NEUROIMMUNOLOGY

Neuroinflammation: An astrocyte perspective

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Astrocytes are abundant glial cells in the central nervous system (CNS) that play active roles in health and disease. Recent technologies have uncovered the functional heterogeneity of astrocytes and their extensive interactions with other cell types in the CNS. In this Review, we highlight the intricate interactions between astrocytes, other CNS-resident cells, and CNS-infiltrating cells as well as their potential therapeutic value in the context of inflammation and neurodegeneration.

INTRODUCTION

Astrocytes are the most abundant glial cells in the central nervous system (CNS), where they perform a wide range of homeostatic functions. These functions include, among others, providing support to other CNS-resident cells such as neurons by buffering excess neurotransmitters and regulating synaptic and blood-brain barrier (BBB) function (*1*–*4*). Many of these homeostatic functions are impaired in the context of neurologic disorders. In addition, activation states induced on developmentally defined astrocyte populations (*4*–*10*) contribute to the pathology of multiple sclerosis (MS) (*11*–*21*), Alzheimer's disease (AD) (*21*–*27*), Parkinson's disease (PD) (*21*, *28*–*32*), Huntington's disease (HD) (*21*, *33*–*35*), and other disorders (*36*, *37*). Cell-cell interactions are central modulators of astrocyte homeostatic functions and disease-associated responses. Therefore, a comprehensive understanding of astrocyte communication with CNS-resident and CNS-recruited cells is crucial to define the mechanisms of disease pathogenesis and develop therapeutic interventions for neurologic diseases.

REACTIVE ASTROCYTES IN NEUROINFLAMMATION

Astrocytes react to acute or chronic pathological stimuli by remodeling their morphological, genomic, metabolic, and functional features through a process called "reactive astrogliosis" (*3*, *4*). Although some aspects of reactive astrogliosis are shared across stimuli, the responses induced in astrocytes vary depending on the specific stimulus or disease, time, and CNS location involved, resulting in astrocyte phenotypes with diverse and sometimes opposing roles in diseases (*1*–*4*, *11*, *12*, *38*, *39*).

Technical developments including single-cell RNA sequencing (scRNA-seq) (*15*, *16*, *40*–*42*), spatial transcriptomics (*5*, *15*, *43*), and platforms for the identification of cell-cell interactions (*44*, *45*) have opened new avenues for the study of astrocyte heterogeneity in health and disease, identifying astrocyte populations or activation states on the basis of cell morphology, molecular profile, cellular function, and cell-cell interactions (*46*). Because of the cross-sectional nature of these studies, it is unclear whether many of these astrocyte subsets constitute developmentally defined astrocyte populations (developmentally induced astrocytes) or, instead, represent multiple activation states induced by different stimuli (stimulus-induced astrocytes) (*4*). These uncertainties can only be resolved with comprehensive lineage tracing studies performed during development, homeostasis, and in the context of pathology-linked stimuli. In the meantime, these limitations should be kept in mind when interpreting reports about astrocyte heterogeneity.

During homeostasis, astrocyte subtypes exhibit distinct genomic and functional profiles linked to their location and interactions with neurons and other cells in the CNS (*5*, *40*, *41*, *43*, *47*–*49*). However, in the context of CNS inflammation and neurodegeneration, astrocytes adopt cellular states linked to the activation or repression of specific genomic modules by disease-specific stimuli (*4*, *50*). For instance, a combination of scRNA-seq and proteomics identified astrocytes that express tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) in response to interferon-γ (IFN-γ) produced by natural killer (NK) cells under homeostatic conditions; these astrocytes operate in CNS borders to limit inflammation by inducing T cell apoptosis (*16*). In contrast, scRNA-seq studies identified a pathogenic astrocyte state controlled by MAF basic leucine zipper transcription factor G (MAFG)/methionine adenosyltransferase 2α (MAT2α) and driven by granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by proinflammatory T cells, which promotes CNS pathology in MS and in the murine experimental autoimmune encephalomyelitis (EAE) model (*15*). In PD, astrocyte states linked to neurodegeneration have been identified on the basis of the expression of vimentin and LIM homeobox 2, as well as the up-regulation of CD44 and genes related to the unfolded protein response (*29*, *30*). Similarly, Hasel *et al.* identified two astrocyte reactivity states after lipopolysaccharide (LPS) administration. One of these astrocyte states is characterized by an enrichment of the metalloproteinase inhibitor *Timp1*, suggestive of neuroprotective and antioxidant functions. The other astrocyte state is characterized by the expression of genes linked to interferon signaling, angiogenesis, and antigen presentation (*50*). Together, these findings illustrate the heterogeneity of astrocytes in the context of CNS homeostasis and pathology.

Importantly, more than 97% of astrocyte end feet contact at least one blood vessel (*51*), enabling astrocyte membrane channels, transporters, and receptors to sense and react not only to CNS intrinsic cues but also to molecules in the circulation (*52*). In this context, cytokines, metabolites, and other cellular products, as well as environmental factors, such as environmental chemicals and microbial metabolites, cooperate to modulate astrocyte responses linked to antigen presentation, costimulation, and apoptosis (Table 1). For example, the commensal flora provide small

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Table 1. Modulators of astrocyte responses in CNS inflammation. IL-1β, interleukin-1β; ROS, reactive oxygen species; S1P1, sphingosine 1-phosphate receptor 1; NFAT, nuclear factor of activated T cells; MAVs, mitochondrial antivirals; DAMPs, damage-associated molecular patterns.

