1 **The role of astrocytes in remyelination**

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Abstract

Remyelination is the regeneration of myelin sheaths following demyelination. This regenerative process is critical for the re-establishment of axonal conduction velocity and metabolic support to the axons. Successful remyelination in the central nervous system (CNS) generally depends on the activation, proliferation and differentiation of oligodendrocyte progenitor cells (OPCs). However, other cell types play critical roles in establishing where a lesion is conducive for regeneration. In the last few years, several studies have described beneficial and detrimental roles played by astrocytes in remyelination. This review will discuss recent developments in the concept of astrocyte reactivity, what is known about the astrocytic contribution to remyelination and highlight future avenues of investigation.

Keywords: oligodendrocyte; myelin; astrocyte; microglia; ageing; remyelination; progenitor

Myelin and the importance of remyelination

In the CNS, myelin is generated by oligodendrocytes and is composed of lipid-rich, tightly overlapping membranous extensions which ensheath axons. This provides the axon with an insulating layer, increasing its resistance and decreasing its capacitance, thereby reducing radial loss of electrical current during the propagation of action potentials along the axon. As a result, action potentials only need to be actively regenerated at specialised high-density clusters of ion channels between segments known as nodes of Ranvier. Therefore, myelination of axons both greatly reduces the energy required and increases the speed with which axons can propagate action potentials per unit distance [1]. Monocarboxylate transporters on the oligodendrocyte cell membrane allow lactate transport to the axon, facilitating ATP production via oxidative phosphorylation [2].

Unlike neurons, oligodendrocytes and their myelin sheaths can be regenerated following their loss, a process known as remyelination. Remyelination occurs in both animal models of demyelination and in humans with demyelinating diseases such as multiple sclerosis (MS) [3]. The regenerative response following demyelination often involves the generation of new oligodendrocytes and subsequent formation of new myelin sheaths. In contrast to most other neural cell types, new oligodendrocytes can be generated throughout life via the activation of a pool of tissue resident adult progenitor cells known as oligodendrocyte progenitor cells (OPCs). Upon demyelination, OPCs in the vicinity of the lesioned area become “activated” – an umbrella term for a series of changes which allow them to migrate to and proliferate within the lesion and differentiate into new mature oligodendrocytes. Activation of OPCs involves, *inter alia*, the upregulation of transcription factors such as Sox2 and Tcf4, the former of which sustains proliferation with the latter being critical for differentiation [4-7]. The increased expression of growth factors within the lesion, such as fibroblast growth factor 2 (FGF2) and platelet-derived growth factor (PDGF), promotes the proliferation of OPCs, which differentiate into oligodendrocytes, expressing myelin genes in a manner dependent on the enhancer binding activity of myelin regulatory factor [8, 9]. These newly formed oligodendrocytes then ensheath demyelinated axons with new myelin [10, 11]. Although remyelination often occurs through the

proliferation and differentiation of OPCs into oligodendrocytes, two recent studies have indicated an alternative mechanism in which remyelination occurs via new process formation by existing oligodendrocytes [12, 13]. Relatively little is known yet about this form of remyelination, and in this review we will focus on the former, more thoroughly understood process of remyelination by differentiating OPCs.

Many other cell types play key roles in regulating the process by which OPCs give rise to new remyelinating oligodendrocytes. Activated microglia and infiltrating monocyte-derived macrophages are essential for remyelination as they secrete important growth factors for OPC proliferation and differentiation as well as the phagocytic removal of remyelination-inhibiting myelin debris [14, 15]. In addition to the involvement of innate immunity, regulatory T cells, pericytes, and axons also influence remyelination [16-18].

This article will review the recent literature examining the contribution of astrocytes to remyelination. It will include an overview of the latest developments in astrocyte reactivity and polarisation, a discussion of the permissive and inhibitory roles played by astrocytes during remyelination, and highlight age-related changes in astrocyte function that may impact remyelination. We propose a model reconciling when the detriments of astrocytes may outweigh their benefits and outline potential therapeutic strategies to harness these cells for regeneration.

Astrocyte development and phenotypic plasticity

In mammals, astrocytes arise from radial glial cells in the ventricular zone [19]. In mice, this differentiation occurs at approximately embryonic day 12.5 in the mouse spinal cord and embryonic day 16 in the mouse brain in which migration and asymmetric proliferation produce clusters of immature astrocytes [19-21]. These immature astrocytes undergo a second wave of local symmetric proliferation to establish a mature population of astrocytes [19]. During development, astrocytes are critical for successful myelination, secreting several growth factors required for oligodendrogenesis [20]. In adulthood, astrocytes are regionally diverse, forming non-overlapping tiles within the CNS and are important for many homeostatic functions such as

synapse formation, synaptic pruning and modulation of neurotransmitters such as glutamate [22, 23]. Additionally, they contribute to the formation and maintenance of the blood-brain barrier and provide glucose, lactate, and trophic factors to neurons [23]. They are also important for the brain's clearance mechanisms, such as the glymphatic system [24, 25]. Histological markers of astrocytes include nestin, vimentin, glial fibrillary acidic protein (GFAP), the glutamate transporter GLAST, the calcium binding protein S100b, and aldehyde dehydrogenase 1 family, member L1 (Aldh1L1) [23]. All astrocytes express Aldh1L1, whereas only subsets of astrocytes express the other markers [23].

