NEURAL REGENERATION RESEARCH
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Review

Star power: harnessing the reactive astrocyte response to promote remyelination in multiple sclerosis

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https://doi.org/10.4103/1673-5374.380879

Date of submission: January 27, 2023

Date of decision: May 5, 2023

Date of acceptance: May 23, 2023

Date of web publication: July 20, 2023

Abstract

Astrocytes are indispensable for central nervous system development and homeostasis. In response to injury and disease, astrocytes are integral to the immunological- and the, albeit limited, repair response. In this review, we will examine some of the functions reactive astrocytes play in the context of multiple sclerosis and related animal models. We will consider the heterogeneity or plasticity of astrocytes and the mechanisms by which they promote or mitigate demyelination. Finally, we will discuss a set of biomedical strategies that can stimulate astrocytes in their promyelinating response.

Key Words: astrocytes; demyelination; drug-based therapies; myelin repair; oligodendrocyte precursor cells; reactive astrogliosis

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Introduction

Multiple sclerosis (MS, **Box 1**) is a debilitating autoimmune disease characterized by chronic damage to myelin. Previous research has focused on the immune compartment in the development and progression of MS as reviewed in (Dendrou et al., 2015; Prinz and Priller, 2017); however, there is emerging evidence that central nervous system (CNS) resident cells also contribute to MS pathology (Healy et al., 2022). Specifically, astrocytes that become reactive in response to injury or disease, have been shown to influence diverse mechanisms involved in the pathology of MS (reviewed by Ponath et al., 2018), hence play also a crucial role in demyelination and remyelination (**Box 2**). Astrocytes can trigger demyelination through primary damage to myelin (Wan et al., 2022) or oligodendrocytes via the upregulation of for example apoptosis-related interleukins (Sanchis et al., 2020; Bretheau et al., 2022). In contrast, astrocytes can promote remyelination through the secretion of trophic factors that aid the maturation and/or differentiation of precursors (OPCs) (Butti et al., 2019; Lohrberg et al., 2020). An emerging question in neurobiology is: how many and how different are the astrocyte types that drive disease pathology? As per a recent consensus article (Escartin et al., 2021), the determination of reactive astrocyte diversity relies on identifying profiles according to a combined evaluation of the CNS region, tissue type (developing, healthy or diseased), sex, and species analyzed together with their functional profiles, multi-omic (transcriptomic, proteomic, epigenomic, etc.) signatures, and morphologies (Escartin et al., 2021).

Nonetheless, transcriptomic evaluations of astrocytes have begun to identify gene expression signatures that are associated with diverse functional types. For example - and in the absence of a new applicable classification - "A1" astrocytes whose gene signature includes complement component 3 (C3) expression have previously been associated with a neurotoxic phenotype (Zamanian et al., 2012; Liddelow et al., 2017; Guttenplan et al., 2021). These C3-expressing astrocytes are present in MS (Liddelow et al., 2017) and its animal model, experimental autoimmune encephalomyelitis (EAE, **Box 3**) (Tassoni et al., 2019). Another "A1" gene signature is depicted by high transcript levels of MAF bZIP transcription factor G (*Mafg*) and methionine adenosyltransferase 2 alpha (*Mat2α*) but concurrent low transcript expression for nuclear factor erythroid 2-related factor 2 (*Nrf2*), which is associated with a proinflammatory phenotype in EAE (Wheeler et al., 2020). These markers could recently also be identified in the chronic cuprizone (CPZ)-mediated animal model for MS (**Box 3**) (Silva Oliveira Junior et al., 2022). However, as defined by Escartin et al. (2021), astrocytes likely exist as a continuum of diverse states and functions, depending on context, hence do not polarize into simple binary phenotypes such as "good (A1)" or "bad (A2)", but can even show simultaneous features/signatures assigned to neuroprotective or neurotoxic functions (Das et al., 2020; Hasel et al., 2021; Silva Oliveira Junior et al., 2022).