Category	Name	Role	References
Cytokine	IL-1β	Induces astrocyte proinflammatory gene expression	(*13*, *15*)
	TNF-α	Induces astrocyte proinflammatory gene expression	(*13*–*15*)
		Induces astrocyte neurotoxic activity	
	IFN-γ	In pathogenic conditions, induces astrocyte pro-inflammatory and neurotoxic gene expression	(*14*, *16*)
		In homeostatic conditions, drives TRAIL expression in astrocytes, inducing T cell apoptosis	
	IL-6	Induces astrocyte proinflammatory gene expression	(*3*, *57*)
	IL-1α + TNF-α + C1q	Induces C3 expression in astrocytes	(*16*, *21*, *57*, *78*)
		Induces astrocyte production of neurotoxic lipids	
		Down-regulates homeostatic gene expression	
	GM-CSF	Induces astrocyte proinflammatory gene expression	(*15*, *16*)
		Suppresses TRAIL expression in astrocytes	
DAMPs	ROS	Boosts NF-κB activation	(*158*)
	Myelin	Activates NF-κB	(*159*)
		Promotes immune cell infiltration	
Metabolic molecule	LacCer	Induces astrocyte proinflammatory gene expression	(*14*, *93*)
		Interferes with astrocyte metabolic support of neurons	
	S1P1	Induces astrocyte proinflammatory gene expression	(*18*, *20*)
		Induces astrocyte neurotoxic activity	
	Nicotinamide adenine dinucleotide metabolism	Induces astrocyte proinflammatory gene expression	(*160*)
Environmental factors	Linuron	Boosts XBP1 and NF-κB proinflammatory transcriptional programs	(*13*)
	Fine particulate matter (PM2.5)	Induces astrogliosis	(*161*)
		Induces astrocyte-driven myeloid cell polarization into proinflammatory phenotypes	
		Induces astrocyte neurotoxic activity	
Intracellular mediators	NF-κB	Activates diverse proinflammatory gene expression	(*13*–*15*) (*158*, *159*)
	IRE1α-XBP1	Activates diverse proinflammatory gene expression	(*13*)
		Promotes EAE development	
	MAFG/MAT2α	Suppresses antioxidant and anti-inflammatory gene expression	(*15*)
	STAT3	Drives production of factors involved in tissue repair	(*3*, *57*) (*25*, *37*, *56*)
		In EAE, induces proinflammatory gene expression	
		In AD, promotes disease pathogenesis	
		In SCI, restricts the spread of inflammatory cells	
	Calcineurin-NFAT	Induces astrocyte proinflammatory gene expression	(*160*)
	cPLA2-MAVs	Activates NF-κB	(*14*)
		Inhibits hexokinase-2–mediated lactate production	

molecules that regulate the activity of the aryl hydrocarbon receptor (AHR) in astrocytes (*53*, *54*), which limits the nuclear factor κB (NF-κB)–driven expression of proinflammatory cytokines and chemokines and, consequently, CNS inflammation (*55*). Conversely, the herbicide linuron boosts the activation of the transcription factors NF-κB and X-box–binding protein 1 (XBP1) in astrocytes through a sigma receptor 1 (SigmaR1)–inositol–requiring enzyme-1α (IRE1α)–dependent mechanism. This environmental chemical-driven pathway boosts the expression of proinflammatory genes (*Il6*, *Ccl2*, *Csf2*, and *Nos2*) that contribute to the pathogenesis in MS and EAE (*13*) and is actively suppressed by signaling through the mineralocorticoid receptor nuclear receptor subfamily 3 group c member 2 and its corepressor nuclear receptor corepressor 2 (*17*).

Astrocyte reactivity and specific signaling pathways linked to it are also differentially modulated across various CNS disorders. For example, multiple studies highlighted the importance of signal transducers and activators of transcription 3 (STAT3) signaling in reactive astrocytes (*4*, *56*). Selective STAT3 inactivation in astrocytes reduces β-amyloid (Aβ) plaques and improves spatial learning and memory in the amyloid precursor protein/presenilin 1 model of AD (*25*). Moreover, interleukin-6 (IL-6) signaling through STAT3 regulates astrocytes linked to neurotoxicity during CNS inflammation (*57*). However, in the context of traumatic injury, reactive astrocytes form borders around CNS lesions, which restrict inflammation (*56*). Astrocyte-specific STAT3 inactivation impairs locomotor recovery and markedly increases proinflammatory gene transcription in spinal cord injury (SCI), emphasizing the role of STAT3-controlled astrocyte products in CNS repair (*37*). Thus, STAT3 in astrocytes controls CNS inflammation and neurodegeneration in a context-specific manner.

These findings highlight the need to define the complex interactions existing between STAT3 and other signaling pathways that determine the functional outcome of astrocyte responses. Most importantly, these studies highlight the heterogeneity of astrocyte responses in CNS pathology, which include both disease-promoting and disease-arresting or -resolving responses involving astrocyte interactions with CNS-resident and peripheral cells recruited to the CNS (Figs. 1 to 3). Therefore, unraveling the mechanisms that regulate astrocyte responses, subtypes, and states, as well as their interactions with CNS-resident and CNS-recruited cells, holds central importance to develop efficacious therapies for neurologic diseases.

ASTROCYTE INTERACTIONS WITH CNS-RESIDENT CELLS IN NEUROINFLAMMATION

Astrocyte interactions with neurons

Astrocyte-neuron interactions have been extensively investigated (Fig. 1) (*58*). Astrocytes play important roles in neuronal development and synapse maturation (*8*). In addition, astrocytes modulate synaptic transmission and circuit function. For example, astrocytes participate in "tripartite synapses," functional units formed by astrocytic processes and neuronal synapses (*59*), which enable efficient astrocyte-neuron bidirectional cross-talk. Astrocytes support synaptic function by secreting synaptogenic factors (*60*–*63*), phagocytosing structural synapses (*64*, *65*), and buffering synaptic glutamate (*66*). In the context of neurologic diseases, these and other homeostatic astrocyte functions involved in synaptic support are impaired. For example, complement $C3^+$ astrocytes induced by microglial TNF (tumor necrosis factor), IL-1α, and complement component 1q (C1q) lose their expression of synaptogenic factors (*60*–*63*) and phagocytosis receptors (*64*, *65*), resulting in deficits in astrocyte-driven synaptogenesis and synaptic pruning, perturbing circuit rewiring and integrity. Furthermore, in MS and PD, reactive astrocytes lose the expression of the glutamate reuptake transporters glutamate transporter 1 and glutamate aspartate transporter 1 (GLAST) (*67*–*69*), resulting in increased concentrations of extracellular synaptic glutamate and, consequently, excitotoxicity-driven neuronal death.

