lanjakornsiripan et al., 2018; Stogsdill et al., 2017). Astrocytes are the most abundant cell population in the CNS and play irreplaceable roles in CNS homeostasis. Astrocytes contribute to the formation and integrity of the blood–brain barrier (BBB), affect axonal outgrowths, support neurons, and govern synapse formation and activity (Clarke and Barres, 2013). When CNS injuries happen, astrocytes become activated, which can be clearly identified by the dramatically upregulated expression of glial fibrillary acidic protein (GFAP), and undergo a series of changes termed as reactive astrogliosis. The activation starts at the early stage before the infiltration of leukocytes and might be initially mediated by inflammatory factors which spread quickly cross the BBB and enter the CNS parenchyma (Chanaday and Roth, 2016). In response, several signaling pathways are activated in astrocytes (Haroon et al., 2011; Kim et al., 2011a; Wang et al., 2013b), particularly, the canonical nuclear factor-κB (NF-κB) pathway, which is essential for driving the inflammation in CNS diseases. It has been shown that EAE severity can be significantly altered by the astrocyte-specific ablation of key signaling molecules related to the NF-κB signaling cascade (Brambilla et al., 2009; Kang et al., 2010; Raasch et al., 2011; van Loo et al., 2006; Wang et al., 2013b).

As crucial immune-regulating cells in the CNS, astrocytes play both detrimental and protective roles in these neuroinflammatory diseases and therapeutic manipulation of astrocytes is emerging as a promising treatment option for MS. In this review, we summarize the current understanding of astrocytes in MS and its animal models, particularly EAE.

## 2. Detrimental aspects

MS is primarily initiated and further worsened by leukocytes which infiltrate into the CNS and disturb normal neuronal functions. The infiltration of leukocytes to the CNS parenchyma is critically regulated by astrocytes, as proposed in the "two waves' theory" (Bartholomaus et al., 2009; Engelhardt and Sorokin, 2009; Kebir et al., 2007; Reboldi et al., 2009). After priming in peripheral lymphatic organs, antigen-specific T cells enter the perivascular spaces (wave I), where they are reactivated by perivascular/meningeal antigen-presenting cells (APCs). Reactivated T cells undergo clonal expansion and produce pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-17, granulocyte–macrophage colony-stimulating factor (GM-CSF), and interferon (IFN)-γ, which activate adjacent CNS-resident cells, particularly astrocytes and microglia, to produce chemoattractant chemokines and cytokines, leading to an enhanced recruitment of immune cells to the CNS parenchyma (wave II) (Sofroniew, 2015; Zepp et al., 2011). Astrocytes play indispensable roles in the progression from wave I to wave II and the formation of the detrimental positive-feedback loop of inflammation (Kang et al., 2010; Wang et al., 2019). A recent study shows that the genetic variant rs7665090$^{G}$, which enhances NF-κB activation and leukocyte-recruiting gene production in astrocytes, is associated with MS (Ponath et al., 2018). In addition to chemokines and cytokines, hundreds of genes relevant to antigen presentation, oxidative stress, immune receptors, inflammation, BBB disruption, and signal transduction are increased in astrocytes upon inflammatory stimulation (Falsig et al., 2006). Meanwhile, protective factors like neurotrophins which are important for neuronal survival are downregulated (Falsig et al., 2006). Thus, reactive astrocytes are capable of accelerating the inflammatory cascades and aggravating neurological disorders (Fig. 1; Table 1).

### 2.1. Breakdown of the blood brain barrier

The CNS homeostasis is guaranteed by the BBB, a physical structure established by endothelial cells (ECs), pericytes, and basement membrane. The BBB is ensheathed by the end-feet of astrocytes which form the glia limitans. The extracellular parts between ECs are filled with junctions, including adherens and tight junctions, to control the endothelial permeability. Of note, various CNS disorders such as neuroinflammatory and neurodegenerative diseases are associated with BBB dysfunction, which can be regulated by astrocytes (Cabezas et al., 2014). In MS and acute EAE, tight junction proteins such as claudins (CLDNs) and occludin are reduced and the BBB permeability is increased (Haghjooy Javanmard et al., 2012; Morgan et al., 2007; Wolburg et al., 2003). The mechanism of BBB breakdown is not completely understood, although it has been shown that the permeability can be enhanced by cytokines, chemokine, matrix metalloproteinases (MMPs), and reactive oxygen species (ROS) (Minagar and Alexander, 2003). With respect to ECs, reactive astrocytes can release some of those molecules, such as IL-1β, TNF, glutamate, and nitric oxide (NO), to downregulate junction proteins and induce the apoptosis of ECs (Didier et al., 2003; Gimenez et al., 2004; Haarmann et al., 2015; Parfenova et al., 2006; Rochfort et al., 2016; Stamatovic et al., 2003; Thiel and Audus, 2001; Vazana et al., 2016). In addition, astrocytes are the major source of CC-Chemokine ligand 2 (CCL2) in the CNS (Van Der Voorn et al., 1999), which has a profound impact on ECs. CCL2 has been shown to disassemble adherens junctions (Roberts et al., 2012) and mediate the reorganization and internalization of tight junction proteins which reduces surface level of CLDN5 and occludin (Stamatovic et al., 2003; Stamatovic et al., 2009). Moreover, astrocyte-derived vascular endothelial growth factor-A (VEGF-A) was originally identified as a factor that is in charge of EC growth, but in pathologic condition, over-expressed VEGF-A activates endothelial nitric oxide synthase (eNOS) to generate NO in ECs (Argaw et al., 2012). Along with other contributors, immunity-related GTPase family M protein (IRGM) and thymidine phosphorylase (TYMP) negatively regulate CLDN5 and occludin (Chapouly et al., 2015; Wang et al., 2013a). On the other hand, the protective factor angiotensinogen (AGT), which is involved in the localization and function of occludin, is reduced in astrocytes (Wosik et al., 2007).

Glia limitans, which is formed mainly by the endfeed of astrocytes, is another physical barrier that limits the invasion of leukocytes into the brain parenchyma. However, astrocytes are diminished in newly forming MS lesions (Prineas and Lee, 2019) and detached from the blood vessels (Eilam et al., 2018) which indicates that the structure of glia limitans is damaged. Leukocytes in the perivascular spaces might contribute to the destruction by producing MMPs, which, in turn, cleave dystroglycan (Agrawal et al., 2006; Masaki, 2015; Masaki et al., 2013), the anchor between endfeet of astrocytes and the basement membrane. Collectively, the BBB, as the first line of defense against the invasion of leukocytes into the CNS, is damaged at the early stage of MS and EAE, permitting the massive infiltration of immune cells. In this process, astrocytes facilitate the development of the diseases by contributing to BBB disruption.