Ultimately, the understanding of astrocyte diversity is important when considering (astrocyte-mediated) therapeutic strategies for MS. Interestingly, Gorter and Baron (2022) recently listed a few Food and Drug Administration (FDA)-approved agents for MS, such as siponimod, as well as novel promyelinating compounds that may exert their beneficial effects via astrocyte modulation. Whether their mode of action relies on the manipulation of diverse astrocyte types is an outstanding question.

In this review, we will examine astrocyte types in MS through the lens of de- and remyelination. We will also highlight current treatment strategies that alter the balance of astrocyte types to promote remyelination.

Search Strategy and Selection Criteria

The authors obtained their information from published articles collected using databases PubMed (NLM, National Library of Medicine), ScienceDirect (Elsevier), and Web of Science (Clarivate) until December 2022. Keywords and terms such as multiple sclerosis, astrocyte(s), white matter, de-/remyelination, pro-recovery, pro-inflammatory, and specific markers such as Lcn2, S100a10, and Mafg were either used individually or in combination to search appropriate information without limiting the year of publication. However, this review aimed at citing the most recent articles, whilst older original publications describing initial findings were also necessary to cite.

Reactive Astrocytes in Multiple Sclerosis: Friend or Foe?

Historically, reactive astrogliosis was interpreted as an unchangeable maladaptive response, and ablation of this mechanism was thought to be beneficial (Jäkel and Dimou, 2017). More recent studies have shown that astrocytes play roles in both demyelination ("pro-disease") and remyelination ("pro-recovery") processes. Note, those reactive astrocytes naturally compose the normal appearing white matter and grey matter areas in MS lesions (Schirmer et al., 2021; Trobisch et al., 2022), highlighting their contribution also in the early phases of MS.

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Funding: *This work was supported by the Heart and Stroke Foundation and Ontario Institute of Regenerative Medicine (New Ideas Grant), Canada First Research Excellence Fund (Medicine by Design), the National Sciences and Engineering Research Council, the Jürgen Manchot Foundation, the Christiane and Claudia Hempel Foundation for Clinical Stem Cell Research and the James and Elisabeth Cloppenburg, Peek and Cloppenburg Düsseldorf Stiftung (to PK).*

How to cite this article: *Silva Oliveira Junior M, Reiche L, Daniele E, Kortebi I, Faiz M, Küry P (2024) Star power: harnessing the reactive astrocyte response to promote remyelination in multiple sclerosis. Neural Regen Res 19(4):578-582.*

Box 1 | **Multiple sclerosis (MS) at a glance**

The chronic, inflammatory, demyelinating, and neurodegenerative central nervous system (CNS) disorder multiple sclerosis (MS) is an immune-mediated disease caused by complex interactions between several cell types (leucocytes, CNS-resident innate cells) and gene-environment axis (extensively reviewed by Filippi et al., 2018 and Dobson and Giovannoni, 2019). Focal lesions/plaques, the regions of demyelination that are pathological hallmarks of all MS phenotypes, are found in the white and grey matter and can occur in the brain, optic nerve, and spinal cord (Gilmore et al., 2009; Green et al., 2010; Petrova et al., 2018).

The appearance and development of symptoms (wide-ranging, e.g., sensory-, motor- and or visual impairments, cognitive deficits, memory loss, and many more) can vary and also depend on the disease stages. While most patients experience a relapsing-remitting MS (RRMS) disease course, a minor fraction of patients suffers from primary-progressive MS (PPMS). RRMS is characterized by an abrupt onset of symptoms that fade over time, yet recovery of lesions varies between patients. Most symptoms arise during the relapsing stages when immune attacks occur. Here, cells of the innate and adaptive immune systems (myeloid cells, $CD4^+$ and $CD8^+$ T cells, and B cells) infiltrate the CNS parenchyma, distributing perivascularly around post-capillary venules of the blood-brain barrier (BBB). Through cell interactions and induced secretion of soluble factors [cytokines, lipids, reactive oxygen species (ROS), and others], infiltrating immune cells together with CNS-resident activated microglia and astrocytes contribute to oligodendrocyte injury, demyelination, and axonal damage (Filippi et al., 2018; Li et al., 2018). Eventually and over time, also in these patients a more progressive disease course is observed with no more apparent immune cell infiltration but ongoing and over taking neurodegenerative processes to occur.