Additional mechanisms mediate astrocyte-neuron communication. For example, astrocytes metabolize glucose into lactate, supplying it to neurons to support their metabolism. This "lactate shuttle" is mediated by monocarboxylic acid transporters, whose expression is not confined to tripartite synapses (*70*). The metabolic cross-talk between astrocytes and neurons is perturbed during inflammation, boosting neurotoxicity (*70*). The metabolic remodeling of astrocytes induced by proinflammatory cytokines boosts the production of lactosylceramide (LacCer), which activates cytosolic phospholipase A2 (cPLA2). cPLA2 activation triggers its physical interaction with the CARD domain of mitochondrial antiviral signaling (MAVS) protein, resulting in the activation of NF-κB–driven proinflammatory responses (*14*). This cPLA2-MAVS interaction also displaces hexokinase 2 from its interaction with MAVS, limiting lactate production and further stressing neurons. Similar observations have been made in HD (*71*), AD (*72*), and PD (*73*), highlighting the importance of astrocyte-neuron metabolic decoupling in CNS inflammation.

In the mature brain, each astrocyte interacts with and maintains neurons and synapses within a specific territory that does not overlap with that of neighboring astrocytes (*74*). Endo and colleagues recently reported shrunken astrocyte territories in a preclinical AD model (*75*). Moreover, they identified *Fermt2* and *Ezr* as regulators of astrocyte territory. Interestingly, the decreased expression of these territory-related genes has been detected in several neurological diseases, including MS and PD, suggesting additional mechanistic links between impaired homeostatic astrocyte functions and CNS pathology (*75*). However, the mechanisms involved in the dysregulation of these homeostatic astrocyte functions are still not completely understood.

Accumulating evidence of astrocyte-driven neurotoxicity has been described. NF-κB activation in astrocytes promotes the production of neurotoxic nitric oxide (NO) (*13*, *76*). Sajio *et al.* (*32*) reported that down-regulation of nuclear receptor–related factor 1 protein, a PD risk factor, results in the production of neurotoxic NO and reactive oxygen species. In addition, Bi *et al.* (*77*) reported that, in a model of TDP43 proteinopathy, reactive astrocytes secrete lipocalin2, which is also toxic to neurons. Moreover, microglia-induced reactive astrocytes present in HD, AD, PD, and MS brain samples promote neuronal death through the secretion of neurotoxic fatty acids (*21*, *78*), suggesting a common mechanism of astrocyte-driven disease pathology across neurologic diseases. The glucagon-like peptide 1 receptor agonist is reported to block the microglia-driven induction of these neurotoxic astrocytes (*79*). However, the existence of disease-specific triggers of astrocyte activation linked to specific transcriptional and cellular responses suggests that multiple astrocyte states with neurotoxic activity can be induced. It further suggests that multiple mechanisms of astrocyte-driven neurotoxicity may exist, even in the context of the same disease.

Conversely, reactive astrocyte-driven neuroprotective mechanisms have also been identified. L'Episcopo *et al.* (*80*) suggested that reactive astrocytes are one of the sources of wingless-type MMTV integration site 1 (Wnt1), which is deeply involved in dopaminergic (DAergic) neuron development and recovery. The authors showed that astrocytes express *Wnt1* in response to 1-methly-4-phenyl1–1,2,3,6-tetrahydropyridine (MPTP)–driven DAergic neuron degeneration. Astrocyte-produced Wnt1 binds Frizzled and β-catenin in DAergic neurons, promoting DAergic neuron survival, repair, and neurogenesis. Further support for the physiologic relevance of neuroprotective astrocyte mechanisms was provided by Anderson and colleagues (*36*), who defined a central role for reactive astrocytes in axon regeneration in the context of