### 2.2. Recruitment and activation of leukocytes

MS and EAE are considered to be induced by immune cells, especially antoreactive $CD4^{+}$ T cells. Among the $CD4^{+}$ T cells, Th1 (Kudriaeva et al., 2017), Th17 cells (Prajeeth et al., 2017), and GM-CSF-expressing T cells (Codarri et al., 2011) are the major effector cells, which activate and cooperate with other leukocyte populations

**Table 1**
The Function of Disease-promoting Molecules Expressed by Astrocytes in MS/EAE.

| | Molecule | Function |
|---|---|---|
| BBB destruction | IL-1β (Didier et al., 2003), TNF (Rochfort et al., 2016), CCL2 (Stamatovic et al., 2003), NO (Thiel and Audus, 2001), glutamate (Vazana et al., 2016), VEGF-A (Argaw et al., 2012) | Induction of the apoptosis of EC<br>Downregulation of junction proteins |
| Pro-inflammation | IL-15 (Estess et al., 1999), IL-6 (Watson et al., 1996), tPA (Wang et al., 2014) | Activation of ECs to express chemokines |
| | MMPs (Maeda and Sobel, 1996) | Degradation of basement membrane components |
| | CD44 (Haegel et al.,1993), CXCL10 (Mills Ko et al., 2014), CXCL12 (McCandless et al., 2008), CCL2 (Carrillo-de Sauvage et al., 2012; Kim et al., 2014), CCL20 (Ambrosini et al., 2005; Ambrosini et al., 2003) | Recruitment of leukocytes and microglia |
| | CD24 (Liu et al., 2007), IL-15 (Broux et al., 2015) | Activation of $CD4^+$ T cells |
| | BAFF (Krumbholz et al., 2005), IL-6 (Kitani et al., 1992), IL-15 (Armitage et al., 1995; Saikali et al., 2010) | Enhancement of $CD8^+$ T and B cell responses |
| | IL-6 (Savarin et al., 2015), LT-α (Plant et al., 2005), LacCer (Mayo et al., 2014) | Activation of microglia |
| | CD40 (Kim et al., 2011; Kim et al., 2010) | Activation of mast cells |
| | MHC (Hoftberger et al., 2004; Zeinstra et al., 2000) | Antigen presentation |
| Regeneration inhibition | MMPs (Maeda and Sobel, 1996), calpain (Shields et al., 1999) | Myelin breakdown |
| | Glial scar (Bannerman et al., 2007) | Blockage of OPCs migration to the lesions |
| | CXCL1 (Vora et al., 2012), netrin-1 (Tepavcevic et al., 2014), Sema3A (Boyd et al., 2013) | Inhibition of OPCs migration |
| | Jagged1 (John et al., 2002), IL-6 (Petkovic et al., 2016), FGF-2 (Zhou et al., 2006), BMP4 (Sabo et al., 2011), CXCL10 (Moore et al., 2015), TNF (Bonora et al., 2014) | Inhibition of OPCs differentiation |
| | ECM components (Bugiani et al., 2013; Gutowski et al., 1999; Keough et al., 2016; Sloane et al., 2010; Stoffels et al., 2013) | Inhibition of the regeneration |
| | Glutamate (Wang et al., 2017) | Excitotoxicity |
| | ROS (Mossakowski et al., 2015), NO (Liu et al., 2001; Tran et al., 1997) | Induction of the death of ECs, oligodendrocytes, OPCs, and neurons |

BAFF: B-cell activating factor; BMP4: bone morphogenic protein 4; EC, endothelial cell; ECM: extracellular matrix; FGF-2: fibroblast growth factor 2; LacCer: lactosylceramide; LT-α: lymphotoxin-alpha; MHC: major histocompatibility complex; MMPs: matrix metalloproteinases; NO: nitric oxide; OPCs: oligodendrocytes progenitor cells; ROS: reactive oxygen species; tPA: tissue plasminogen activators; VEGF-A: vascular endothelial growth factor-A.

(Kaskow and Baecher-Allan, 2018) and CNS-resident cells (Rothhammer et al., 2018; Liddelow et al., 2017; Kim et al., 2011) to drive the inflammation and cause tissue damage in EAE.

The transendothelial passage is a prerequisite for the invasion of circulating leukocytes to the CNS. ECs become activated with increased expression of adhesion molecules and chemokines in MS lesions (Alexander et al., 2011). By producing factors like IL-15, IL-6, and tissue plasminogen activators (tPA), reactive astrocytes can also upregulate adhesion molecules, such as E-selectin, VCAM, ICAM, and the CD44 ligand hyaluronan, on ECs, thereby enhancing the attachment of T cells (Estess et al., 1999; Wang et al., 2014; Watson et al., 1996). In addition, in acute lesions, the loss of astrocytic Cx43 is associated with an increased expression of adhesion molecules and more activated phenotype of ECs (Boulay et al., 2015). Components of the basement membrane coating ECs can be degraded by proteases such as MMPs and astrocytes constitute a significant source of these proteases (Maeda and Sobel, 1996). The further recruitment of effector cells to the CNS parenchyma requires the crossing through glia limitans. Astrocytes are a major source of chemokines, including CCL2, CCL20, CXCL10, and CXCL12 (Alter et al., 2003; Ambrosini et al., 2005; Haegel et al., 1993; Ransohoff et al., 1993; Seguin et al., 2003). $CCL2^+$ astrocytes establish a close attachment with adjacent leukocytes and sustain the recruitment (Carrillo-de Sauvage et al., 2012; Kim et al., 2014). As compared with control mice, EAE symptoms of astrocyte-specific CCL2-deficient mice were significantly reduced, accompanied with diminished accumulation of pro-inflammatory M1 macrophages in the CNS and increased retention of Th17 cells in perivascular spaces (Moreno et al., 2014). CCL20 expressed by astrocytes and epithelial cells is critical for the initiation of EAE by recruiting $CCR6^+$ cells (Ambrosini et al., 2003; Reboldi et al., 2009). Astrocyte-derived CXCL10 promotes the accumulation of $CD4^+$ T cells in perivascular spaces (Mills Ko et al., 2014). Elevated expression of CXCL12 by astrocytes in MS tissue facilitates the migration of leukocytes into the CNS (McCandless et al., 2008).