Such other factors contributing to neurodegeneration and ongoing tissue injury (Filippi et al., 2018) include acute or chronic oxidative stress via innate and adaptive immune cell activation, loss of (myelin) trophic support, altered glutamate homeostasis, and a pro-inflammatory environment that may be driven by meningeal immune cell infiltrates and CNS-innate microglia and astrocytes in MS active lesions.

Over time, demyelinated tissues undergo scarification, which is organized by astrocytes, meningeal cells, and infiltrating peripheral immune cells. Scarification aims to decrease brain tissue destruction; however, it also enhances disability and disease progression.

Box 2 | **Remyelination – regenerative but insufficient process in multiple sclerosis (MS)**

Demyelination, or loss of myelin is followed by a spontaneous, regenerative response, called remyelination. Remyelination is a complicated multi-step process that can reverse deficits in conduction and aims to protect unsheathed axons from secondary degeneration. In the central nervous system (CNS), remyelination is mediated by newly generated oligodendrocytes. Both parenchymal oligodendrocyte precursor cells (OPCs), a population of widespread resident adult multipotent progenitors that comprise 5% of total brain cells (Franklin et al., 2021), and neural stem cells (NSCs) located within the germinal niche can generate such new oligodendrocytes. Moreover, even Schwann cells (SCs), the myelinating glia of the peripheral nervous system (PNS), were revealed to contribute to this CNS regenerative response (reviewed by Chen et al., 2021). Briefly, OPCs migrate to lesion sites (Levine and Reynolds, 1999), (eventually) proliferate (Choi et al., 2018) and predominantly differentiate into new myelin-forming oligodendrocytes. Nonetheless, extended myelin damage as well as a number of identified inhibitory components (Kremer et al., 2011) impede subventricular zone (SVZ)- and parenchymal-derived OPCs from maturating (see Figure 1), impairing a last-long reparative response of such progenitors (Xing et al., 2014; Brousse et al., 2015). In general, remyelination depends on several factors and steps, such as pivotal myelin debris clearance via e.g. microglia (Kotter, 2006; Lampron et al., 2015) or accurate OPC differentiation, easily disrupted via pro-inflammatory milieu induced by infiltrating leucocytes and CNS-innate glial cells (microglia, astrocytes), rendering it susceptible to an inadequate/insufficient process.

Box 3 | **Short note on animal models used for multiple sclerosis (MS)**

To investigate pathological mechanisms of MS and study therapeutic interventions, several animal models have been developed to mimic specific aspects of MS pathology, particularly the acute inflammatory stage (reviewed by Gharagozloo et al., 2022 and Leo and Kipp, 2022). The most commonly used (and within this review cited) models are the toxin-mediated oligodendrocyte death and demyelination inducing cuprizone (CPZ) model and the experimental autoimmune encephalomyelitis (EAE), which results in a T cell-mediated autoimmune attack against myelin sheaths via systemic injection of myelin peptides together with an adjuvant.

As Gorter and Baron (2022) highlighted, further complexity in studying MS is added by the indication that demyelinating and ongoing remyelination processes coexist. However, in experimental animal models for MS, demyelination, and remyelination are often considered to be separated processes occurring at different time points; hence none of the existing MS models can fully replicate the actual biology of chronic demyelination in MS. Nevertheless, these models showed to exhibit similarities in underlying pathways associated with immune and astroglial responses, neurodegeneration, oligodendroglial damage, and remyelination deficits some of which are described in more detail in this review.