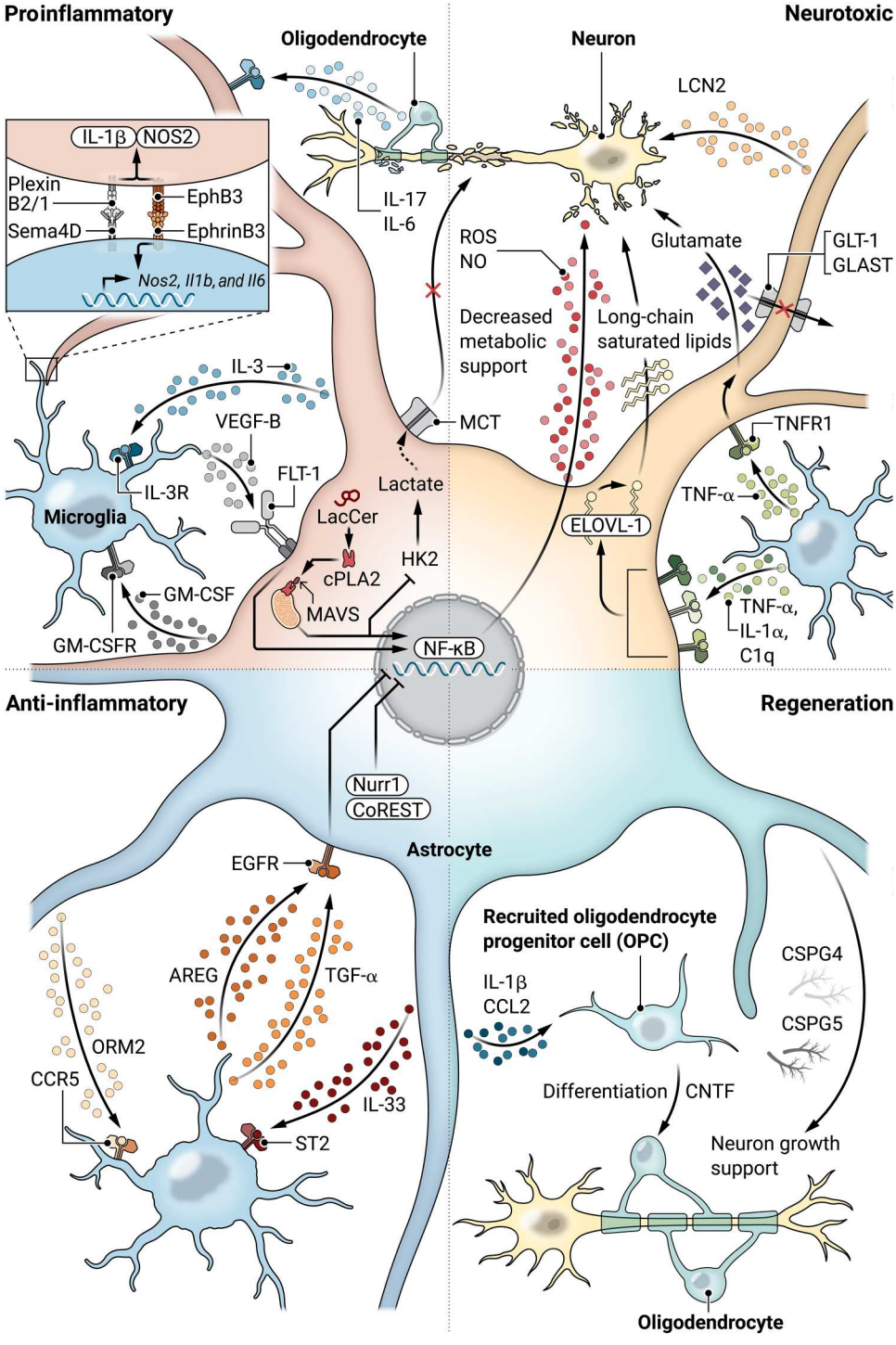

Fig. 1. Astrocyte cross-talk with CNS-resident cells. Astrocytes play a key role in regulating inflammation within the central nervous system (CNS). As central coordinators, they extensively interact with other CNS-resident cells. This interplay involves the release and modulation of various cytokines, chemokines, neuromodulators, and surface molecules, which collectively control neuroinflammation and neurodegeneration through the regulation of proinflammatory, toxic, anti-inflammatory, and regenerative processes. Upon neuroinflammation, astrocytes start to interact with nearby CNS-resident cells, such as microglia and oligodendrocytes. Astrocytes bidirectionally communicate with microglia through cytokines and surface-to-surface interactions, which not only turn on proinflammatory responses but also inhibit astrocyte-mediated homeostatic function. In addition, oligodendrocytes secrete cytokines such as IL-17 and IL-6 to promote proinflammatory astrocyte activities (top left, proinflammatory). Conversely, astrocytes can release several anti-inflammatory factors that suppress microglial proinflammatory responses. In addition, microglial cytokines can also suppress astrocyte proinflammatory activities by inhibiting NF-κB activation (bottom left, anti-inflammatory). Astrocytes induce neuronal death by releasing various factors such as fatty acids, reactive oxygen species, and LCN2. In addition, astrocyte-mediated neurotoxicity can occur because of disruptions in astrocyte homeostatic processes, such as lactate metabolism and glutamate buffering. Microglia-derived cytokines further promote astrocyte-mediated neurotoxicity (top right, neurotoxic). Astrocytes are involved in regeneration. OPCs recruited to lesions by astrocyte-secreted chemokines differentiate into mature oligodendrocytes, promoting remyelination. Reactive astrocytes also induce neuronal growth by releasing axon growth–supportive CSPGs, such as CSPG4 and CSPG5 (bottom right, regeneration). CCR5, C-C chemokine receptor type 5; CNTF, ciliary neurotrophic factor; CoREST, corepressor of RE1-silencing transcription factor; CSPG4, chondroitin sulfate proteoglycan 4; CSPG5, chondroitin sulfate proteoglycan 5; Elovl-1, elongation of very long-chain fatty acids 1; EGFR, epidermal growth factor receptor; GLT-1, glutamate transporter-1; GM-CSFR, granulocyte-macrophage colony-stimulating factor receptor; HK2, hexokinase 2; IL-3R, interleukin-3 receptor; Lcn2, lipocalin-2; MCT, monocarboxylate transporter; Nos2, nitric oxide synthetase 2; NURR1, nuclear receptor–related factor 1 protein; ST2, interleukin 1 receptor–like 1; TNFRI, TNF receptor type 1.

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SCI, establishing that reactive astrocytes express *cspg4* and *cspg5*, which support axon growth. Collectively, these findings highlight the multiple and sometimes opposing roles played by astrocyte-neuron interactions in the pathology of neurologic diseases. The generation of astrocyte single-cell datasets in multiple neurologic diseases and their preclinical models will enable the identification of common and disease-specific mechanisms operating in astrocytes, as illustrated by recent studies by Burda and colleagues (*37*). Moreover, the examples mentioned in this section suggest that, when studying mechanisms of astrocyte-driven neuronal damage, it is important to differentiate between the active induction of neurotoxicity and the impairment of astrocyte functions that

support neuron health and survival, both of which may result in neuronal death in vitro.

