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Astrocyte crosstalk in CNS inflammation

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Abstract

Astrocytes control multiple processes in the nervous system in health and disease. It is now clear that specific astrocyte subsets or activation states are associated with specific genomic programs and functions. The advent of novel genomic technologies has enabled rapid progress in the characterization of astrocyte heterogeneity and its control by astrocyte interactions with other cells in the central nervous system (CNS). In this review, we provide an overview of the multifaceted roles of astrocytes in the context of CNS inflammation, highlighting recent discoveries on astrocyte subsets and their regulation. We explore mechanisms of crosstalk between astrocytes and other cells in the CNS in the context of neuroinflammation and neurodegeneration, and discuss how these interactions shape pathological outcomes.

Keywords

astrocyte; neuroinflammation; glial cells; multiple sclerosis; cell interactions; trained immunity

Introduction

Astrocytes are abundant central nervous system (CNS) glial cells, which have emerged as key players in health and disease. Developmentally, astrocytes arise from neural progenitor cells (NPCs) within the subventricular zone (SVZ) and populate the entire brain by migrating along radial glia processes (Ge et al., 2012; Molofsky and Deneen, 2015). Once astrocytes reach their final destination, axis patterning cues guide the maturation of astrocytes into regionally defined subgroups with a high degree of functional specialization, laying the foundation for their multifaceted roles in health and disease (Deneen et al., 2006; Ge et al., 2012; Hochstim et al., 2008; Molofsky and Deneen, 2015; Molofsky et al., 2014; Tsai et al., 2012). Astrocytes are key constituents of the glia limitans, and thus actively contribute to the formation and maintenance of the blood brain barrier (BBB), which separates the peripheral blood circulation from the highly controlled CNS microenvironment

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(Abbott et al., 2006; Sofroniew, 2015a). Furthermore, astrocytes secrete neurotrophic factors to regulate synaptogenesis, neuronal differentiation, and neuronal survival (Allen et al., 2012b; Christopherson et al., 2005; Chung et al., 2015; Molofsky et al., 2014; Wheeler and Quintana, 2019). Once neuronal synapses are established, astrocytes actively modulate synaptic transmission through the release and clearance of neurotransmitters, and the regulation of extracellular ion concentration (Haim and Rowitch, 2017; Santello and Volterra, 2009; Walz, 2000).

Increased resolution into complex cellular networks enabled by new methodologies such as single-cell RNA-sequencing (scRNA-seq), spatial transcriptomics, and cell-specific CRISPR-based perturbation studies suggests that astrocytes actively contribute to the pathogenesis of multiple neurological disorders. Indeed, astrocytes respond to inflammatory signals and can themselves promote inflammation, which makes them important players in neurologic diseases like multiple sclerosis (MS), Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD) and amyotrophic lateral sclerosis (ALS) (Di Giorgio et al., 2007; Diaz-Castro et al., 2019; Gu et al., 2010; Habib et al., 2020; Molofsky and Deneen, 2015; Solano et al., 2008; Tong et al., 2014; Wheeler et al., 2020a; Wheeler and Quintana, 2019). Thus, it is not surprising that the communication between astrocytes and CNS-resident or CNS-infiltrating cells plays a central role in tissue physiology and pathology (Anderson et al., 2016; Anderson et al., 2018; Chao et al., 2019; Faulkner et al., 2004; Liddelow et al., 2017; Lin et al., 2017; Nagai et al., 2019; Rothhammer et al., 2016; Wheeler et al., 2020b; Wheeler et al., 2019). However, the mechanisms involved are not completely understood. In this review, we explore the communication between reactive astrocytes and other cells in the CNS, and discuss how these bidirectional signaling events regulate CNS inflammation and pathological outcomes.

Astrocytes in CNS Inflammation

It is now clear that astrocyte reactivity is a heterogeneous process resulting in a spectrum of molecular, cellular, and functional changes which have provided the basis for the study of astrocyte heterogeneity in health and disease (Anderson et al., 2014; Ben Haim and Rowitch, 2017; Khakh and Deneen, 2019). Although the outcome and individual aspects of astrogliosis might differ, scientists have traditionally viewed the increased expression of glial fibrillary acidic protein (GFAP) as a marker of astrocyte activation and a hallmark of multiple CNS pathologies (Sofroniew, 2009). Interestingly, GFAP was first isolated from demyelinated MS plaques, providing one of the first molecular links between astrocytes and MS (Eng and Vanderhaegen, 1970). Over 50 years later, the repertoire of disease-associated astrocyte markers has grown. Indeed, advancements in genomics and spatial transcriptomics have fueled the identification of novel pathways that control astrocyte function in health and neuroinflammation (Bayraktar et al., 2020; Liddelow and Barres, 2017; Saunders et al., 2018; Wheeler et al., 2020b; Zeisel et al., 2018; Zeisel et al., 2015). Based on these studies, it is now clear that different astrocyte subpopulations either promote, or limit disease pathogenesis in a highly context-dependent manner (Bayraktar et al., 2020; Liddelow and Barres, 2017; Liddelow et al., 2017; Lin et al., 2017; Molofsky et al., 2014; Rothhammer et al., 2016; Wheeler et al., 2020b; Wheeler and Quintana, 2019).

CNS inflammation in MS is associated with BBB breakdown and the recruitment of peripheral immune cells. In this context, astrocytes sense and respond to pro-inflammatory cytokines secreted by CNS-resident and CNS-recruited peripheral immune cells, thereby modulating the responses of neighboring cells throughout the CNS (Rothhammer and Quintana, 2015; Sofroniew, 2015b). *In vivo* ablation studies in the mouse experimental autoimmune encephalomyelitis (EAE) model of MS suggest that astrocytes limit disease development in early disease stages (Liedtke et al., 1998; Mayo et al., 2014; Toft-Hansen et al., 2011; Voskuhl et al., 2009). In contrast, selective ablation of reactive astrocytes during the chronic phase of EAE ameliorated disease, decreasing microglial activation and monocyte infiltration (Mayo et al., 2014).

Astrocyte signaling pathways seem to converge on common downstream transcriptional regulators during inflammation. For example, nuclear translocation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) heterodimer is a central step in astrocyte activation and contributes to the progression of EAE and other CNS pathologies (Blank and Prinz, 2014; Brambilla et al., 2005; Brambilla et al., 2012; Brambilla et al., 2014; Brambilla et al., 2009; Loo et al., 2006; Rothhammer and Quintana, 2019). Selective blockade of astrocyte NF-κB signaling in models of CNS inflammation/injury including EAE (Brambilla et al., 2014; Brambilla et al., 2009; Loo et al., 2006; Wang et al., 2013a), spinal cord injury (SCI) (Brambilla et al., 2005) and optic neuritis (Brambilla et al., 2012) improves clinical outcomes and is associated with decreased levels of pro-inflammatory cytokines and oxidative stress, pointing to a central role for NF-κB in the response of astrocytes to inflammatory stimuli and other insults. The nuclear translocation of NF-κB is regulated by multiple pathways that can broadly be divided into drivers and suppressors of NF-κB activation.