Reactive astrocytes can exacerbate the damage by activating both infiltrating and CNS-resident immune cells. The role of astrocytes as APCs is still controversial. On one hand, they show high levels of major histocompatibility complex (MHC) II in active MS lesions (Hoftberger et al., 2004; Zeinstra et al., 2000) and are able to present myelin antigens to T cells (Kort et al., 2006; Soos et al., 1998; Tan et al., 1998). On the other hand, no consensus has been reached concerning the expression of costimulatory molecules on astrocytes, since results from different studies vary dramatically (Cross and Ku, 2000; Satoh et al., 1995; Zeinstra et al., 2003; Nikcevich et al., 1997). Astrocytes, together with microglia drive the polarization of $CD4^+$ T cells to pro-inflammatory phenotypes and enhance the pro-inflammatory capabilities of T cells (Beurel et al., 2014; Broux et al., 2015; Carson et al., 1999; Liu et al., 2007; Miljkovic et al., 2007). Furthermore, soluble factors released by astrocytes control $CD8^+$ T cell and B cell responses, including maturation, survival, cytotoxicity, and maintenance (Armitage et al., 1995; Kitani et al., 1992; Krumbholz et al., 2005; Saikali et al., 2010; Touil et al., 2018). Microglia and mast cells are crucial immune-regulatory cells in the CNS (Lenz and Nelson, 2018). Astrocytes are able to promote the activation and accumulation of microglia in the lesions by releasing factors such as IL-6, lactosylceramide (LacCer), and lymphotoxin-alpha (LT-α) (Mayo et al., 2014; Plant et al., 2005; Savarin et al., 2015). Mast cells are found at the border of MS lesions and can be bidirectionally activated by astrocytes through CD40-CD40L (Kim et al., 2011a; Kim et al., 2010).

### 2.3. Demyelination and failure of remyelination

Axons are insulated with myelin sheaths created by oligodendrocytes and demyelination is a pathological hallmark of MS and EAE. The degradation of the major myelin proteins is the first step of myelin breakdown which further makes myelin sheaths unstable (Belogurov et al., 2015; Weil et al., 2016). Proteases such as MMPs and calcium-activated neutral protease (calpain) participate in this process. In addition to myelin-specific T cells and macrophages, astrocytes are also found to be one source of these factors (Maeda and Sobel, 1996; Shields et al., 1999).

Upon demyelination, oligodendrocyte progenitor cells (OPCs), the precursors of oligodendrocytes, migrate to the injury site and differentiate into mature oligodendrocytes to rewrap the exposed axons (remyelination). Although there are abundant OPCs in the adult brain (Boyd et al., 2013), remyelination does not occur in a number of MS patients and oligodendrocytes are found to be absent in the

demyelinated lesions (Lucchinetti et al., 1999). The failure of remyelination may manifest at various steps in the transition from OPCs to mature oligodendrocytes, such as migration, differentiation, and maturation (Franklin, 2002).

Oligodendrocytes can establish heterotypic coupling with astrocytes by connexins (Cxs), typically, oligodendrocytic Cx47 and astrocytic Cx43, which facilitates the myelination (Basu and Sarma, 2018). The stability of Cx47 requires the support from astrocytic Cx43 (May et al., 2013), thus it is not surprising that astrocytic Cx43 loss is accompanied by reduced Cx47 in MS lesions (Masaki, 2015). In addition, together with leukocytes and microglia, reactive astrocytes create a microenvironment rich in pro-inflammatory factors and reactive species. Both oligodendrocytes and OPCs are quite vulnerable in this context and tend to undergo apoptosis (Kim et al., 2011b; Li et al., 2008; Su et al., 2011).

In both MS and EAE, decreased remyelination was found to be associated with insufficient migration of OPCs to demyelinated lesions (Boyd et al., 2013). It is widely accepted that reactive astrocytes block the migration of OPCs by forming a physical barrier called glial scar, and consequently, OPCs are sequestered at the edge of the lesions (Bannerman et al., 2007). Moreover, astrocytes impede the migration by secreting soluble factors, such as netrin-1 (Tepavcevic et al., 2014), CXCL1 (Vora et al., 2012), and the chemorepellent Sema3A (Boyd et al., 2013).

Mature oligodendrocytes can hardly be found in chronic MS lesions, although in most cases, there are sufficient OPCs (Kuhlmann et al., 2008). Therefore, the differentiation of OPCs into mature oligodendrocytes might be hindered. The differentiation of OPCs is mainly suppressed by the Notch signal (Jurynczyk et al., 2008; Yu et al., 2018), as inhibition of Notch pathway significantly improves remyelination and recovery from EAE (Jurynczyk et al., 2005). The Notch receptor on OPCs can be activated by astrocytes through the ligand Jagged1, which induces expression of the inhibitory protein Hes5 to maintain the undifferentiated state, and levels of Jagged1 on astrocytes are negatively correlated with the remyelination status (John et al., 2002). The differentiation of OPCs can be disturbed by other factors released by astrocytes, like fibroblast growth factor-2 (FGF-2) (Zhou et al., 2006), bone morphogenic protein 4 (BMP4) (Sabo et al., 2011), and cytokines, such as CXCL10, TNF, and IL-6 (Bonora et al., 2014; Moore et al., 2015; Petkovic et al., 2016). Astrocytes are an important source of extracellular matrix (ECM) molecules. In chronic lesions, the ECM composition increases and deposits around the glial scar (Bugiani et al., 2013; Gutowski et al., 1999; Keough et al., 2016; Sloane et al., 2010; Stoffels et al., 2013), which becomes inhibitory to axonal and neuronal regeneration. Besides that, astrocytes have been shown to produce less cholesterols, which are required for myelin production in oligodendrocytes, thereby reducing remyelination (Itoh et al., 2018).

### 2.4. Neurotoxic effect

Without the protection and support of myelin sheath, axons become unstable and sensitive to damage (Piaton et al., 2010). Substantial injury and deficiency of axons have been confirmed in both EAE and MS lesions (Bjartmar et al., 2000; Wujek et al., 2002). The destruction of axons and neurons is mediated by multiple factors including inflammation, excitatory neurotransmitter, oxidative stress, and dysfunction of energy metabolism. As an essential component in the CNS, astrocytes might be associated with axonal and neuronal damage throughout the disease process (Wang et al., 2005). The connection between astrocytes and neurons becomes abnormal (Eilam et al., 2018), leading to insufficiency of energy supply, mitochondrial dysfunction, failure in neurogenesis, and even death of neural cells (Zhang et al., 2018). Moreover, astrocytes become neurotoxic by (i) producing inflammatory cytokines to cause neuronal damage (Hashioka et al., 2015; Rothhammer and Quintana, 2015; Ye et al., 2013), (ii) diminishing expression of neurotrophic factors (Prajeeth et al., 2017), (iii) downregulating neural activities through secretion of extracellular vesicles containing miRNAs which target neurotrophin pathways (Chaudhuri et al., 2018), (iv) reducing the ability to buffer glutamate, and (v) generating oxidative stress.