Masvekar et al. (2019) identified several biomarkers via cerebrospinal fluid analysis of MS patients that possibly enable a correlation between MS progression, toxic astrogliosis, and microglial activation. Seen from a physiological point of view, astrocytes (together with endothelial cells and pericytes) mediate the controlled entrance of nutrients and ions from the periphery into the CNS while preventing the access of pathogens (blood-brain barrier; BBB). Via direct communication with T cells, astrocytes can either block or promote T cell migration into the CNS at the BBB (Williams et al., 2020). Dysregulation of BBB tight junctions such as observed in response to autoantibodies targeting aquaporin 4 (AQP4), in the disease neuromyelitis optica (Lennon et al., 2004) contributes to demyelination (Soerensen et al., 2021). Although Lennon and colleagues (2004) could not detect anti-AQP4 autoantibodies in the cerebrospinal fluid of MS patients, nor in the CPZ-dependent demyelination model (Rohr et al., 2020), altered AQP4 expression levels in MS lesions (Rohr et al., 2020) as well as upon CPZ application (Zhan et al., 2020) supports the assumption that astrocytes at the BBB may be involved in the initial stages of MS lesion formation (Gorter and Baron, 2022). In EAE, prior to immune cell infiltration into the parenchyma, reactive astrocytes seem to phagocyte myelin debris, resulting in the induction of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and secretion of cell-recruiting chemokines, hence triggering self-activation and resulting in an astroglial-mediated influx of leukocytes (Ponath et al., 2017). Thus, reactive astrocytes direct damage without a first interaction with leucocytes during demyelination, suggesting that the initial lesion observed in MS can be potentially co-regulated by astrocytes and not entirely/directly by leucocytes as once thought (Schirmer et al., 2021). For an even more detailed overview of the many demyelination-promoting roles, reactive astrocytes can acquire, see also (Ponath et al., 2018; Gorter and Baron, 2022; Salles et al., 2022).

On the other hand, key studies examining the role of astrocytes in MS have demonstrated that they are also essential for myelin repair. Depletion of reactive astrocytes in mice exposed to CPZ prevented remyelination due to microglial dysfunction and accumulation of myelin debris (Skripuletz et al., 2013). Similarly, in an osmolyte-induced demyelinating model, lack of astrocytes in lesions diminished OPC maturation, therefore impairing the generation of new oligodendrocytes and remyelination of denuded axons (Lohrberg et al., 2020). Moreover, in EAE glial scar formation was shown to be myelin protective and appeared to support the presence/accumulation of OPCs in normal appearing white matter areas, which in turn also promoted remyelination in the cerebellum and spinal cord (Haindl et al., 2019).

Genes/Factors Associated with Diverse Astrocyte Subtypes in Multiple Sclerosis

Although the spectrum of astrocyte types in MS has not been defined yet, it is clear that astrocytes play diverse roles and contribute to both disease progression and repair. Using single cell- and single nucleus RNA sequencing approaches, recent studies revealed marker genes that are enriched in specific astrocyte subtypes/states (Schirmer et al., 2019; Wheeler et al., 2020; Trobisch et al., 2022). Below, we will review these genes/pathways in the context of de- and remyelination in MS and preclinical models, focusing on CPZ-mediated demyelination and EAE (**Box 3**). Of note, most EAE studies focus on either spinal cord lesions (e.g., Wanner et al., 2013; Jin et al., 2022) or investigated whole brain isolates (e.g., Wheeler et al., 2020; Sanmarco et al., 2021), taking probably not fully into account that astrocytes show remarkable regional differences in their heterogeneity (Itoh et al., 2017; Silva Oliveira Junior et al., 2022; Trobisch et al., 2022). Using Ribotag technology, regional differences in astrocytes could already be described in EAE, with spinal cord-, cerebellar-, and cortical astrocytes displaying changes in genes related to cholesterol synthesis (e.g., Hmgcs1, Hmgcr, Msmo1), while such alterations were not observed in hippocampal astrocytes (Itoh et al., 2017).