Nuclear translocation of NF-κB in astrocytes is triggered by pro-inflammatory stimuli such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-17 (Qian et al., 2007), reactive oxygen species (ROS) (Chandel et al., 2000), phagocytosed myelin (Ponath et al., 2017), Toll-like receptor (TLR) engagement (Kawai and Akira, 2007) and other factors associated with CNS inflammation (Fig. 1) (Filippi et al., 2018; Reich et al., 2018). In addition, sphingolipids like sphingosine 1-phosphate (S1P) also drive NF-κB activation and play important roles in the regulation MS and EAE (Rosen and Goetzl, 2005; Rothhammer et al., 2017) (Fig. 1). S1P is a biologically active phospholipid generated from ceramide which controls proliferation of several cell types and leukocyte trafficking from lymphoid tissues into circulation (Rivera et al., 2008). Interestingly, astrocytes upregulate the expression of the sphingolipid receptor S1PR1 upon activation, and conditional ablation of S1PR1 in astrocytes results in diminished EAE severity and increased neuronal survival (Choi et al., 2011). Modulation of S1PR1 by the FDA-approved agonist fingolimod suppresses NF-κB translocation in astrocytes, reducing the production of IL-6, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokine (C-C motif) ligand 2 (CCL2) and nitric oxide (NO) levels (Rothhammer et al., 2017).

Lactosylceramide (LacCer), another ceramide-derived sphingolipid, has also been implicated in the regulation of astrocyte responses during CNS inflammation (Mayo et al., 2014). LacCer synthesis is catalyzed by β−1,4-galactosyltransferase 6 (B4GALT6), an

enzyme whose expression is controlled by NF-κB (Chatterjee et al., 2008), and which is upregulated in astrocytes during the progressive phase of EAE in non-obese diabetic mice (Mayo et al., 2014) (Fig. 1). LacCer produced by activated astrocytes enhances IRF-1 and NF-κB recruitment to the promoter regions of *Ccl2, Csf2* and *Nos2,* which subsequently induces cytokine production, microglial activation, and pro-inflammatory monocyte recruitment. Selective inactivation of B4GALT6 in astrocytes suppressed this effect and reduced the infiltration of pro-inflammatory monocytes into the CNS (Mayo et al., 2014), collectively highlighting the relevance of astrocytic sphingolipid signaling in the context of CNS inflammation.

Based on the potential deleterious consequences of its dysregulated activation, it is not surprising that multiple mechanisms limit NF-κB activation in astrocytes. One of these mechanisms involves the ligand- activated transcription factor aryl hydrocarbon receptor (AHR), whose activity is modulated by small molecules provided, for example, by cellular and commensal flora metabolism (Gutiérrez-Vázquez and Quintana, 2018; Wheeler et al., 2017) (Fig. 1). Indeed, the metabolism of dietary tryptophan by the intestinal microbiota is an important physiologic source of AHR agonists (Rothhammer and Quintana, 2019). Following activation by its agonists, AHR can limit NF-κB signaling through several mechanisms including those mediated by the suppressor of cytokine signaling 2 (SOCS2) (Rothhammer et al., 2016; Yeste et al., 2016), and also AHR direct dimerization with the NF-κB subunits RelA and RelB (Rothhammer and Quintana, 2019; Salisbury and Sulentic, 2015; Vogel et al., 2014; Vogel et al., 2007). Accordingly, dietary metabolites derived from tryptophan suppress NF-κB signaling in astrocytes and limit CNS inflammation in an AHR-dependent manner (Rothhammer et al., 2016). Specific inactivation of *Ahr* in astrocytes worsens EAE and increases the expression of pro-inflammatory cytokines (IL-6, IL-12, IL-23, GM-CSF, NO), chemokines (CCL2, CCL20, CXCL10) and other molecules associated with astrocyte reactivity (vimentin, GFAP).

Interestingly, some gut commensal bacteria known to produce AHR agonists are ampicillin-sensitive (Zelante et al., 2013); their elimination by ampicillin administration at late stages of EAE worsens disease outcome. This disease worsening and the concomitant increased expression of pro-inflammatory genes in astrocytes is reversed by the administration of indoxyl-3-sulfate (I3S), an AHR agonist whose levels in circulation are controlled by the gut flora (Rothhammer et al., 2016), overall highlighting how AHR participates in the control of NF-kB activation and CNS inflammation by the gut-CNS axis.

Astrocyte Interactions with Microglia during Neuroinflammation

Astrocytes and other glial cells, including microglia and oligodendrocytes, form and maintain a highly controlled microenvironment essential for efficient neuron function within the CNS (Allen and Lyons, 2018). While glial cells were initially thought to merely provide trophic support for neurons, it is now clear that a closely intertwined neuron-glia network is a key prerequisite for adequate CNS function (Chung et al., 2015; Fields and Stevens-Graham, 2002; Keren-Shaul et al., 2017; Liddelow and Barres, 2017; Wallace and Raff, 1999; Wheeler et al., 2020b).

Astrocytes, microglia, and their interactions control CNS physiology in health and disease (Colombo and Farina, 2016; Glass and Saijo, 2010; Goldmann and Prinz, 2013; Keren-Shaul et al., 2017; Liddelow and Barres, 2017; Prinz et al., 2019; Rothhammer et al., 2018; Rothhammer and Quintana, 2019; Sofroniew, 2009; Vainchtein et al., 2018; Wheeler et al., 2020b). The molecular tête-à-tête between astrocytes and microglia begins early during their colonization of the CNS parenchyma and plays an essential role in CNS health and neuronal transmission (Pfrieger and Barres, 1997). Bidirectional communication between astrocytes and microglia modulates CNS inflammation through the secretion of multiple cytokines and inflammatory mediators. For example, Liddelow and colleagues (2017) reported that LPS-activated microglia induce a neurotoxic phenotype in reactive astrocytes. Specifically, the authors found that microglial secretion of IL-1α, TNF-α, and complement component 1q (C1q) induces a transcriptional response in astrocytes characterized by the production of an as-yet unidentified neurotoxic factor, decreased phagocytic activity, and the reduced expression of neurotrophic factors (Fig. 2A). Based on the expression of complement component 3 (C3), a putative marker of these neurotoxic astrocytes, the authors detected this neurotoxic astrocyte subset in several neurodegenerative disorders like HD, AD, and MS, suggesting that common mechanisms mediate microglia- astrocyte crosstalk in these diseases.

Astrocyte-microglia communication likely involves multiple mechanisms. One recent study identified positive and negative microglial regulators of astrocyte pathogenic responses. Rothhammer et al (2018) reported that AHR signaling in microglia regulates the expression of pro-inflammatory genes *(Ccl2, Illb, Nos2)* in astrocytes by modulating the microglial expression of vascular endothelial growth factor (VEGF)-B and transforming growth factor (TGF)-α (Fig. 2A). Microglial VEGF-B boosts NF-κB translocation in astrocytes via FLT-1 signaling to drive their pathogenic activities during EAE, while TGF-a acts via the ErbB1 receptor in astrocytes to limit EAE progression and induce the production of neuroprotective factors (White et al., 2008). Interestingly, the production of these factors in microglia is regulated by the intestinal flora via metabolites that cross the BBB and control microglial transcriptional programs (2016).