Glutamate is a neurotransmitter involved in the communication among neurons and has essential roles in the development and function of the CNS. The basal amount of extracellular glutamate, which is buffered by astrocytes, is relatively low. However, the level rises strikingly in patients with MS or neurodegenerative diseases (Al Gawwam and Sharquie, 2017; Ben Haim et al., 2015). Excessive glutamate exerts toxicity, leading to the death of oligodendrocytes and neurons (Macrez et al., 2016). The high levels of glutamate are caused by the increased production and the decreased degradation. On one hand, the production is enhanced in neurons and induced in immune cells and CNS cells (Tang et al., 2017; Ye et al., 2013). It has been shown that the synthesis and release of glutamate by astrocytes are promoted by TNF (Wang et al., 2017). Consistently, glutamate carboxypeptidase II (GCPII), which participates in glutamate synthesis, is increased in astrocytes at the peak of EAE (Ha et al., 2016). On the other hand, astrocytes are responsible for uptaking excessive glutamate and maintaining the homeostasis (Rose et al., 2017). Glutamate assimilated by astrocytes is converted by glutamine synthetase to inactive glutamine which will be absorbed by neurons for recycling. However, the uptake and recycling systems are defective in astrocytes in various neurological diseases including EAE (Hardin-Pouzet et al., 1997; Pajarillo et al., 2019; Zeis et al., 2015).

Levels of reactive species including reactive oxygen species (ROS) and reactive nitrogen species (RNS) are elevated in both MS and the acute stage of EAE (Haider et al., 2011; Nikic et al., 2011). Reactive species give rise to oxidative stress and suppress mitochondrial respiration in CNS cells, leading to BBB breakdown, oligodendrocyte death, axonal destruction, and neuronal loss. Reactive species are generated by various cell types during CNS autoimmunity (Fischer et al., 2012; Liu et al., 2001), and meanwhile, the neutralizing system becomes dysfunctional (Gilgun-Sherki et al., 2004). It has been shown that in astrocytes, NADPH oxidase 1 (NOX1), which catalyzes the production of superoxide radical ($O2^-$), ascends during EAE and in MS lesions (Mossakowski et al., 2015). The most important and well-studied RNS is NO. Low levels of NO are indispensable for signal transduction between neurons and glial cells, but at high concentrations, it turns to be cytotoxic. Excessive amounts of NO and its derivative product peroxynitrite ($ONOO^-$), a strong oxidant, are found in MS lesions (Cross et al., 1998). NO is catalyzed by nitric oxide synthase (NOS), especially inducible NOS (iNOS), in pathologic circumstances. Astrocytes, along with macrophages/microglia, are major donors for NO (Liu et al., 2001; Tran et al., 1997), and the proinflammatory cytokines, such as IL-1β, IL-17, and IFN-γ, can induce the expression of iNOS in astrocytes to produce more NO (Chao et al., 1997; Trajkovic et al., 2001; Yoo et al., 2008). In addition to cytokines, activation of TrkB on astrocytes can also boost the production of NO (Colombo et al., 2012). On the other hand, β2 adrenergic receptors, which are beneficial for neurons by suppressing iNOS activity as well as promoting energy generation, glutamate uptake, and neurotrophin production, are lost in astrocytes of MS patients (De Keyser et al., 1999).

## 3. Beneficial aspects

Although reactive astrocytes have been shown to aggravate the inflammation and suppress the regeneration, more severe EAE was observed in mice lacking reactive astrocytes (Lopes Pinheiro et al., 2016; Toft-Hansen et al., 2011), indicating that astrocytes play overall protective roles in this autoimmune disease. Indeed, astrocytes are protective in a variety of aspects, including restoration of BBB integrity, suppression of inflammation, supporting remyelination and axonal regeneration as well as neuronal protection (Fig. 2; Table 2).