Astrocyte interactions with oligodendrocytes

Oligodendrocytes are classically considered the target of inflammatory responses in MS (*81*), but recent evidence also suggests active roles for oligodendrocytes in CNS inflammation (Fig. 1). Multiple cytokines, immune mediators, and their receptors are expressed by oligodendrocytes. For example, Kim and colleagues (*82*) reported that astrocytes promote microglial TNF-α release, which binds TNF receptor 1 expressed in oligodendrocyte precursor cells (OPCs) and induces cytotoxicity in a contact-dependent manner.

Conversely, astrocytes have also been shown to play multiple roles in remyelination (*83*). OPCs are recruited to CNS lesions in response to IL-1β and C-C motif chemokine ligand 2 (CCL2) produced by astrocytes (*84*). Once at the lesions, OPCs differentiate into mature oligodendrocytes in response to ciliary neurotrophic factor (*85*). Interestingly, the down-regulation of the Nrf2 pathway in astrocytes promotes oligodendrocyte survival and remyelination (*86*). Luteolin, which inhibits Nrf2 signaling, promotes remyelination, suggesting that astrocyte-oligodendrocyte interactions may offer new targets to treat demyelinating disease.

In addition, oligodendrocytes produce proinflammatory cytokines (e.g., IL-1β, CCL2, IL-17, and IL-6), which promote proinflammatory astrocyte responses (*1*). Moreover, it was recently reported that oligodendrocytes disrupt the BBB by down-regulating tight junction proteins during MS pathogenesis (*87*). This active BBB disruption is driven by oligodendrocyte competition with astrocyte end feet–ensheathing blood vessels. In the light of reports of age-linked impaired remyelination, it is important to establish whether astrocyte-oligodendrocyte interactions are perturbed during aging (*88*), an important point for the development of therapeutic strategies to promote remyelination, particularly in neurologic diseases where remyelination deficits and disease progression are linked with aging, such as MS (*89*).

Astrocyte interactions with microglia

Microglia-dependent developmental synapse pruning is promoted by IL-33 secreted from astrocytes, highlighting the importance of astrocyte-microglia cross-talk in neural circuit development (Fig. 1) (*90*). In addition, microglial factors regulate astrocyte pathogenic activities during CNS inflammation (*21*, *78*, *79*). For example, Bezzi *et al.* (*91*) found that microglial TNF-α induces stromal cell–derived factor 1 (also known as CXCL12)–CXCR4–driven glutamate release by astrocytes, promoting neuronal death. Similarly, microglial TNF-α, IL-1α, and C1q were shown to induce a neurotoxic phenotype in astrocytes (*21*). Moreover, microglial vascular endothelial growth factor B (VEGF-B) and transforming growth factor–α (TGF-α) differentially regulate proinflammatory gene expression in astrocytes during EAE and MS (*92*). Microglial VEGF-B promotes VEGF receptor 1 (FLT-1)–driven NF-κB activation, boosting astrocytic pathogenic activities in EAE. Conversely, microglial TGF-α limits EAE progression by activating epidermal growth factor receptor/ErbB1 signaling. Interestingly, the microglial production of VEGF-B or TGF-α is regulated by microbial metabolites of dietary tryptophan, which cross the BBB and regulate AHR signaling in microglia and astrocytes (*55*, *92*), providing insights to the control of CNS-resident cells and their cross-talk by the gut-brain axis.

Astrocytes can also modulate microglial responses in the context of CNS pathology. B4GALT6-driven LacCer production induces GM-CSF secretion by astrocytes, modulating the transcriptional response of microglia and CNS-infiltrating monocytes (*93*). Similarly, a SigmaR1-IRE1α-XBP1 axis operating in astrocytes drives not only astrocyte-intrinsic responses that promote CNS pathology but also microglial pathologic responses through yet-uncharacterized astrocyte-microglia communication mechanisms (*13*). Kiss and colleagues (*94*) recently reported that astrocyte-produced IL-3 induces disease-promoting responses in microglia and monocytes, contributing to the pathology of MS, although IL-3–driven control of microglia by astrocytes may limit pathology in AD (*95*). Conversely, Jo *et al.* (*96*) reported that astrocytes can suppress microglial activation in the context of systemic LPS-driven CNS inflammation through the production of orosomucoid-2 (Orm2). These findings highlight the complexity of astrocyte-microglia interactions and identify important roles for IL-3, GM-CSF, and Orm2 in the control of microglia by astrocytes.

Astrocyte-microglia cross-talk is diverse and complex, with both pro- and anti-inflammatory outcomes and feedback mechanisms. To decipher the complexity of astrocyte-microglia interactions, we designed a forward-genetic screening platform based on the coculture in droplets of microglia-astrocyte pairs in which genes have been systematically inactivated in microglia to determine the effect of this perturbation in astrocytes; we named this platform systematic perturbation of encapsulated associated cells followed by sequencing (SPEAC-seq) (*44*). In its first iteration, we coencapsulated transgenic primary astrocytes, which express green fluorescence protein upon NF-κB activation with microglia transduced with genome-wide CRISPR-Cas9 library. This approach identified a regulatory circuit, whereby IL-33 released by astrocytes in the context of inflammation triggers microglial production of amphiregulin (AREG), which acts on astrocytes to limit their proinflammatory responses.

Microglia-astrocyte interactions can also involve physical contact through membrane-bound molecules. Using rabies barcode interaction detection followed by sequencing (RABID-seq) in an EAE model, we identified PlexinB2/1–semaphorin 4D (Sema4D) and ephrin type B receptor 3 (EphB3)–EphrinB3 signaling as a potential mediator of astrocyte-microglia interactions (*45*); these interactions were later validated in human systems. Most importantly, the inactivation of these interactions suppressed microglial and astrocyte proinflammatory responses, highlighting the potential value of astrocyte-microglia interaction pathways as therapeutic targets for neurologic diseases.