Complement factors

The complement system is revealed to be implied in MS pathogenesis (Saez-Calveras and Stuve, 2022). Complement factor 1q (C1q) is activated and highly expressed following CPZ-mediated demyelination, in EAE, and is also upregulated in brain lesions of MS patients (Ingram et al., 2014; Watkins et al., 2016). C1q can induce the expression of yet another complement protein C3 in astrocytes (**Figure 1**; Liddelow et al., 2017). These C3-producing cells fail to provide metabolic support to neurons (Goetzl et al., 2018) and oligodendrocytes (Itoh et al., 2017; Tassoni et al., 2019), induce nodal loss, and impair myelin deposition (Ingersoll et al., 2010; Brennan et al., 2015). In addition, C3 can bind to myelin on oligodendrocytes and exacerbate EAE (Jégou et al., 2007). Of interest, increased astroglial production of C3 has also been linked to the progression of MS (Bhargava et al., 2021). Surprisingly, Guttenplan et al. (2021) demonstrated that C3 expression of cultured astrocytes did not result in the death of oligodendrocytes *in vitro*. Additionally, during both spontaneous- and drug-induced remyelination in a CPZ model, astroglial subpopulations expressing C3 in combination with possible myelin-beneficial/neuroprotective factors S100a10, Stat3, and Timp1 were observed (Silva Oliveira Junior et al., 2022), suggesting alternative roles for this complement protein, which may be context-dependent.

Sterile alpha and toll-interleukin receptor (TIR) motif containing 1

Sterile alpha and toll-interleukin receptor (TIR) motif containing 1 (Sarm1) is the key marker of axonal loss in Wallerian degeneration (Gerdts et al., 2015)

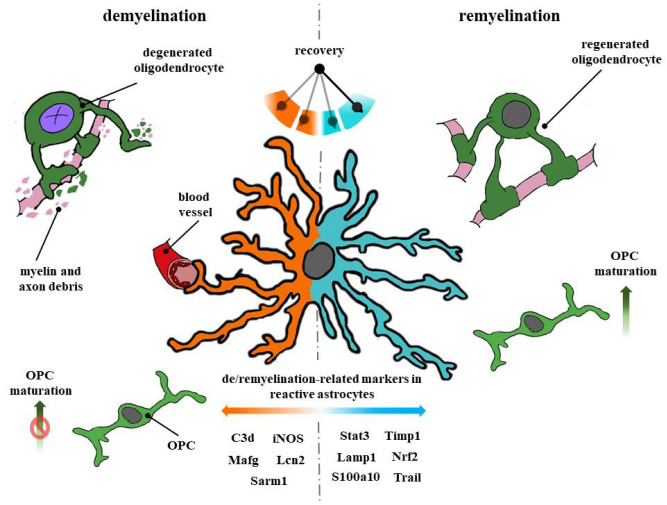

Figure 1 | **Molecules expressed by reactive astrocytes during de- and remyelination of the central nervous system.**
Reactive astrocytes are a heterogeneous cell population. This is highlighted by the distinct pattern of molecules these cells can express and release during disease. Such molecules can be either related to demyelination, oligodendrocyte degeneration, and impairment of OPC maturation (orange branch; e.g., C3/C3d, Mafg, iNOS, Lcn2, Sarm1) or to remyelination, OPC maturation and oligodendrocyte regeneration (blue branch; e.g. Stat3, Timp1, Lamp1 and Trail, Nrf2, S100a10). Future studies and therapies could focus on steering the pendulum of reactive astrocyte subpopulations towards a remyelinating- and overall more beneficial phenotype (blue branch) to promote recovery. Created using GIMP (GNU Image Manipulation Program, free and open-source editor), ArtFlow Studio App, and Microsoft PowerPoint. C3/C3d: Complement factor 3d; iNOS: inducible nitric oxide synthase; Lamp1: lysosome-associated membrane glycoprotein 1; Lcn2: lipocalin 2; Mafg: MAF bZIP transcription factor G; OPC: oligodendrocyte precursor cell; S100a10: S100 calcium-binding protein a10; Sarm1: sterile alpha and toll-interleukin receptor (TIR) motif containing 1; Stat3: signal transducer and activator of transcription 3; Timp1: tissue inhibitor of metalloproteinases 1; Trail: tumor necrosis factor-related apoptosis-inducing ligand. Green upward arrows: OPC maturation; orange circle with diagonal stroke: blocked/impaired due to demyelination-related markers.