Other mechanisms by which microglia actively control astrocyte functions in neuroinflammation include stromal cell-derived factor (SDF)-1a signaling through C-X-C chemokine receptor type 4 (CXCR4), reported to drive glutamate release by astrocytes. Bezzi and colleagues (2001) showed that SDF1α-CXCR4 signaling in the presence of TNF-α leads to increased intracellular Ca^{2+} levels and astrocyte glutamate release. Microglial TNF-α production promotes astrocyte glutamate release, which boosts neuron excitotoxicity (Fig. 2B). In summary, these findings illustrate how microglial factors modulate astrocyte responses, and consequently CNS pathology.

The interactions mentioned above highlight the importance of microglia to astrocyte communication in the regulation of CNS inflammation and neurodegeneration. Indeed, is important to consider the reciprocal regulation of microglia by astrocytes. GM-CSF is a known regulator of microglial activation, participating in numerous pro-inflammatory processes essential for EAE development (Hamilton, 2008; McQualter et al., 2001; Wheeler et al., 2020b). Interestingly, GM-CSF is produced by astrocytes as determined by GM-CSF

fate-mapping and other studies (Komuczki et al., 2019; Wheeler et al., 2019). Along these lines, Mayo et al. demonstrated that B4GALT6/LacCer-dependent signaling in reactive astrocytes modulates transcriptional programs in microglia and CNS-infiltrating monocytes via the production of GM-CSF (Mayo et al., 2014) (Fig. 2A).

Similar observations have been made for IL-6, a potent mediator of CNS inflammation with important roles in EAE development (Atreya et al., 2000; Gruol and Nelson, 1997; Heink et al., 2017; Samoilova et al., 1998). So far, only a few studies have examined the direct role of astrocyte-derived IL-6 on neuroinflammation, but recent data by Sanchis and colleagues (2020) demonstrates that conditional ablation of IL-6 in astrocytes ameliorates EAE in a sex-dependent manner. This effect may partially be mediated by the reduced activation of microglia, as global IL-6 depletion studies demonstrated reduced expression of MHC-II and pro-inflammatory genes (Garner et al., 2018; Savarin et al., 2015). The notion that astrocytes promote microglia pro-inflammatory functions through the secretion of IL-6, GM-CSF and other signaling factors is further supported by a recent study that investigated the contribution of environmental factors to the pathogenic activities of astrocytes during neuroinflammation (Wheeler et al., 2019). This study identified a novel signaling pathway driven by sigma receptor 1 (SigmaR1) and inositol-requiring enzyme-1α (IRE1α), leading to the activation of the transcription factor X-box binding protein 1 (XBP1) (Fig. 1), which enhances astrocyte-driven CNS inflammation and controls monocyte and microglia responses during EAE. CRISPR/Cas9-based inactivation of *Sigmar1, Ern1* (encoding IRE1α), or *Xbp1* in astrocytes, decreased pro-inflammatory gene expression in microglia and monocytes, suggesting that SigmaR1-IRE1α-XBP1 signaling modulates astrocyte-microglia crosstalk (Wheeler et al., 2019). The activation of the unfolded protein response in astrocytes also contributes to prion-induced neurodegeneration, suggesting that therapeutic targeting of this pathway may be broadly applicable to multiple neurologic diseases (Smith et al., 2020).

The complexity of the bidirectional communication between microglia and astrocytes during neuroinflammation was further highlighted by a study investigating the effects of IL-10/TGF-β signaling in CNS-resident cells during inflammation (Norden et al., 2014). In the context of EAE, astrocytes produce TGF-β in response to microglia-derived IL-10, which acts on microglia to limit pro-inflammatory gene expression, while it upregulates the expression of anti-inflammatory genes (Fig. 2A). Collectively, these data suggest that astrocytes modulate microglial transcriptional states as part of a bidirectional dialogue that coordinates the responses of CNS-resident cells. Similar mechanisms of astrocyte-microglia crosstalk participate in CNS development and neural circuit formation, highlighting the relevance of glial communication during development and under healthy conditions. For example, astrocyte-derived IL-33 has been proposed to function as a rheostat, modulating microglial synapse engulfment through mechanisms that control NF-κB signaling and immune functions *(Tnf, Cxcl2, Cxcl10)* (Nguyen et al., 2020; Vainchtein et al., 2018).

Astrocyte Interactions with Oligodendrocytes during Neuroinflammation

Oligodendrocytes had classically been viewed as immunologically inert—bystanders of pathogenic glial and immune cell responses (Zeis et al., 2016). However, this idea has been

recently challenged by several studies which demonstrate that oligodendrocytes play an active role in CNS immunomodulation (Falcão et al., 2018; Gibson et al., 2019; Huynh et al., 2014; Jakel et al., 2019; Moyon et al., 2015; Peferoen et al., 2014; Zeis et al., 2016; Zeis and Schaeren-Wiemers, 2008). Bidirectional communication between astrocytes and oligodendrocytes plays a vital role in this process, as oligodendrocytes express a wide array of receptors responsive to inflammatory stimuli secreted by astrocytes (Moyon et al., 2015; Omari et al., 2005; Zeis and Schaeren-Wiemers, 2008) and *vice versa* (Moyon et al., 2015; Ramesh et al., 2012; Tzartos et al., 2008). The exact mechanisms underlying the interrelationship between astrocytes and oligodendrocytes remain largely elusive, but accumulating evidence derived from *in vitro* and *in vivo* models of neuroinflammation suggests that their functions are closely intertwined. For instance, it has been shown that activated astrocytes promote apoptosis of oligodendrocytes via TNF (Gomez-Rivera et al., 2017; Kim et al., 2011; Valentin-Torres et al., 2018), Fas ligand (FasL) (Li et al., 2002) and the secretion of glutamate (Bezzi et al., 2001), leading to reduced remyelination, myelin clearance and subsequent neuronal death (Butts et al., 2008) (Fig. 2B). This process has been postulated to amplify, or even initiate CNS autoimmunity (Traka et al., 2016), although inconsistent results call for the reevaluation of this “inside-out” hypothesis of the origin of CNS inflammation (Locatelli et al., 2012). Conversely, astrocytes can also promote neuroprotective oligodendrocyte functions through the recruitment of oligodendrocyte progenitor cells (OPCs) to sites of inflammation via the secretion of CXCL1, IL-8 and CCL-2 (Moyon et al., 2015; Omari et al., 2005) (Fig. 2B). Together with the production of ciliary neurotrophic factor (CNTF), these astrocyte activities promote the differentiation of OPCs into mature myelinating cells, which increases remyelination in areas of CNS inflammation and, consequently, help restore nerve conduction (Domingues et al., 2016).