ASTROCYTE-PERIPHERAL IMMUNE CELL INTERACTIONS IN NEUROINFLAMMATION

Astrocyte interactions with T cells

Astrocytes are major components of the BBB, forming the glia limitans, a barrier that encloses pericytes, endothelial cells, and the basal lamina, restricting the entry of leukocytes into the CNS (Fig. 2) (*56*). However, BBB disruption and dysfunction can promote leukocyte invasion into the CNS parenchyma as described in MS, stroke, and AD (*97*). In this context, astrocytes are one of the first CNS-resident cells encountered by infiltrating T cells, regulating not only T cell migration but also activation (*56*) (Fig. 3). For example, astrocytes in MS lesions express IL-27, which limits

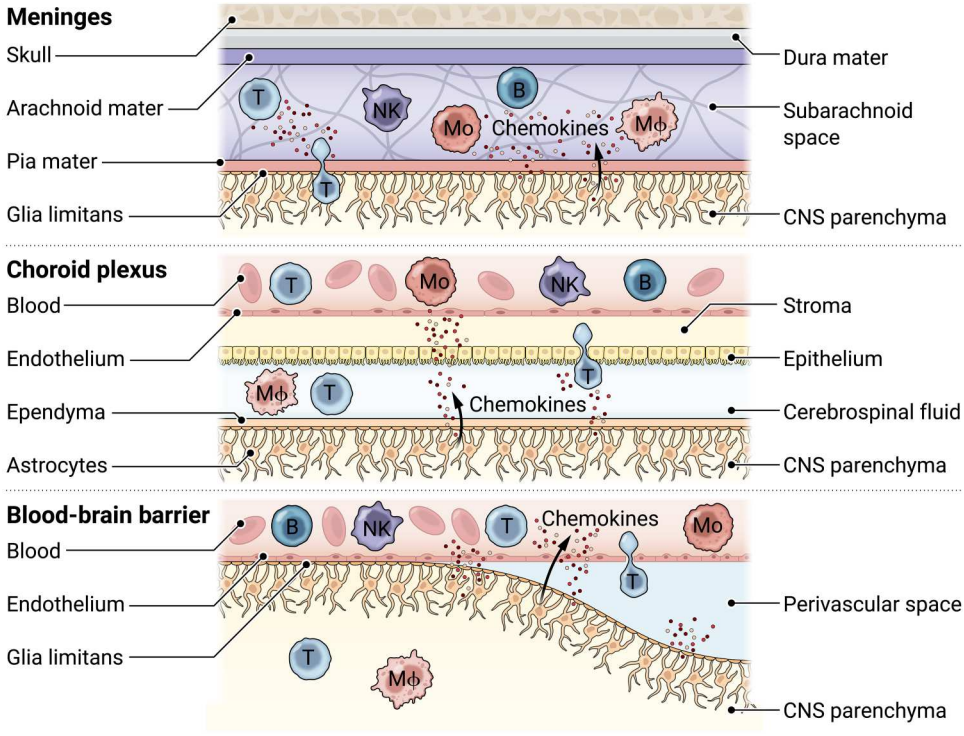

Fig. 2. Astrocyte cross-talk within the CNS borders. Astrocytes play important roles in the control of the barriers that separate the blood vessels, perivascular spaces, cerebrospinal fluid (CSF), and meninges from the CNS parenchyma. In the context of CNS inflammation, these borders become dysfunctional, and astrocytes produce and secrete a wide range of molecules and chemokines to attract circulating peripheral immune cells, including T cells, B cells, NK cells, monocytes, and macrophages into the CNS. Mϕ, macrophage; Mo, monocyte, NK, natural killer cells.

proinflammatory T helper 17 (T_H17) cell responses while promoting the differentiation of anti-inflammatory type 1 regulatory (Tr1) cells and FoxP3$^+$ regulatory T (T_{reg}) cells (*98*–*100*). Astrocyte IL-27 production has been shown to limit proliferation and cytokine production (IFN-γ, IL-17, TGF-β, and IL-4) in myelin-specific T cells (*101*). Astrocytes also induce cytotoxic T lymphocyte–associated protein 4, CD39, and CD73 expression in CD4$^+$ T cells, further limiting their activation (*102*, *103*). Last, astrocytes induce T cell apoptosis through the expression of FasL and TRAIL (*16*, *104*).

Conversely, astrocytes in response to ischemic stroke express IL-15, which recruits CD8 T cells and boosts their effector function during brain damage (*105*). Moreover, astrocytes express major histocompatibility complex (MHC) class II and costimulatory molecules (e.g., CD80 and CD86) in active MS lesions (*106*, *107*), but the physiological importance of these findings is not fully understood. IFN-γ up-regulates MHC class II and costimulatory molecule expression in primary murine astrocytes in vitro (*108*–*110*), but studies on human fetal astrocytes failed to detect IFN-γ–induced CD80 (B7-1) and CD86 (B7-2) expression (*111*). Considering the protective role of IFN-γ signaling in astrocytes in the context of CNS inflammation (*16*, *112*), further studies should interrogate the effects of IFN-γ on the expression of not only MHC but also cytokines, checkpoint, and other molecules relevant for the regulation of T cell responses.

Astrocytes are an important source of chemokines, such as CCL1, CCL2, CCL20, and CXCL10 (*113*–*117*). NF-κB–driven CCL2 and CXCL10 expression in astrocytes recruits proinflammatory T cells and monocytes to the CNS, promoting MS and EAE pathology (*113*–*115*, *118*). In addition, the activation of the receptor activator of NF-κB (RANK) in astrocytes by T_H17 cell–expressed RANK ligand triggers the production of CCL20, boosting the recruitment of effector T cells during CNS inflammation (*116*). Similarly, TGF-β–activated kinase 1–driven CXCL1 production promotes the migration of CXCR2$^+$ CD4 T cells to the spinal cord gray matter and, consequently, neuronal damage and motor dysfunction (*117*). Astrocyte-produced chemokines (CCL1 and CCL20) also recruit T_{reg} cells in the context of stroke (*119*).