and one of the fundamental enzymes that regulate demyelination in EAE (Jin et al., 2022) and neuromyelitis optica (Herwerth et al., 2022). Specific deletion of Sarm1 in astrocytes using GFAP and Aldh1L1 drivers, resulted in lower infiltration rates of $CD45^+$ cells into the spinal cord, in upregulation of glial cell line-derived neurotrophic factor and downregulation of NF-κB expression (Jin et al., 2022), all of which correlate with improved EAE outcomes. Interfering with glial cell line-derived neurotrophic factor expression in these knockout mice resulted in increased NF-κB protein levels, decreased myelin basic protein protein expression in the spinal cord, and overall worsened EAE clinical scores (Jin et al., 2022), hence strongly supporting a role of astrocytic Sarm1 expression in demyelination.

Lipocalin 2

Lipocalin 2 (Lcn2) is an inflammatory modulator, expressed by neurons, microglia, and astrocytes and suggested to be involved in demyelinating pathologies (Nam et al., 2014; Gasterich et al., 2022). Lcn2 is increased in progressive MS and is seen to inhibit remyelination *in vitro* (Al Nimer et al., 2016). Similarly, in EAE, full genetic ablation of Lcn2 reduced demyelination by decreasing the production of matrix metalloproteinases (Nam et al., 2014). In contrast, recent findings showed that Lcn2 deficient mice under acute CPZ-mediated demyelination exhibit a higher degree of T cell infiltration, loss of oligodendroglial lineage cells, and increased levels of demyelination (Gasterich et al., 2022). Lcn2-deficient EAE mice instead demonstrated no change in their clinical outcomes (Gasterich et al., 2022). These findings support a role for Lcn2 in early demyelination and lesion formation. While Lcn2 expression has been reported to be upregulated in astrocytes in optic neuritis in EAE (Chun et al., 2015; Tassoni et al., 2019), a specific role of astrocytic Lcn2 expression in demyelination or remyelination has, however, not been assigned yet.

Signal transducer and activator of transcription 3

Signal transducer and activator of transcription 3 (Stat3) is a key regulator of reactive astrocytes across different CNS pathologies (see **Figure 1**; Ben Haim et al., 2015; Sofroniew, 2020; Escartin et al., 2021; Abubakar et al., 2022; Choi et al., 2022) and its expression revealed to be important upon injury or disease. Seminal studies in spinal cord injury demonstrated that in *Stat3* knockout mice lesion spreading, demyelination, reduction in the border-forming response and impaired axonal regeneration occurred (Okada et al., 2006; Herrmann et al., 2008; Ben Haim et al., 2015; Anderson et al., 2016). Related to white matter, demyelination, and MS, a single study on lysolecithin-induced demyelination showed that astrocyte-specific ablation of *Stat3* decreased remyelination levels (Monteiro De Castro et al., 2015). Moreover, in EAE, proliferative border-forming reactive astrocytes were found to surround blood vessels and to prevent T cell and macrophage infiltration in the parenchyma (Spence et al., 2011; Wanner et al., 2013).

Lysosome-associated membrane glycoprotein 1 and tumor necrosis factor-related apoptosis-inducing ligand

Lysosome-associated membrane glycoprotein 1 (Lamp1) and tumor necrosis factor-related apoptosis-inducing ligand (Trail) were identified as important reactive astrocyte factors in EAE mice limiting disease progression induced via an interferon-gamma axis (Sanmarco et al., 2021). Both Lamp1 knockdown, as well as the absence of Trail expression in astrocytes, resulted in an increase in EAE severity by reducing $CD4^+$ T cell apoptosis. Trail expression, which is responsible for the induction of T cell apoptosis via the death receptor 5 was demonstrated to depend on natural killer cell-derived interferon-gamma expression (Johann and Waisman, 2021; Sanmarco et al., 2021). As this mechanism exhibits a positive impact on this subpopulation of reactive astrocytes, it is worth mentioning that interferon-gamma is also known to delay the differentiation of both grey and white matter OPCs (Lentferink et al., 2018) and to induce a proinflammatory/neurotoxic gene signature in astrocytes similar to the stimulation with C1q, IL1α, TNFα or in response to lipopolysaccharides (Hasel et al., 2021). Hence, depending on time and disease, the same factor can induce different responses of astrocytes, highlighting a heterogeneous yet also plastic feature of these cells during demyelination.