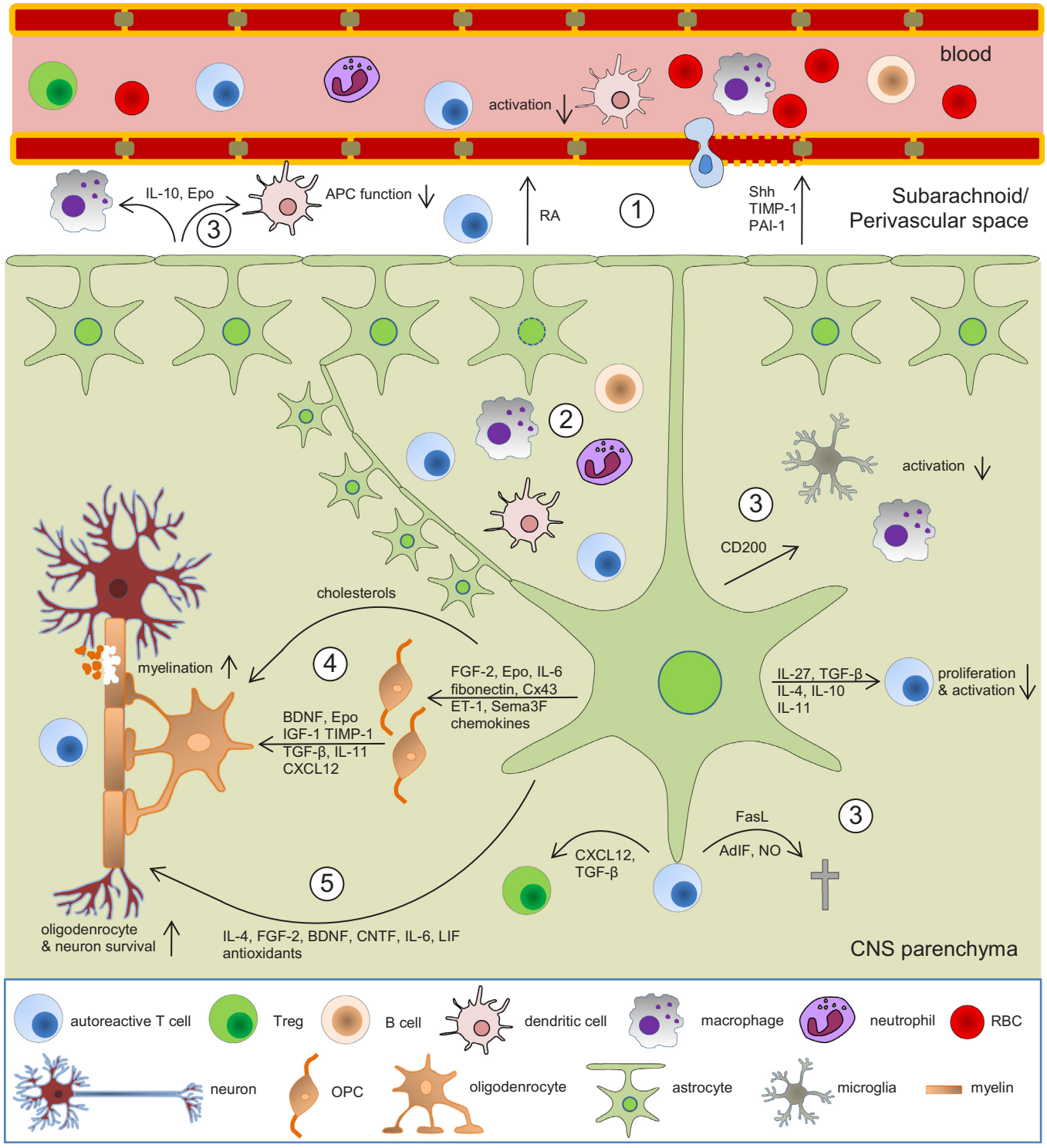


**Fig. 2.** Schematic model of protective aspects mediated by astrocytes in EAE and MS. Astrocytes have been shown to be indispensable in the amelioration and recovery of EAE and MS. Astrocyte-derived factors reduce the inflammation-induced activation of ECs and preserve the expression of junction proteins, thereby reducing the adhesion of immune cells on ECs and restoring the BBB property. At chronic lesions, astrocytes form glial scar to restrain the spread of leukocytes and inflammation. In addition to limiting the invasion of leukocytes, astrocytes also restrain their activity in the CNS. Astrocytes inhibit the activity of infiltrating T cells in many ways, including polarizing autoreactive T cells to a regulatory phenotype and inducing the apoptotic elimination of encephalitogenic T cells. Astrocytes have been found to promote the remyelination by facilitating the migration, proliferation and differentiation of OPCs. Besides, astrocytes enhance the myelin producing ability of oligodendrocytes by producing cholesterols. Lastly, the neuronal function is safeguarded by astrocytes, which support the survival of oligodendrocytes and neurons by releasing neurotrophic, anti-inflammatory, and anti-oxidative factors.

**Table 2**
The Function of Disease-inhibiting Molecules Expressed by Astrocytes in MS/EAE.

| | Molecule | Function |
|---|---|---|
| BBB restoration | RA (Mizee et al., 2014) | Inhibition of the activation of EC |
| | TIMP-1 (Pagenstecher et al., 1998), PAI-1 (Teesalu et al., 2001), peroxiredoxin 6 (Yun et al., 2015) | Neutralization of MMPs and tPA |
| | Shh (Alvarez et al., 2011; Xia et al., 2013) | Enhancement of the expression of junction proteins and reduction of the chemokines in ECs |
| | Cx43 (Masaki, 2015; Masaki et al., 2013), dystroglycan (Agrawal et al., 2006), | Support of glia limitans |
| Anti-inflammation | Glial scar (Voskuhl et al., 2009) | Limitation of injury and inflammation |
| | IL-10 (Mittal and Roche, 2015), Epo (Zhang et al., 2012) | Suppression of APCs |
| | CXCL12 (Meiron et al., 2008), TGF-β (Gimsa et al., 2004) | Promotion of regulatory T cell phenotype |
| | CD200 (Koning et al., 2009) | Suppression of macrophages |
| | IL-10 (Baert et al., 2019; Hulshof et al., 2002), IL-27 (Lalive et al., 2017), TGF-β (Gimsa et al., 2004), IL-4 (Hulshof et al., 2002), IL-11 (Gurfein et al., 2009) | Anti-inflammatory factors |
| | Gal-9 (Steelman et al., 2013), NO (Xiao et al., 2000), FasL (Wang et al., 2013c), AdIF (Hara et al., 2011) | Induction of T cell death |
| Remyelination | IL-4 (Paintlia et al., 2006), FGF-2 (Azin et al., 2015), BDNF (Wong et al., 2013), CNTF (Steelman et al., 2016), IL-6 (Steelman et al., 2016; Sun et al., 2015), LIF (Steelman et al., 2016) | Protection of OPC and neuron from death |
| | Fibronectin (Stoffels et al., 2015), FGF-2 (Azin et al., 2015), Epo (Sugawa et al., 2002), IL-6 (Filipovic and Zecevic, 2008), CXCL12 (Patel et al., 2012) | Promotion of OPC proliferation |
| | ET-1 (Gadea et al., 2009), FGF-2 (Clemente et al., 2011), Sema3F (Boyd et al., 2013), CXCL1 (Omari et al., 2005), CXCL8 (Omari et al., 2005), CXCL10 (Omari et al., 2005), CXCL12 (Tian et al., 2018) | Facilitation of OPC migration |
| | IGF-1 (Wilson et al., 2003), TIMP-1 (Crocker et al., 2006), CXCL12 (Patel et al., 2012; Kremer et al., 2016), BDNF (Van't Veer et al., 2009), Epo (Zhang et al., 2005), netrin-1 (Tepavcevic et al., 2014), IL-11 (Maheshwari et al., 2013; Zhang et al., 2006), TGF-β (Palazuelos et al., 2014), CNTF (Stankoff et al., 2002) | Promotion of OPC maturation to oligodendrocytes |
| | CCL2 (Cohen et al., 2014), CXCL12 (Cohen et al., 2014), HGF (Cohen et al., 2014) | Upregulation of the number of oligodendrocytes differentiated from NPCs |
| Antioxidation | Antioxidative enzymes (Holley et al., 2007; Nijland et al., 2014; van Horssen et al., 2006; van Horssen et al., 2008; Voigt et al., 2017) | Neutralization of the oxidative stress |

APCs: antigen-presenting cells; AdIF: astrocyte-derived immune suppressor factor; BDNF: brain-derived neurotrophic factor; CNTF: ciliary neurotrophic factor; Cx43: connexins 43; Epo: erythropoietin; EC, endothelial cell; ET-1: endothelin-1; FasL: Fas ligand; Gal-9: galectin-9; HGF, hepatocyte growth factor; IGF-1: insulin-like growth factor 1; LIF: leukemia inhibitory factor; NPCs, neural precursor cells; PAI-1: plasminogen activator inhibitor-1; RA: retinoic acid; TIMP-1: tissue inhibitor of metalloproteinase-1.