These seemingly opposing outcomes of astrocyte-oligodendrocyte interactions highlight the need for studies focused on the identification of the specific astrocyte and oligodendrocyte subsets that participate in these interactions. Indeed, it was recently shown that reactive astrocytes contribute to oligodendrocyte cell death in a microglia-dependent manner in a mouse model of chemotherapy (Gibson et al., 2019). These data, coupled with new tools that enable the dissection of oligodendrocyte networks (Mount et al., 2019), promise to lend new insight into the interactions between astrocytes and oligodendrocytes. Other studies suggest that oligodendrocytes contribute to CNS inflammation through additional mechanisms beyond myelination. For example, Falcão and colleagues (2018) reported that oligodendrocytes participate in phagocytosis, antigen presentation, and the activation of memory and effector CD4 T cells. Oligodendrocytes also secrete the pro-inflammatory cytokines IL-1β, CCL-2, IL-17 and IL-6 (Moyon et al., 2015; Ramesh et al., 2012; Tzartos et al., 2008), which induce NF-κB signaling and pro-inflammatory functions in astrocytes (Fig. 2B). In addition, oligodendrocytes reportedly contribute to CNS inflammation by disrupting BBB integrity (Niu et al., 2019), at least partially through the competition of oligodendrocytes with astrocyte endfeet for cerebral vasculature, which subsequently leads to the downregulation of tight-junction integrity (Niu et al., 2019). Finally, single nuclei RNA-sequencing (snRNA-seq) studies of the white matter of MS patients suggest these pathogenic functions might be associated to distinctive oligodendrocyte sub-populations (Jakel et al., 2019). These findings highlight the importance of bi-directional communication

between specific astrocyte and oligodendrocyte populations for the pathogenesis of neurological disorders and set the stage for future investigations of their interactions.

Astrocyte Interactions with Neurons during Neuroinflammation

Astrocytes provide critical trophic support for neurons and play essential roles in health and development (Allen et al., 2012a; Allen and Barres, 2009; Allen and Eroglu, 2017; Christopherson et al., 2005; Chung et al., 2015). While initially considered as ‘brain glue’, providing a structural scaffold necessary for neuronal function, it is now clear that astrocyte-neuron interactions reach far beyond the simplistic idea of structural aid (Allen and Barres, 2009; Liddelow and Barres, 2017). Indeed, astrocyte-neuron interactions contribute to the pathogenesis of multiple neurologic diseases, and the neurotoxic capabilities of reactive astrocytes have been widely discussed (Anderson et al., 2014; Liddelow and Barres, 2017; Wheeler et al., 2020b; Zamanian et al., 2012), although a *bona fide* astrocytic neurotoxic factor remains to be discovered.

In this context, multiple studies have shown that the activation of NF-κB signaling in astrocytes during CNS inflammation triggers the production of NO (Locatelli et al., 2018; Rothhammer and Quintana, 2015; Wheeler et al., 2019), which shows detrimental effects on neurons when in excess (Calabrese et al., 2007). Indeed, a study by Colombo et al. (2012) presents an interesting conundrum of neurotrophin-induced NO neurotoxicity in astrocytes. While BDNF and NO foster neuronal survival under healthy conditions, elevated BDNF levels and the upregulation of its receptor, tropomyosin-related kinase B (TrkB) on activated astrocytes result in excessive NO production *in vitro* and, consequently, NO-driven neurotoxicity (Figs. 1,2B) (Colombo et al., 2012). Accordingly, the astrocyte-specific inactivation of TrkB ameliorates EAE and decreases neurodegeneration. In addition to NO-driven neurotoxicity, reactive astrocytes can also promote neuronal death through deficits in the control of neurotransmitter uptake and release. As described above, this effect is partially regulated by microglial CXCR4-dependent release of excessive amounts of glutamate during neuroinflammation, ultimately resulting in excitotoxicity and neuronal loss (Bezzi et al., 2001) (Fig. 2B). In a model of HD, Tong and colleagues demonstrated that accumulation of mutant huntingtin (mHTT) in striatal astrocytes was associated with the reduced expression of the inward rectifying K^+ channel Kir4.1, resulting in increased extracellular K+ levels and consequently, neuronal excitotoxicity (Tong et al., 2014). Other roles of astrocytes in excitotoxicity include the reduced expression of the glutamate uptake transporters GLAST and GLT-1 in models of neuroinflammation (Pitt et al., 2000), AD (Matos et al., 2008) and ALS (Pardo et al., 2006), as well as reduced GABAergic neurotransmission in HD (Yu et al., 2018), highlighting the role of altered glial neurotransmitter recycling as a common mechanism of neurodegeneration in multiple diseases.

Besides the excessive secretion of cytotoxic species and the dysregulation of neurotransmitter uptake and release, alterations in the metabolic crosstalk between astrocytes and neurons also contribute to neurodegeneration in MS and other diseases. Chao et al (Chao et al., 2019) demonstrated that LacCer-induced activation of cytosolic phospholipase A2 (cPLA2) and its interaction with the mitochondrial antiviral signaling protein (MAVS) alters astrocyte metabolism, impairing the metabolic support of neurons via

the lactate shuttle (Suzuki et al., 2011). Specifically, the LacCer-induced binding of cPLA2 to MAVS disrupts the complex of MAVS with hexokinase-2 (HK2), decreasing glycolysis and lactate production (Fig. 1). Under healthy conditions, lactate provided by astrocytes supports the metabolic needs of neurons (Magistretti and Allaman, 2018). However, the decreased metabolic support of neurons by astrocytes amplifies neurodegeneration. Similar observations of dysfunctional metabolic coupling between astrocytes and neurons have been made in the context of AD (Merlini et al., 2011), PD (Öhman and Forsgren, 2015), HD (Diaz-Castro et al., 2019; Polyzos et al., 2019), and ALS (Ferraiuolo et al., 2011). Although much of these data are derived from *in vitro* work, these findings strongly suggest that astrocytes can promote neuronal death by multiple mechanisms including excitotoxicity and dysfunctional metabolism. This astrocyte-driven neurotoxicity could synergize with deficits in the regulation of behavior by astrocytes in specific neural circuits, which may also contribute to and amplify neurologic disability (Adamsky et al., 2018; Nagai et al., 2019; Yu et al., 2018). New approaches will be needed to validate our current understanding of astrocyte-induced neurotoxicity *in vivo* and examine how therapeutic strategies could be used to reprogram reactive astrocytes in a neuroprotective state.

Astrocyte Interactions with Endothelial Cells during Neuroinflammation

Astrocyte foot processes form the glia limitans, which together with capillary endothelial cells, pericytes, and the basal lamina constitute the BBB that separates the CNS from the peripheral blood circulation (Abbott et al., 2006; Chow et al., 2020; Obermeier et al., 2013; Sofroniew, 2015b). Under healthy conditions, the BBB regulates the influx of hydrophilic substances, protects the brain from circulating pathogens, and contributes to the partial ‘immune privilege’ of the CNS (Abbott et al., 2006; Kipnis, 2016; Louveau et al., 2015b; Obermeier et al., 2013; Sofroniew, 2015b). Astrocytes and endothelial cells act as gatekeepers of the CNS and their crosstalk is essential to restrict leukocyte trafficking into the parenchyma. In the context of neuroinflammation, bidirectional communication between astrocytes and endothelial cells promotes BBB leakiness and allows for the infiltration of peripheral immune cells. Astrocyte-derived VEGF plays a central role in this process and participates in a signaling cascade that eventually results in increased BBB permeability (Sofroniew, 2015b). Indeed, Argaw and colleagues (2012) demonstrated that VEGF-A production in astrocytes is upregulated in response to IL-1β, a cytokine produced by activated microglia during neuroinflammation (Liddelow et al., 2017; Prinz et al., 2019; Wheeler et al., 2020b). VEGF-A induces the endothelial nitric oxide synthase (eNOS)-dependent downregulation of tight-junction proteins claudin-5 (*Cldn5*) and occludin *(Ocln)* in endothelial cells, which eventually disrupts tight-junctions and BBB integrity. In line with these findings, conditional ablation of *Vegfa* in astrocytes ameliorates EAE, and is characterized by a reduction in leukocyte infiltration, demyelination, and oligodendrocyte loss (Argaw et al., 2012).