Mafg/Nrf2/Mat2a axis

Oxidative stress is one of the main processes behind oligodendrocyte loss in MS (Lassmann, 2019; Carlström et al., 2020). In astrocytes, Nrf2 and Mafg regulate the activation of the glutathione peroxidase (GPx) system (Hirotsu et al., 2012). The GPx system is crucial for antioxidant activity, metabolic transition, and DNA methylation in mammals (Nguyen et al., 2016; Carissimi et al., 2018) but was also found to control OPC maturation and survival of oligodendrocytes during demyelination (French et al., 2009; Hughes and Stockton, 2021). Astrocytic production of GPx4, a cofactor of the GPx system, prevents ROS overproduction and ferroptosis in EAE, thereby limiting cell loss (Hu et al., 2019). While Nrf2 was recently found to mark astrocytes with a non-neurotoxic activity in MS and EAE (Wheeler et al., 2020), Mafg upregulation is correlated with the production of proapoptotic molecules (Hirotsu et al., 2012; Wang et al., 2021). Wheeler et al. (2020) have shown that ablation of Mafg in astrocytes ameliorates the clinical course of EAE and directs astrocytes into a proremyelination state, as Mafg antagonizes the Nrf2 receptors in astrocytes, thereby blocking the activation of the GPx system. This mechanism is dependent on Mat2α, which controls DNA methylation, thereby preventing Nrf2 production that leads to aberrant Mafg expression. The authors concluded that the GPx system's reactivation in astrocytes depends on the GPx-Nrf2 pathway, which improves ROS catabolism in astrocytes, depriving oxidative stress and minimizing demyelination (Wheeler et al., 2020).

S100 calcium-binding protein a10

The calcium-binding protein S100 calcium-binding protein a10 (S100a10) has been reported to be expressed by a subset of "A2" reactive astrocytes that are associated with an anti-inflammatory gene signature (Zamanian et al., 2012; Liddelow et al., 2017). S100a10 expression in EAE was investigated and found to be reduced in the hippocampus mediated via the Nlr family pyrin domain containing 3 inflammasome (Hou et al., 2020). Of interest, treatment with MCC950, a selective inhibitor of Nlr family pyrin domain containing 3, resulted in increased levels of S100a10 expression, a concomitant reduction in numbers of C3-expressing (hence activated) astrocytes, and lead to overall improved EAE outcomes (Hou et al., 2020).

Tissue inhibitor of metalloproteinases 1

Tissue inhibitor of metalloproteinases 1 (Timp1) is an extracellular protein and endogenous regulator of matrix metalloproteinases. It is well documented that astrocytes secrete Timp1 in response to myelin injury (Pagenstecher et al., 1998; Nygårdas and Hinkkanen, 2002; Crocker et al., 2006; Moore et al., 2011), and global Timp1 ablation has been shown to impair spontaneous remyelination during EAE (Crocker et al., 2006). It has also been observed that OPCs treated with conditioned media from Timp1-deficient astrocytes are inhibited in their differentiation (Moore et al., 2011). It was furthermore shown that astrocyte-derived Timp1 promotes OPC maturation into oligodendrocytes and that astrocyte-specific ablation of this molecule impairs spontaneous myelin repair in demyelinated mice (Houben et al., 2020). More recently, Timp1-positive astrocytes were detected to occur specifically within white matter tracts following lipopolysaccharide application, a model mimicking bacterial infection, which suggests region-specific roles or manifestations of this astroglial phenotype (Hasel et al., 2021).