Importantly, the relationship between astrocytes and T cells is bidirectional; T cells can also shape astrocyte responses. Astrocytes express receptors for IL-17 and GM-CSF, cytokines produced by proinflammatory T_H17 cells linked to the pathology of MS, EAE, and other diseases (*15*, *120*–*123*). T_H17-derived IL-17 was initially thought to up-regulate NF-κB activator 1 (Act1)–dependent proinflammatory cytokine (GM-CSF) and chemokine production (CXCL1, CXCL2, and CCL20) in astrocytes, boosting leukocyte recruitment to the CNS during EAE (*120*). However, it was later found that these effects of IL-17 were mostly associated with neural/glial antigen 2–expressing glial cells (*123*). Hence, our understanding of the effects of IL-17 signaling in the control of astrocyte responses is still limited. However, GM-CSF was found to promote the MAFG/MAT2α-dependent differentiation of proinflammatory astrocyte states in MS and EAE (*15*) while limiting astrocyte expression of the inducer of T cell apoptosis TRAIL (*16*).

In addition, astrocyte interactions with T_{reg} cells have been reported to limit CNS inflammation (*124*). For instance, CNS-infiltrating T_{reg} cells suppress neurotoxic astrogliosis during stroke

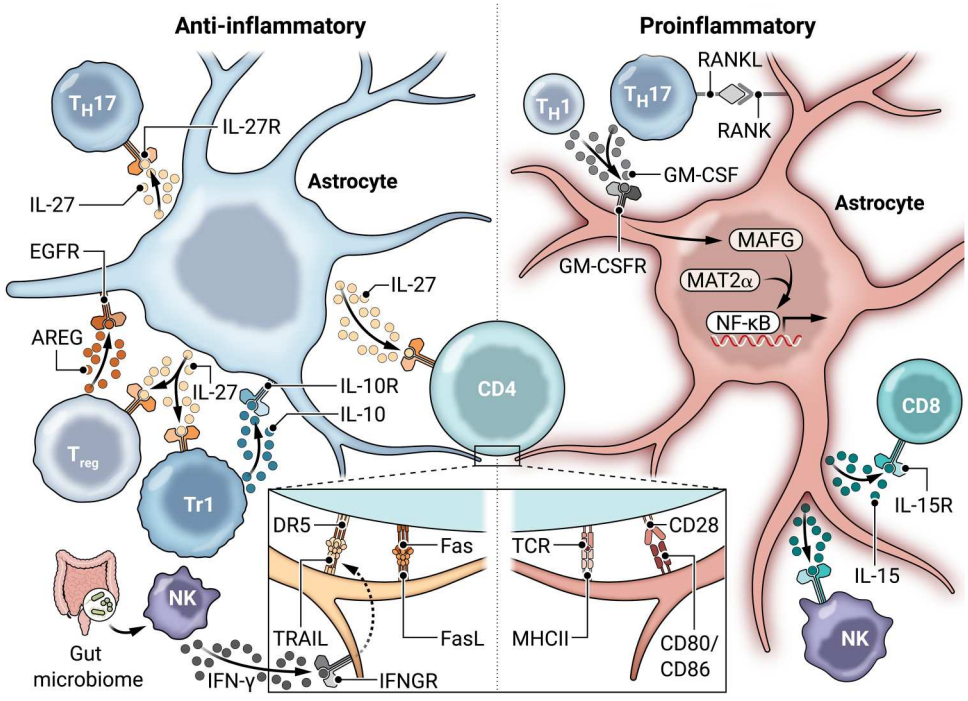

Fig. 3. Astrocyte cross-talk with peripheral immune cells. Upon crossing CNS barriers, soluble factors and cell-cell communications mediate astrocytes and leukocyte interactions by shaping the transcriptional programs of these cells, either alleviating or aggravating neuroinflammation and neurodegeneration. Astrocytes express TRAIL and FasL, promoting T cell apoptosis. In addition, astrocytes limits T cell responses while promoting the differentiation of Tr1 cells and T_{reg} cells through the production of IL-27. Tr1 cells and T_{reg} cells regulate pathogenic activities of astrocytes by cytokines such as IL-10 and AREG (left). Conversely, astrocytes can boost effector functions of peripheral immune cells including NK cells and CD8 T cells through the production of IL-15. T_H17 cells promote pathogenic activities of astrocytes by expressing RANKL and GM-CSF (right). IFNGR, interferon-γ receptor; IL-10R, interleukin-10 receptor; IL-15R, interleukin-15 receptor; IL-27R, interleukin-27 receptor.

through the production of AREG, a molecule linked to tissue repair in other tissues such as the gut (*119*). Moreover, Tr1 cells suppress pathogenic astrocyte activities through IL-10 in EAE (*125*, *126*). Interestingly, astrocyte–T cell interactions are detected in virus-based barcoded methods designed to study cell-cell communication (*45*); future studies using these and other methods are likely to dissect intricate mechanisms of communication between specific astrocyte and T cell subsets. Together, these findings highlight the importance of astrocyte–T cell communication during neuroinflammatory reactions and suggest that T cell subsets induced with nanomaterials (*127*–*129*) or engineered probiotics (*130*, *131*) may be used for the therapeutic modulation of astrocyte responses.

Astrocyte interactions with mononuclear phagocytes

The recruitment of peripheral mononuclear phagocytes, including monocytes and dendritic cells, plays important roles in CNS inflammation (Fig. 3) (*132*). In MS and EAE, astrocyte-derived CCL2 recruits proinflammatory monocytes to the CNS (*113*, *133*, *134*). CCL2 deletion in astrocytes decreases the recruitment and polarization of proinflammatory monocyte-derived macrophages (*133*) linked to demyelination and neuronal death (*135*). However, astrocyte-derived CCL2 can also recruit macrophages that promote tissue repair (*136*), suggesting that astrocytes can promote both proinflammatory and repair mechanisms in a context-specific manner. In addition, these findings highlight our limited understanding of the molecular mechanisms mediating the recruitment of specific peripheral myeloid cell subsets by astrocytes and the functional heterogeneity of those subsets.