Astrocytes also produce factors that boost BBB integrity during inflammatory conditions. For example, astrocytes promote BBB stability via the production of sonic-hedgehog (Shh) (Alvarez et al., 2011), a morphogen that has numerous roles during development and adulthood (Fuccillo et al., 2006; Ihrie et al., 2011). Stimulation of human astrocytes with TNF-α and IFN-γ leads to increased expression of *Shh* and subsequent upregulation of

endothelial cell tight-junctions. Of note, SHH^+ immunoreactive astrocytes are detected around MS demyelinating lesions, and SHH receptor expression is upregulated in endothelial cells (Alvarez et al., 2011). Collectively, these data highlight the importance of the control of the BBB by astrocyte-endothelial cell interactions during CNS inflammation, as well as the need to identify astrocyte subsets with seemingly opposing roles on BBB integrity.

Astrocyte Interactions with Peripheral Immune Cells during Neuroinflammation

The CNS parenchyma is usually considered an ‘immune privileged’ compartment under healthy conditions, which provides limited access to peripheral antibodies and leukocytes (Louveau et al., 2015a; Ransohoff and Engelhardt, 2012). However, astrocytes are amongst the first CNS-resident cells encountered by CNS-infiltrating leukocytes during neuroinflammation. Moreover the anatomical location of astrocyte endfeet enables them to react to soluble factors in the meningeal space (Iliff et al., 2012; Sofroniew, 2015b). As activated immune cells migrate from the periphery into the CNS, bidirectional interactions with astrocytes actively shape the recruitment, diapedesis and extravasation of leukocytes past endothelial barriers into perivascular spaces and the CNS parenchyma. CCL2 and CXCL10 are chemokines secreted by activated astrocytes that control the recruitment of perivascular leukocytes into the CNS (Fig. 2C) (Kim et al., 2014; Mills Ko et al., 2014; Paul et al., 2014). Interestingly, both CCL2 and CXCL10 are controlled by NF-κB (Brambilla et al., 2012; Brambilla et al., 2009), and have been shown to play important roles during CNS inflammation. For example, astrocyte-derived CCL2 is critical for both the onset (Huang et al., 2001) and the progression of EAE (Kim et al., 2014; Moreno et al., 2014), as its deletion is associated with decreased leukocyte infiltration and a transcriptional shift of macrophages towards an anti-inflammatory phenotype. Similar observations have been made for astrocyte-derived CXCL10, as the conditional ablation of CXCL10 results in decreased accumulation of leukocytes in perivascular spaces (Mills Ko et al., 2014). While CCL2 and CXCL10 represent signaling molecules through which astrocytes control the recruitment of monocytes, macrophages and T cells to the CNS (Gerard and Rollins, 2001), astrocyte-derived CXCL12 regulates the recruitment of pathogenic B-cells (Krumbholz et al., 2006).

Astrocytes also control peripheral leukocytes once they have been recruited to the CNS. Following activation, astrocytes upregulate the expression of FasL to induce cell death in infiltrating lymphocytes via caspase signaling (Choi et al., 1999; Wang et al., 2013b). Conditional ablation of FasL expression by astrocytes worsens EAE, further supporting an anti-inflammatory role of astrocyte-induced apoptosis (Wang et al., 2013b). In contrast, Krumbholz and colleagues (2005) defined a mechanism through which astrocyte-derived BAFF supports B-cell survival in inflammatory diseases and primary B cell lymphoma. In support of these findings, BAFF is expressed by human astrocytes and increased BAFF levels are detected in the cerebral spinal fluid of MS patients. These opposing effects of astrocytes on T- and B-cell survival are in agreement with astrocyte targeting studies in early versus late stages of EAE, therefore highlighting the time-dependency (likely associated to the dominance of different activation states during the disease course) of their functions in

disease (Liedtke et al., 1998; Mayo et al., 2014; Toft-Hansen et al., 2011; Voskuhl et al., 2009). While ablation of astrocytes during early stages potentially prevent astrocyte-induced cell death in infiltrating leukocytes and consequently allows for the spread of peripheral immune cells in the CNS, loss of astrocytes during late stages might in turn hinder pathogenic B-cell functions and reduce CNS inflammation.

In addition, astrocytes can sense and respond to various inflammatory cues once leukocytes are engrafted within the CNS parenchyma. For example, T_H1 cell-derived IFN-γ upregulates astrocyte expression of IFN-g receptor 1 (IFNGR1) and MHC-II, allowing them to act as nonprofessional antigen-presenting cells (APCs) (Fontana et al., 1984; Gold et al., 1996; Hashioka et al., 2010; Soos et al., 1998; Sun and Wekerle, 1986; Yang et al., 2012). Furthermore IL-17, the signature cytokine of pathogenic T_H17 cells, and GM-CSF, produced by pathogenic T_H1 and T_H17 cells, activate pro-inflammatory transcriptional programs in astrocytes (Elain et al., 2014; Kang et al., 2010; Wheeler et al., 2020b; Yi et al., 2014) (Fig. 2C). Taken together, these findings highlight the important functions of astrocytes in the potentiation of inflammatory cascades in the CNS. In a positive feedback loop, astrocytes can respond to pro-inflammatory cytokines secreted by infiltrating lymphocytes with the production of chemokines that further attract peripheral immune cells to the CNS, ultimately leading to chronic CNS inflammation and neurodegeneration.

Epigenetic Alterations in Astrocytes during CNS Inflammation

The chronic exposure to inflammatory signals and crosstalk with CNS-resident and non-resident cells alters astrocyte transcriptional programs, inducing “memory” responses stabilized by epigenetic modifications (Saijo et al., 2009; Wheeler et al., 2020b). In the context of inflammation, “memory” is usually associated with the response of T cells and B cells to repetitive encounters with the same antigen. Thus, a first encounter with a stimulus (“priming”) elicits transcriptional modifications, which lead to a different response in terms of quantity and quality, upon later encounter with the same stimulus. Immune memory can manifest as “immune training”, which describes an enhanced and diversified response to re-stimulation; or “immune tolerance,” which refers to a dampened response upon secondary stimulation (Neher and Cunningham, 2019; Nott and Glass, 2018; Wendeln et al., 2018).