### *3.1. Restriction of leukocytes infiltrating into the CNS parenchyma*

Under normal conditions, astrocytes contribute to the construction and maintenance of BBB. Still in MS lesions, reactive astrocytes are capable of releasing protective factors which can partly restore BBB function. The activation of ECs is a crucial step associated with BBB breakdown and it can be suppressed by retinoic acid (RA) (Mizee et al., 2014). In MS lesions, astrocytes might be a potential source of RA, as astrocytes show a sustained and robust expression of retinaldehyde dehydrogenase 2, the enzyme that catalyzes RA synthesis (Mizee et al., 2014). Moreover, junction proteins can be preserved by astrocytes, since they are the major cells expressing the endogenous inhibitors tissue inhibitor of metalloproteinase-1 (TIMP-1) and plasminogen activator inhibitor-1 (PAI-1) to counteract the activity of extracellular proteolytic enzymes (Pagenstecher et al., 1998; Teesalu et al., 2001). In addition, MMP-9 can also be inhibited by the antioxidative protein peroxiredoxin 6 which is increased in MS and EAE lesions and is primarily expressed by astrocytes (Yun et al., 2015). Astrocytes facilitate the formation of endothelial junctions (Alvarez et al., 2011; Xia et al., 2013) and reduce the adhesion of Th1 and Th17 cells on ECs (Alvarez et al., 2011) by secreting high amount of sonic hedgehog (Shh), which can activate the hedgehog pathway in ECs.

In response to injury, a glial scar is formed by perivascular astrocytes to restrain the egress and spread of leukocytes from perivascular spaces to the CNS parenchyma (Voskuhl et al., 2009). The mechanism on scar formation has not been fully elucidated, but it has been revealed that astrocytes experience a series of changes, which are orchestrated by multiple factors like cytokines, chemokines, and growth factors derived from leukocytes and local CNS cells. It is supposed that scar formation is tightly regulated by the signal transducer and activator of transcription 3 (STAT3) signaling (Okada et al., 2006; Renault-Mihara et al., 2017) and astrocyte-specific STAT3 ablation leads to a less reactive and unintegrated scar (Herrmann et al., 2008). The reorganization of the cytoskeleton molecules and tightened astrocytic network also contribute to scar formation, as loss of the intermediate filament proteins, like GFAP, nestin, and vimentin, as well as junction proteins fail to restrain the leukocytes (Horng et al., 2017; Pekny et al., 1999). In addition, the survival of astrocytes is crucial for the barrier function. Our studies revealed that knockout of astrocytic glycoprotein 130 (gp130), a crucial receptor for cytokines of the IL-6 family, caused apoptosis of astrocytes in inflammatory lesions, leading to wide-spread infiltration of encephalitogenic T cells in the CNS and more severe EAE (Haroon et al., 2011). In MS lesions, heat shock protein alphaB-crystallin (CRYAB) is highly expressed and phosphorylated, which confers astrocytes the resistance to T cell-induced apoptosis (Kuipers et al., 2017; Ousman et al., 2007).

### *3.2. Suppression of immune response*

As discussed before, astrocytes have the potential to serve as APCs (Constantinescu et al., 2005). However, rather than activating disease-aggravating Th1 cells, astrocytes have a preference to present autoantigens to Th2 cells which participate in anti-inflammatory responses and contribute to the recovery (Aloisi et al., 1998). Moreover, the antigen-presenting capacity of other APCs can be inhibited by IL-10 (Mittal and Roche, 2015) and glycoprotein erythropoietin (Epo) (Zhang et al., 2012), both of which are produced by astrocytes in EAE and MS (Hulshof et al., 2002; Kang et al., 2009). Furthermore, astrocytes create an immunosuppressive environment fostering immune tolerance. Astrocytes have been shown to induce a regulatory T phenotype among infiltrating autoreactive T cells (Gimsa et al., 2004; Meiron et al., 2008; Trajkovic et al., 2004) and inhibit macrophages through the immune inhibitory receptor CD200 (Koning et al., 2009).

IFN-γ is predominantly produced by autoreactive T cells and plays

various roles in CNS autoimmunity. It is pro-inflammatory in the early stage of EAE. Recently, we have shown that OTUB1, a deubiquitinating enzymes, ameliorates EAE by suppressing IFN-γ-induced astrocyte activation (Wang et al., 2019). In sharp contrast, IFN-γ turns to be neuroprotective in the late stage (Arellano et al., 2015). When IFN-γ signaling is absent in astrocytes, demyelination and clinical scores of EAE are increased without apparent remission, accompanied with an impaired expression of anti-inflammatory factors IL-10 and IL-27 in astrocytes (Hindinger et al., 2012). Moreover, IFN-γ promotes the secretion of soluble factors in astrocytes to suppress microglia activation (Savarin et al., 2015), neuronal apoptosis (Sun et al., 2017), and myelin-specific IgG production by B cells (Xiao et al., 1998). IFN-γ induces endogenous negative modulators suppressors of cytokine signaling (SOCS)-1 and SOCS-3 (Stark et al., 2004), which in turn suppress NF-κB and MAPK pathways. In addition, astrocytes produce anti-inflammatory molecules like IL-27, IL-4, IL-10, and IL-11 to counteract the inflammatory response (Baert et al., 2019; Gurfein et al., 2009; Hulshof et al., 2002; Lalive et al., 2017). In the recovery stage of EAE, negative costimulatory signals are activated in encephalitogenic T cells, resulting in the exhaustion of T cells. In this regard, galectin-9 (gal-9) on astrocytes inhibits the function of Th1 cells and $CD8^+$ T cells through binding with the receptor T cell immunoglobulin and mucin domain protein-3 (Tim-3) (Steelman et al., 2013; van Nierop et al., 2017). Furthermore, apoptotic T cells are found to colocalize with astrocytes in the CNS parenchyma (Kohji et al., 1998), suggesting that astrocytes might be the major CNS cells that participate in the elimination of T cells. We have shown that astrocytes induce the apoptosis of T cells via Fas ligand (FasL), thereby contributing to the apoptotic elimination of T cells from the CNS and EAE recovery (Wang et al., 2013c). In addition to FasL, astrocytes induce the inactivation and apoptosis of autoreactive $CD4^+$ T cells by astrocyte-derived immune suppressor factor (AdIF) (Hara et al., 2011) and NO (Xiao et al., 2000).