Astrocyte interactions with NK cells

Distinct immunological niches exist at CNS borders. The meninges, which envelop the brain and spinal cord, have been identified as an important site for the communication between peripheral immune subsets and CNS-resident cells in physiological and pathological conditions (*137*, *138*). It was recently reported that NK cells circulating through the meninges induce TRAIL expression in homeostatic astrocytes through the production of IFN-γ, enabling the apoptosis of proinflammatory T cells that express death receptor 5. Of note, NK cells circulating through the meninges acquire the ability to produce IFN-γ in intestinal tissue in response to signals provided by the commensal flora (Fig. 3). These findings identify a mechanism used by the gut-CNS axis to control inflammation (*139*), which not only sheds light on the potential role of the microbiome in the pathology of neurologic diseases but also offers exciting opportunities for therapeutic intervention.

Conversely, astrocytes modulate the activity of NK cells. For example, IL-15 overexpression in astrocytes (glial fibrillary acidic protein–IL-15^{tg}) exacerbates ischemic brain injury, in part, as a result of increased NK cell–mediated immune responses (Fig. 3) (*105*). Collectively, these findings highlight the importance of astrocyte-NK cell cross-talk in the context of CNS homeostasis and pathology, calling for additional studies on the roles of specific NK cell subsets (*140*) in these interactions.

Astrocyte interactions with B cells

B cells play fundamental roles in CNS homeostasis and pathology, as highlighted by the success of treatments targeting B cells in MS and other neurologic diseases (*141*). In MS plaques, astrocytes produce B cell activation factor, which plays crucial roles in the development and survival of B cells, as well as antibody production (*142*). Secreted factors produced by human astrocytes promote the survival and activation of B cell subsets, including memory B cells from patients with secondary progressive MS (*143*). In MS and stroke, astrocytes are also reported to secrete CXCL12 (*144*, *145*), which promotes plasma cell maintenance and survival, suggesting a role of astrocytes in the control of pathogenic B cells in the CNS (*146*).

B cell products also affect astrocyte function and survival. Antibodies reactive with aquaporin 4 drive the pathology of neuromyelitis optica through the induction of astrocyte dysfunction and death (*147*, *148*). Moreover, it was recently reported that B cells in MS produce antibodies reactive with glial cell adhesion molecule (GlialCAM), an immunoglobulin-like cell adhesion molecule expressed by glial cells, including astrocytes (*149*). Although the effects of GlialCAM-reactive antibodies on astrocytes are still unknown, these findings suggest additional roles for astrocytes (or their demise) in MS. Moreover, these findings suggest additional roles for astrocyte–B cell interactions in neurologic diseases. Interestingly, gut-derived immunoglobulin A–producing B cells have been reported to attenuate CNS inflammation (*150*, *151*) and also to produce IL-10, a cytokine known to limit disease-promoting astrocyte activities in MS and EAE (*125*, *150*). Thus, future studies should go beyond the pathogenic effects of astrocyte-reactive antibodies to interrogate the modulation of astrocyte function by B cells and their products, as well as its relevance for the gut-CNS axis in health and disease.

CONCLUSION AND FUTURE PERSPECTIVES

Cell-cell interactions play central roles in the control of astrocyte function in health and disease. These interactions are perturbed in neurologic disorders and potentially represent important targets for therapeutic intervention. Hence, it is important to interrogate cell-cell interactions with unbiased and comprehensive approaches. RABID-seq (*45*), SPEAC-seq (*44*), and spatial transcriptomics (*152*), for example, provide unique opportunities to interrogate the disease-associated connectome of astrocytes and other cells of interest, even outside of the CNS.

An important and related challenge is to select adequate modalities for connectome-targeted therapeutic interventions. CNS-penetrant small molecules offer unique opportunities as therapeutic agents (*14*, *18*, *20*, *45*, *79*). For instance, the CNS-penetrant small molecule A38 has been shown to limit CNS inflammation by inhibiting EphB3 receptor signaling, which was identified as a mediator of astrocyte-microglia interaction in EAE and MS (*45*). In addition, viral vector–based gene therapy approaches may provide unique opportunities for the therapeutic targeting of CNS cell-cell interactions (*153*). Recent advances in adeno-associated virus (AAV) platforms led to the development of BBB-penetrating AAV capsids (*154*). Similarly, antibodies, a tool of choice for the specific modulation of pathways of interest, can be engineered to increase their CNS permeability (*155*), maximizing target engagement. Last, the important role of the gut-brain axis in the regulation of CNS-resident cells suggests that it can be targeted to limit pathogenic responses of CNS-resident cells. In this context, engineered probiotics provide new tools to limit CNS pathology (*156*, *157*). However, important technical challenges remain associated with each of these modalities as related to the specificity of small molecule, the induction of unwanted immune responses by viral vectors and their long-term effects, and the CNS permeability of therapeutic antibodies. Moreover, important questions remain to be addressed for the development of efficacious therapies targeting the connectome of astrocytes and other cells in the CNS: (i) Are there common perturbations of cell-cell interaction mechanisms shared by multiple neurologic diseases? (ii) How do we specifically target subtypes and states of astrocytes or other cell types to reestablish their homeostatic functions and suppress their pathogenic activities? (iii) Which cell-cell interactions can we target to promote repair in the CNS, and how are those mechanisms affected by aging? Addressing these and other related questions will pave the way for the development of efficacious connectome-targeted therapies for neurologic disorders.

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