Pioneering studies have extended the concept of memory to the innate immune response, to describe “trained” innate immunity associated to extensive epigenetic and metabolic remodeling (Netea et al., 2020). Indeed, it has been recently reported that microglia can also undergo training (Nott and Glass, 2018; Nott et al., 2019; Wendeln et al., 2018). This is an important finding in the context of neurological diseases, as epigenetic alterations may stabilize pathogenic activation states in CNS-resident cells, and might therefore offer novel therapeutic targets. Indeed, multiple reports suggest an important role for epigenetic modifications in the control of glial responses during neurologic disorders (Ayata et al., 2018; Baranzini et al., 2010; Huynh et al., 2014; Koch et al., 2013; Kular et al., 2018; Staszewski and Prinz, 2014; Wendeln et al., 2018).

Most work on trained immunity in glial cells has focused on microglia, as they express a multitude of immune receptors (Ayata et al., 2018; Colonna and Butovsky, 2017; Heneka et

al., 2015; Nott et al., 2019; Prinz et al., 2019; Saijo et al., 2009; Wendeln et al., 2018). In a recent study, Wendeln and colleagues (2018) explored the question of whether microglia are trained in the context of neurologic diseases, and potentially contribute to the progression of AD and stroke. These studies established that peripherally applied pro-inflammatory stimuli drive immune training and tolerance mechanisms in microglia through extensive epigenetic reprogramming, inducing changes in microglial responses that persist for at least six months. Furthermore, these studies established that microglia trained by a single injection of lipopolysaccharide (LPS) exacerbate cerebral β-amyloidosis, while repeated LPS stimulation leads to immune tolerance and reduced Aβ-accumulation. Interestingly, these studies also detected reduced numbers of astrocytes in LPS-primed mice. Indeed, pro-inflammatory stimuli have been shown to induce epigenetic alterations in astrocytes, with long-term consequences for neuroimmune crosstalk (Beurel, 2011; Correa et al., 2011; Suh et al., 2010; Wheeler et al., 2020b). Furthermore, studies on the epigenetic control of astrocytes during differentiation and development support potential roles for epigenetic modifications in the regulation of astrocyte responses during neuroinflammation (Hatada et al., 2008; O'Callaghan et al., 2014; Takizawa et al., 2001); future studies should determine whether *bona fide* astrocyte trained responses contribute to the pathogenesis of neurologic disorders.

Histone Modifications

The epigenetic processes supporting trained immunity can broadly be divided into histone modifications and DNA methylation. Histone methylation and acetylation have been linked to the control of astrocytes in CNS inflammation. In a study investigating the effects of aging on histone methylation in astrocytes following ischemia, Chisholm et al. (2015) found that cerebral artery occlusion resulted in an increase of the H3K4me3 histone methylation mark (transcriptional enhancer), while levels of H3K9me3 (transcriptional repressor) were reduced, therefore suggesting an overall increase in transcriptional activity. Interestingly, pathway analysis detected increased VEGF signaling associated to higher H3K4me3 levels and decreased histone deacetylase (HDAC) expression, supporting a long-term effect of astrocyte-derived VEGF production on endothelial cell function and BBB permeability. HDACs have long been targeted in neurological disorders (Falkenberg and Johnstone, 2014) and multiple reports support a role of HDACs in astrocyte activation and neuroimmune crosstalk (Beurel, 2011; Correa et al., 2011; Saijo et al., 2009; Suh et al., 2010).

In another study, Ayata and colleagues (2018) reported that environmental stimuli drive the epigenetic regulation of region-specific clearance activity in microglia. The authors found that exposure to apoptotic cells induce the expression of KDM6A and KDM6B, histone demethylases that catalyze the removal of the transcriptional repressor H3K27me3 histone methylation marks in microglia, leading to the induction of inflammatory gene expression. Similar mechanisms may operate in astrocytes, as soluble factors derived from microglia boost HDAC activity in astrocytes (Correa et al., 2011). Although the specific signals through which microglia control histone modifications in astrocytes are not yet known, these initial findings suggest long-term effects of astrocyte-microglia crosstalk.

A pioneering study by Saijo and colleagues (2009) defined a microglia-astrocyte trans-repression pathway that negatively regulates pro-inflammatory responses and reduces neurotoxicity in the context of PD. The authors demonstrated that microglia and astrocyte activation induces the recruitment of the nuclear receptor related-1 (Nurr1) transcription factor, the co-repressor complex CoREST and NF-κB to target sites that control pro-inflammatory gene expression. The resulting transcriptional suppression of pro-inflammatory mediator expression in microglia and astrocytes prevented the synergistic amplification of pro-inflammatory responses and neurotoxicity. HDAC1 is a component of the CoREST complex. Thus, a Nurr1-mediated negative feedback loop between astrocytes and microglia might participate in the long-term suppression of pro-inflammatory responses. This hypothesis is in line with the findings of Beurel et al (Beurel, 2011), who reported that repeated stimulation of astrocytes with LPS results in HDAC6-induced histone deacetylation and tolerance characterized by decreased IL-6 production. Collectively, these results suggest that histone modifications induced by the crosstalk with other cell types, trigger long-term changes in astrocyte responses.

DNA Methylation

DNA methylation represses gene expression through the addition of methyl groups that impair interactions with transcriptional regulators (Greenberg and Bourc'his, 2019). DNA methylation is tightly regulated during astrocyte development (Fan et al., 2005; Hatada et al., 2008). Similarly, DNA methylation was recently reported to control astrocyte pro-inflammatory responses (Wheeler et al., 2020b), and has been proposed to contribute to CNS pathology in MS (Huynh et al., 2014). Single-cell RNA sequencing identified a subset of astrocytes expanded in EAE and MS. This astrocyte subset was characterized by decreased activation of NRF2, a transcription factor linked to neuroprotective astrocyte functions (Filippi et al., 2018). Follow up genomic analyses identified MAFG, a basic region and leucine zipper (bZIP)-type transcription factor of the family of small MAF proteins, as a negative regulator of NRF2 signaling in activated astrocytes. MAFG heterodimerizes with NRF2 to induce NRF2-driven gene expression, but MAFG homodimers compete for MAFG/NRF2 responsive elements to suppress NRF2-signaling (Katsuoka and Yamamoto, 2016) (Fig. 3). In addition, MAFG cooperates with the methionine adenosyltransferase IIα (MAT2α), which participates in the synthesis of substrates for DNA methylation and has been shown to cooperate with small MAF proteins to act as a transcriptional repressor (Katoh et al., 2011) (Fig. 3). In line with these findings, increased DNA méthylation was detected in NRF2-responsive elements of this astrocyte subset during EAE. Moreover, MAFG- and MAT2α-dependent CRISPR/Cas9-driven inactivation of *Mat2α* or *Mafg* ameliorated EAE.