### 3.3. Remyelination

The immune system attacks the myelin structure, leading to the accumulation of fragmented myelin on the axons. The damaged myelin sheath is dysfunctional and the debris hinders remyelination (Kotter et al., 2006). Therefore, a fundamental prerequisite for remyelination is the removal of the myelin debris which is mainly carried out by macrophages/microglia (Lampron et al., 2015). However, Skripuletz et al. pointed out that the clearance was unsuccessful when astrocytes were ablated (Skripuletz et al., 2013). Mechanistically, astrocytes contribute to the clearance of myelin debris by recruiting more macrophages/microglia to the impaired area. Moreover, debris was found in reactive astrocytes as well, which implies their potential in uptaking myelin (Ponath et al., 2017).

Upon injury, the endogenous self-repair system in the CNS is switched on, among which myelin repair is initiated to restore the axonal function. OPCs migrate to the injury sites and differentiate into mature oligodendrocytes to mediate remyelination. In MS, remyelination broadly occurs at the early stages, but the fate is variable among patients. In some patients, the remyelination is successful (Patrikios et al., 2006) and the number of oligodendrocytes is restored in inactive areas (Lucchinetti et al., 1999). Successful remyelination requires migration, differentiation, maturation, and survival of OPCs. Astrocytes play unique roles in this process by directly interacting with OPCs or producing soluble factors. Here, Talbott et al. showed that OPCs fail to mediate remyelination in demyelinated rats if astrocytes are absent (Talbott et al., 2005). In good agreement, transplanted astrocytes accelerate the speed of remyelination in a demyelination model induced by ethidium bromide (EB) (Franklin et al., 1991). Additionally, demyelination results in axonal transection which extensively exists in MS lesions (Trapp et al., 1998) and astrocytes might be essential for the regrowth (Anderson et al., 2016).

Remyelination is directly mediated by oligodendrocytes and this process strongly relies on astrocytes. Astrocytes support the survival of oligodendrocytes and neurons by releasing multiple soluble factors, such as IL-4, FGF-2, brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), IL-6, and leukemia inhibitory factor (LIF) (Azin et al., 2015; Barres et al., 1993). IL-4 activates peroxisome proliferator-activated receptor-γ (PPARγ) and downregulates iNOS to protect the oligodendrocytes from NO-induced death (Paintlia et al., 2006). IL-6 family cytokines signal through gp130 and activate STAT3 to regulate the survival, proliferation, and differentiation of OPCs (Steelman et al., 2016; Sun et al., 2015). In a murine hepatitis virus-induced demyelination model, CNTF is specifically increased in astrocytes during the remyelination stage, and it might facilitate survival of OPCs and neurons, differentiation and maturation of OPCs, as well as myelin formation (Albrecht et al., 2003; Stankoff et al., 2002). Pre-existing OPCs undergo proliferation under the control of microglia/astrocyte-derived proteins, like fibronectin, FGF-2 (Azin et al., 2015; Voss et al., 2012), Epo (Sugawa et al., 2002), and IL-6 (Filipovic and Zecevic, 2008). For example, in astrocyte-specific fibronectin knockout mice, lower numbers of OPCs were detected in demyelinated lesions (Stoffels et al., 2015). The migration of OPCs to the demyelination areas requires guiding signals from astrocytes, such as endothelin-1 (ET-1) (Gadea et al., 2009), FGF-2 (Clemente et al., 2011), Sema3F (Boyd et al., 2013), and chemokines (Omari et al., 2005). Astrocytes also promote the differentiation of OPCs to mature oligodendrocytes by releasing multiple factors, such as BDNF, Epo, netrin-1, insulin-like growth factor-1 (IGF-1), TIMP-1, and cytokines CXCL12, IL-11, TGF-β. BDNF can bind with the receptor TrkB on both OPCs and oligodendrocytes and regulate the generation of oligodendrocytes as well as myelin thickness (Van't Veer et al., 2009; Wong et al., 2013; Xiao et al., 2010). Immunization of rats with human Epo successfully drives the differentiation of precursors to oligodendrocytes and neurons (Zhang et al., 2005). IGF-1 not only induces the differentiation of OPCs (Wilson et al., 2003), but also increases oligodendrocyte numbers by blocking TNF-induced death and promoting proliferation (Pang et al., 2007). TIMP-1-deficient mice display more severe demyelination without a significant change in autoantigen-specific T cell response and EAE scores (Crocker et al., 2006). CXCL12 favors OPC proliferation, differentiation, and myelin expression (Kremer et al., 2016; Patel et al., 2012). IL-11-positive astrocytes are located at the myelinated border of the lesions and IL-11 protects myelin from phagocytosis and promotes the maturation of OPCs (Maheshwari et al., 2013; Zhang et al., 2006).

In addition to OPCs, neural precursor cells (NPCs) are another source of oligodendrocytes. Myelin sheath generated by NPC-derived oligodendrocytes can reach the normal thickness (Xing et al., 2014). Thus, NPCs have been considered as a target for MS treatment (Xiao et al., 2017). The early migration of substantial numbers of NPCs from the subventricular zone to periventricular lesions and the differentiation proning to oligodendrocytes is observed in EAE mice (Ben-Hur et al., 2003). The process is found to be mediated by CCL2, CXCL12, and hepatocyte growth factor (HGF), all of which are expressed in both astrocytes and microglia in EAE mice (Cohen et al., 2014). Moreover, astrocytes might be a potential backup reservoir for oligodendrocytes (Gabel et al., 2016; Guo et al., 2016). Recently, astrocytes have been shown to be converted by Sox2 to oligodendrocytes in a cuprizone-induced demyelination model (Farhangi et al., 2019), implying that astrocytes might be a potential target for the treatment of demyelination diseases.