Repairing Multiple Sclerosis: How to Modulate Repair via Reactive Astrocytes?

It is clear that reactive astrogliosis is inherently heterogenic (Sofroniew, 2020; Escartin et al., 2021), and it is therefore of interest to develop strategies that target disease promoting cell types and direct them to a proregenerative state. Drug repurposing studies as well as small molecule therapies are possibly the most promising strategies to manipulate astrocyte types/states in MS (Gorter and Baron, 2022). Here we will discuss a few examples of drugs that can alter the balance of demyelinating and remyelinating astrocyte types.

Dimethyl fumarate induces Nrf2, which is essential for redox balance. In EAE, dimethyl fumarate treatment was shown to prevent axonal loss and demyelination (Yadav et al., 2021). Drug treatment reduced cytotoxic macrophages and was shown to diminish C3 protein deposition in the spinal cord as well as to limit the number of C3-expressing astrocytes (Yadav et al., 2021).

Siponimod is a functional agonist of the sphingosine-1 phosphate receptors (S1PR1 and S1PR5). In lysolecithin-induced demyelination, siponimod treatment was shown to attenuate demyelination (O'Sullivan et al., 2016). This effect was suggested to be astrocyte-dependent, as astrocytes showed internalization of S1PR1 and S1PR5 upon lipopolysaccharide treatment *in vitro* as well as during lysolecithin-dependent demyelination *in vivo* (O'Sullivan et al., 2016). Similar to dimethyl fumarate, siponimod also results in astrocyte-specific upregulation of Nrf2 and downregulation of NF-κB (Colombo et al., 2020), suggesting possible alteration of astrocyte types.

Finally, it was observed that the administration of the corticosteroid medrysone (hydroxymethylprogesterone) in mice subjected to CPZ-dependent demyelination resulted in improved oligodendrocyte recovery, node formation, and axonal remyelination. As a specific enhancement of reactive astrocytes that expressed C3 in combination with Stat3, S100a10 or Timp1 was observed, the drug, however, did not affect primary OPC maturation; hence myelin repair effects were directly assigned to medrysone's ability to modulate astrocyte profiles (Silva Oliveira Junior et al., 2022).

These few findings strongly suggest that drug-based therapies aiming at a direct modulation of reactive astrocyte types, indeed change their biochemical signatures towards more neuroprotective/neuroregenerative profiles and thus support tissues where repair is scarce. Other therapeutic strategies to promote CNS repair taking advantage of astrocytic plasticity and functional diversity constitute the direct transplantation of astroglial lineage cells (primary astrocytes, precursor- or induced pluripotent stem cell-derived astrocytes) or trans-differentiation approaches as reviewed by Hart and Karimi-Abdolrezaee (2021).

Concluding Remarks

Although the full spectrum of astrocyte types in MS has not been defined, a few studies have been conducted to link transcriptional and functional identity. Understanding the mechanisms leading to heterogeneity or plasticity among reactive astrocytes could be crucial to develop specific treatments that might be able to address the still clinically unmet need, fostering neuroregeneration in the injured and diseased CNS. Recent findings have shown that modulation of reactive astrogliosis is possible, at least by certain (repurposed) drugs, and that such a modulation is able to generate a repair outcome. This observation should therefore prompt additional investigations using broad substance libraries in order to fully explore the pharmacological potential of steering astrocytes specifically. Moreover, transcriptome and proteome responses of reactive astrocytes after drug exposure might help in aligning these molecular signatures with functional phenotypes – a correlation, which is still insufficiently understood.

Author contributions: *MSOJ and LR equally performed the majority of data search, data collection, and data analysis, and were equally involved in text writing, figure design, and manuscript revision. ED and IK contributed to text writing and data search. MF and PK supported the data search, discussed findings, conceived the final manuscript, took the final decision for submission, and were also responsible for funding acquisition, and revision of the text, content organization, and figure composition. All authors read and approved the final version of the manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Data availability statement: *Not applicable.*

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C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y