Of note, GM-CSF produced by pro-inflammatory T-cells recruited to the CNS drives MAFG/MAT2α signaling in astrocytes, suggesting that the crosstalk between astrocytes and T cells regulates the epigenetic program that stabilizes and controls this astrocyte subset in the context of CNS inflammation (Fig. 3). Taken together, these observations shed new light onto the long-term epigenetic regulation of glial responses and its control by astrocyte-immune cell crosstalk (Ayata et al., 2018; Jakovcevski and Akbarian, 2012; Staszewski and Prinz, 2014). Novel tools, such as spatial transcriptomics (Eng et al., 2019; Moffitt et al.,

2018; Rodriques et al., 2019; Wang et al., 2018), astrocyte-specific optogenetics (Adamsky et al., 2018; Nagai et al., 2019), and neuron-glia circuit mapping in virtual environments (Mu et al., 2019), will deepen our understanding of the epigenetic control of astrocyte responses, while identifying candidate targets for therapeutic intervention.

Concluding remarks

Astrocytes play multiple roles during CNS inflammation. On the one hand, they can restrict the influx of peripheral immune cells into the CNS, while producing neurotrophic factors to promote tissue repair. On the other hand, astrocytes can promote neurodegeneration and inflammation through the recruitment of peripheral inflammatory cells, the activation of CNS-resident microglia and their own intrinsic neurotoxic activities. The proper control of these diverse astrocyte responses requires the precise integration of signaling cues derived from CNS-resident and -recruited cells, highlighting the importance of regional location and cellular environment.

A central question in astrocyte biology has been the extent of astrocyte heterogeneity. The diversity of astrocyte subsets and activation states is now widely appreciated (Anderson et al., 2014; Ben Haim and Rowitch, 2017; Khakh and Deneen, 2019), but many questions still remain outstanding. Future studies should address important questions: (1) How many astrocyte subsets exist? (2) How are they regulated, how plastic are they, and what are their functions? (3) Where are they located? (4) With which cells do they communicate? (5) What are the correlates of these populations in humans? Clues to solving these problems could be gleaned from pioneering fate-mapping and cross-species studies of microglia (Geirsdottir et al., 2019; Ginhoux et al., 2010; Tay et al., 2017).

Novel technologies will also be needed to extensively characterize the astrocytic subsets involved, their cellular interactions, and what defines them in the context of their location in specific CNS microenvironments. For example, high throughput screens for the molecular characterization of astrocytes across brain region and disease states would greatly advance our knowledge of astrocyte heterogeneity. These screens may enable a thorough analysis of the interactions between astrocytes and other cells in the CNS, seeding additional questions: Which molecules are used by astrocytes to communicate with neighboring cells? On what timescale? How plastic are these interactions? Importantly, these analyses may lead to an understanding of how astrocyte interactions with other cell types could be exploited for therapeutic purposes.

In addition, it is important to understand astrocyte networks on a global level. Both functional and structural connectivity-mapping studies are needed to establish how astrocytes interact with neurons, other glial cells, and immune cells in health and disease (Fields, 2013). Analogous approaches have transformed our understanding of neural circuits (Chen et al., 2019; Huang et al., 2020; Kebschull et al., 2016; Oh et al., 2014). In summary, the future of glial biology will likely rest on the integration of multiple high throughput technologies to define the location, plasticity, connectivity, regulation and function of astrocyte subsets across the CNS.

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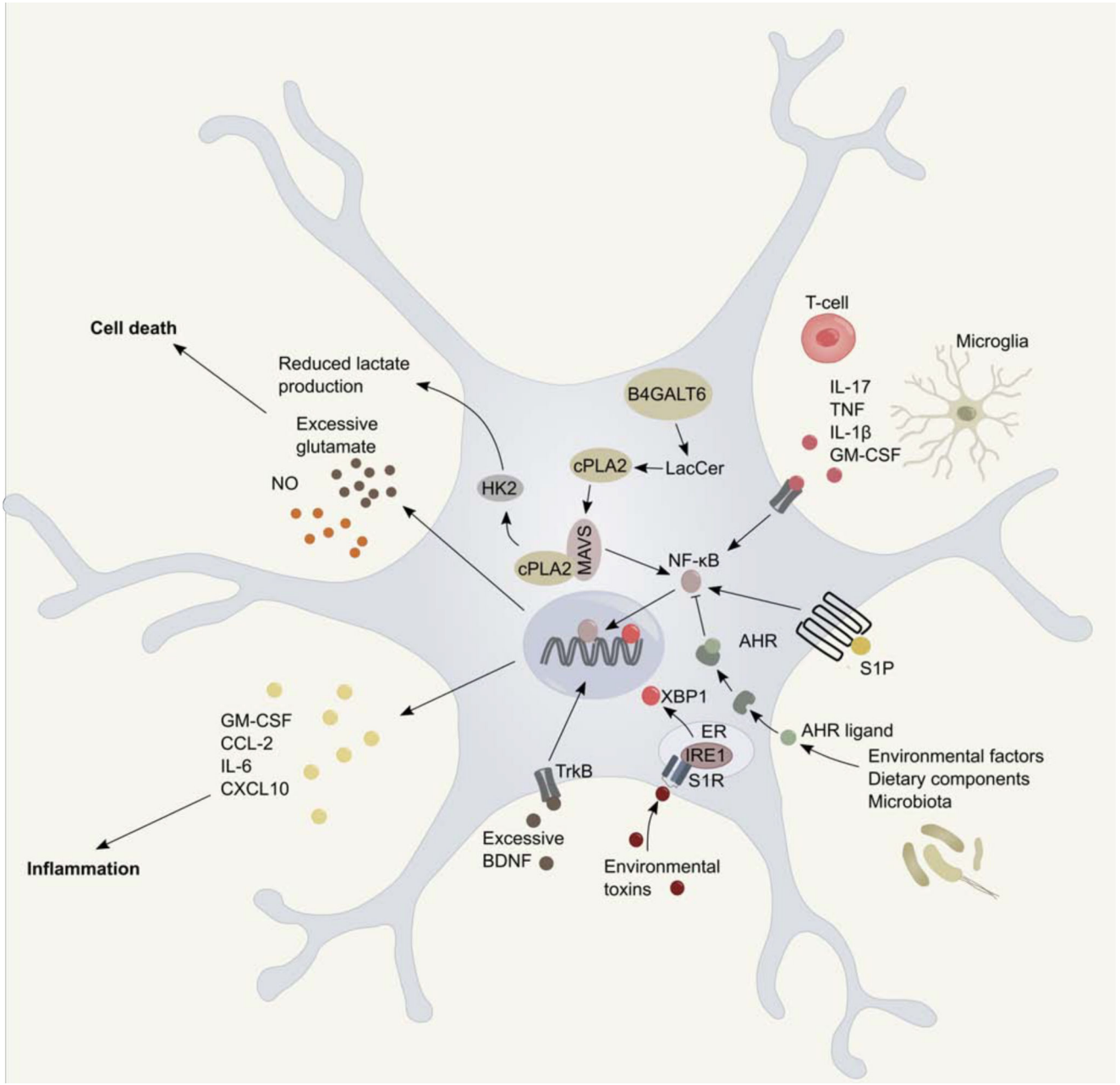

Figure 1. Astrocyte signaling in the context of CNS inflammation.