### 3.4. Antioxidative response

The oxidative stress contributes to the pathogenesis and development of several CNS diseases, such as MS, Parkinson's disease, and Alzheimer's disease (Singh et al., 2019). Correspondingly, the intrinsic anti-oxidative response is brought into operation to reduce the stress, albeit the response is insufficient to completely counterbalance the abundant amount of oxidative species. Reactive astrocytes are the

dominant cell type in charge of this defense against oxidative stress, as in both active and chronic lesions, astrocytes are found to be the major producers of antioxidative enzymes, including catalase, superoxide dismutase 2 (SOD2), heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), thioredoxin 2 (Trx2), and peroxiredoxins (PRDXs) (Holley et al., 2007; Nijland et al., 2014; van Horssen et al., 2006; van Horssen et al., 2008; Voigt et al., 2017). The transcriptional factor nuclear factor E2-related factor 2 (Nrf2) is the key element that governs the expression of antioxidative molecules (Draheim et al., 2016). Nrf2 is controlled by two factors with opposite effects, i.e., the stabilizer DJ-1 and the repressor Kelch-like ECH-associated protein 1 (Keap1). DJ-1 is highly expressed in astrocytes in MS lesions (van Horssen et al., 2010). It stabilizes Nrf2 by preventing its interaction with Keap1 and facilitates the nuclear translocation of Nrf2 to initiate the antioxidant response element (ARE)-related transcription (Mullett and Hinkle, 2009). Nrf2 can be further induced by dimethyl fumarate (DMF), an approved immunomodulator for MS treatment (Linker et al., 2011). Astrocytic Nrf2 ameliorates damage in mouse models of several neurological diseases, such as MS (Draheim et al., 2016), familial amyotrophic lateral sclerosis (Vargas et al., 2008), and Parkinson's disease (Chen et al., 2009). Another transcription regulator proliferator-activated receptor gamma coactivator-1alpha (PGC-1α) is also highly induced in astrocytes in MS lesions. PGC-1α promotes the expression of mitochondrial antioxidants PRDX3 and Trx2 (Nijland et al., 2014), consequently lowering the production of ROS. Additionally, throughout EAE, astrocytes upregulate metal binding proteins metallothioneins I and II (MT-I/II), which might relieve the oxidative stress by regulating the metal metabolism in neurons and OPCs (Jakovac et al., 2018).

## 4. Astrocytes as a therapeutic target for MS

At present, the existing therapies cannot completely cure MS and innovative therapeutic approaches that can promote regeneration and neuroprotection, such as stem cell transplantation, are under development (Riordan et al., 2018). As an abundant and versatile cell population in the CNS, astrocytes have been considered for the treatment of CNS diseases. In a rat model of Parkinson's disease, transplantation of modified astrocytes successfully confers neuronal protection, regeneration, and recovery (Proschel et al., 2014).

So far, 16 drugs have been approved by the Food and Drug Administration (FDA) for the treatment of MS. Most of the drugs suppress the immune responses by either clearing peripheral lymphocytes or enhancing Th2 response. Although none of these drugs specifically targets astrocytes, their influence on astrocytes has been explored in EAE or in vitro. The pro-inflammatory activation of astrocytes, including activation of the NF-κB signaling, is inhibited by fingolimod (Rothhammer et al., 2017), DMF (Kalinin et al., 2013), and laquinimod (Kramann et al., 2016). Fingolimod is an analog of sphingosine-1-phosphate (S1P) which specifically targets sphingosine-1-phosphate receptors (S1PRs). It affects astrocytes in many ways, such as reducing the expression of pro-inflammatory cytokines and enhancing neurotrophic factors (Hoffmann et al., 2015; Rothhammer et al., 2017). Plenty of type I IFN-induced genes are increased in astrocytes in both EAE and MS (Rothhammer et al., 2016). Therapeutically applied IFN-β induces the transcription of SOCS-1 and SOCS-3 (Qin et al., 2008), which inhibits the hyperactivation of astrocytes. DMF is an antioxidant drug and can significantly activate the transcriptional factor Nrf2 in astrocytes (Lin et al., 2011). Glatiramer acetate (GA) restores the attachment of perivascular astrocytes on the blood vessels (Eilam et al., 2018) and reduces the release of CCL5 from astrocytes (Li et al., 2001).

Rothhammer et al. has shown that metabolites of dietary tryptophan mediated by gut microbiota inhibit EAE by restricting astrocyte activity (Rothhammer et al., 2018; Rothhammer et al., 2016). This finding raises new possibilities for targeting astrocytes by manipulating the gut-brain axis. Drugs targeting the gut flora do not have to pass through the BBB and are more patient-friendly. In the future, compounds that specifically regulate astrocyte phenotypes by enhancing neuroprotective functions and/or suppressing pro-inflammatory properties might become effective drugs towards MS. Recently, environmental factors such as the herbicide linuron induce pathogenic activation of astrocytes (Wheeler et al., 2019), implying that elimination of astrocyte-manipulating environmental factors might be favorable for MS treatment.

## 5. Conclusion and perspectives

Depending on the location, stimuli, and microenvironment, astrocytes are highly heterogeneous (Cunningham et al., 2018), which might account for their complex functions in CNS autoimmune diseases. However, the mechanism of astrocyte heterogeneity in MS still need to be explored. It is intriguing to decipher why astrocytes exert both protective and detrimental functions in the same disease. Recently, two distinct phenotypes of astrocytes, termed A1 and A2, with completely opposite functions have been identified (Haindl et al., 2019; Liddelow et al., 2017; Zamanian et al., 2012). A1 astrocytes, which exist dominantly in acute lesions, lose neuroprotective abilities and promote the death of oligodendrocytes and neurons. In sharp contrast, A2 astrocytes, which are found in remyelinating lesions, facilitate neuronal survival and tissue repair. Various mixed A1/A2 phenotypes may occur depending on the stimuli and environment in which astrocytes find themselves. It is possible that at the early stage of an autoimmune attack, the suddenly appeared pro-inflammatory cytokines including TNF switch on the detrimental activity of astrocytes. In the remitting stage, the reduced inflammation and locally increased anti-inflammatory molecules induce the protective properties of astrocytes, which participate in the positive feedback loop potentiating recovery. Alternatively, it is also possible that astrocytes are adapted to the neuroinflammation from the disease onset and try to counteract it by resolving inflammation and promoting damage repair, thereby initiating disease recovery. The exact mechanism warrants further investigations and a fate reporter mouse that allows the track of individual astrocyte history would be helpful in answering these questions. Considering the critical and multifaceted roles of astrocytes in EAE and MS, selectively targeting astrocytes, for example, inhibition of A1 astrocytes or induction of A2 astrocytes, might be a promising therapeutic strategy for this CNS autoimmune disease.

## Author contributions

WY and XW conceived the concept and analyzed the data, WY, DS and XW wrote the manuscript.

## Declaration of Competing Interest

We declare that we do not have conflicting interests.

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