The transcription factor NF-κB controls multiple aspects of astrocyte pro-inflammatory responses. NF-κB signaling is triggered/boosted by cytokines released by microglia and other cells in the inflamed CNS, and by the sphingolipids S1P and LacCer. AHR activation by dietary components, environmental factors or metabolites derived from the commensal flora limits NF-κB activation. Additional inflammatory pathways are triggered by the binding of environmental toxins to S1R/IRE1α and downstream signaling through XBP1.

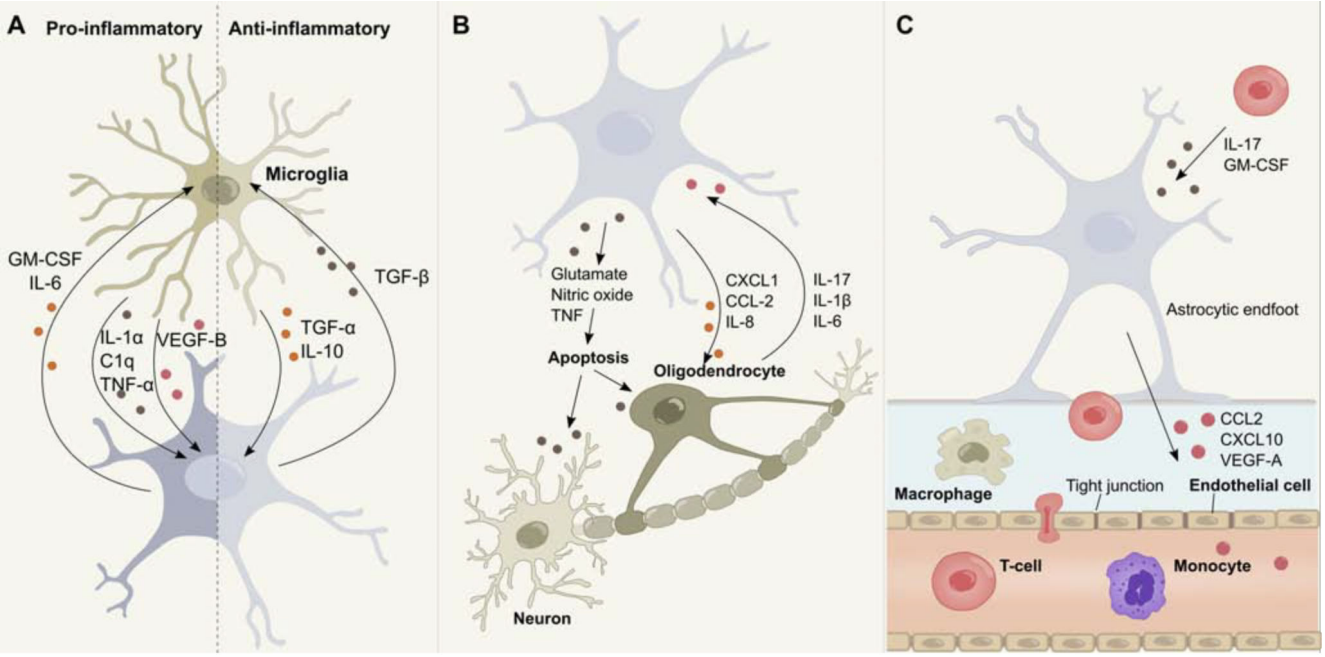

Figure 2. Astrocyte interactions in the context of neuroinflammation.

(A) Bidirectional communication between astrocytes and microglia regulates their responses during CNS inflammation. **(B)** Upon activation, astrocytes release neurotoxic amounts of NO, glutamate or downregulate the uptake of extracellular neurotransmitter, ultimately leading to neuronal and oligodendrocyte death. Astrocytes furthermore control the recruitment of oligodendrocytes through the secretion of multiple cytokines. In addition, astrocytes respond to pro-inflammatory mediators secreted by activated oligodendrocytes. **(C)** Astrocytes control the recruitment of leukocytes into perivascular spaces and the CNS parenchyma through the secretion of multiple molecules. Interactions between activated astrocytes and endothelial cells increase BBB permeability and facilitate leukocyte infiltration, while bidirectional communication between astrocytes and peripheral immune cells potentiates CNS inflammation and contributes to disease progression.

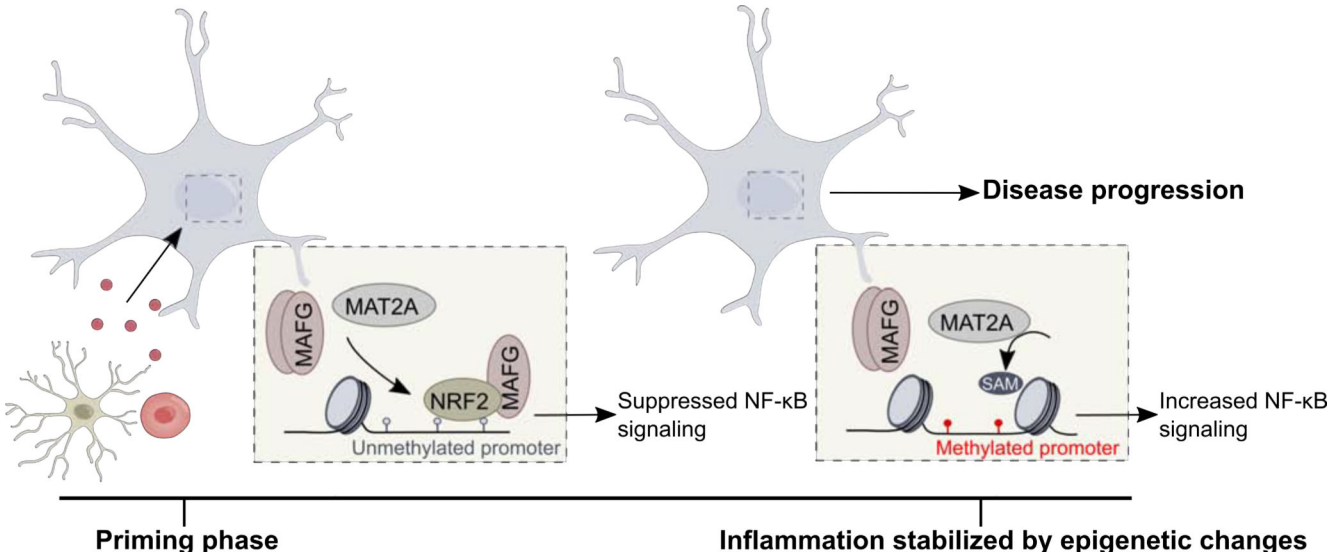

Figure 3. Pro-inflammatory cytokine-induced epigenetic suppression of NRF2 signaling during CNS inflammation.

During initial exposure to inflammatory signals, astrocytes upregulate the formation of MAFG homodimers, which outcompete MAFG/NRF2 heterodimer binding to transcriptional response elements that control NRF2 signaling. In addition, MAT2α cooperates with MAFG and induces DNA methylation marks that restrict chromatin accessibility. Collectively, these epigenetic modifications suppress NRF2-driven inhibition of NF-κB signaling and lead to sustained inflammation.