Astrocyte reactivity

After injury to the CNS, astrocytes become reactive and upregulate cytoskeletal proteins such as GFAP and vimentin [22]. These reactive astrocytes, in which greater than one thousand genes are increased by more than twofold in mice, display cell body hypertrophy, upregulate various cytokines and chemokines, and can proliferate [26-28]. A study conducted in mice showed that this rapid response is transient, with most genes showing a decrease in expression within 1 week after injury [26]. Preventing the acute formation of reactive astrocytes in a traumatic injury mouse model results in greater axonal dieback, suggesting that the early formation of reactive astrocytes is neuroprotective and helps limit damage, if not directly supporting axonal regeneration [29]. The acute astrocyte response in demyelinating injuries can support myelin regeneration. For example, reactive astrocytes in acute MS lesions, many of which show some degree of remyelination, upregulate several remyelination-signalling factors [30]. However, in both traumatic and demyelinating injuries, reactive astrogliosis can evolve into the formation of a dense, complex and transcriptionally inactive astrocytic scar characterised by a dense meshwork of astrocytic processes with significant tissue reorganization that fails to resolve [22, 30-32]. In neither traumatic nor demyelinating injury does the astrocytic scar support regeneration, but in the case of demyelinating injury it can be seen as the consequence of regeneration (remyelination) failure and not its cause.

Recent studies in mice have shown that the nature of the reactive astrocyte response depends on the initial stimulus [26, 33]. In a model of neuroinflammation, in which the bacterial endotoxin lipopolysaccharide (LPS) is administered, the formation of a neurotoxic astrocyte phenotype occurs which is dependent on LPS-stimulated microglia secreting tumour necrosis factor- α , complement component 1q (C1q), and interleukin-1 α [33]. This astrocyte phenotype, which has been termed A1 (but see below discussion of controversies around this terminology), was shown to inhibit OPC proliferation and differentiation in addition to displaying toxicity to both neurons and oligodendrocytes. In contrast, in a model of ischemia, transcriptomic analysis demonstrates an astrocytic signature that appears neuroprotective [26]. This distinct transcriptional state, sometimes termed A2, is associated with the upregulation of genes encoding thrombospondins and neurotrophic factors [33]. Although this genetic signature suggests it might be pro-regenerative, no studies so far (to our knowledge) have provided any functional evidence that this is the case. An in-depth proteomic analysis of the secretome would be critical to validate these transcriptomic signatures [34]. Moreover, the ischemic cues resulting in the A2 phenotype are not yet defined, and it is not known whether this state arises in other physiological or pathological contexts. It is unknown what astrocytic state naturally arises following demyelination, in which myelin debris, apoptotic cell bodies, and damage associated molecular patterns may induce the activation of a unique astrocytic phenotype not yet described. Indeed, there is ongoing debate as to whether the two A1/A2 astrocyte phenotypes provide a full and accurate description of all reactive astrocytes, or whether they exist along a spectrum beyond the two A1/A2 states already described [22]. A recent study in mice, for instance, showed that activation of the unfolded protein response in astrocytes results in a neurotoxic state that is distinct from the A1 and A2 signatures [35]. Moreover, a study comparing the molecular signature of astrocytes in Huntington's disease and two mouse models of Huntington's disease did not find any evidence of an A1 astrocyte signature [36]. Instead, this group found a unique astrocyte molecular signature consisting of 62 genes in both the mouse models and the human specimens. Furthermore, as the microglia response following demyelination in mice transitions from a pro-inflammatory to an immunoregulatory state, it is unknown whether such a transition between states occurs in the astrocyte response to demyelination [15]. This transition in the

murine microglia population seems to be dependent on the necroptosis of the initial wave of pro-inflammatory cells, inviting further questions on how this sequence of events may influence the reactive astrocyte population [37].

Astrocytes in demyelinating diseases

Astrocytes are thought to play a major role in MS and especially in neuromyelitis optica (NMO) [38]. In MS, the astrocytic signature is dependent on the type of lesion [39]. In acute active lesions, there is an immune cell infiltration along with hypertrophic astrocytes expressing increased levels of GFAP and upregulation of several pro-inflammatory cytokines, chemokines as well as remyelination-signalling molecules [30, 40]. Remyelination is observed to variable degrees in acute active lesions, suggesting that the astrocyte response is favourable for remyelination in these types of lesions [9]. In contrast, inactive lesions are associated with a lower degree of inflammation with extensive demyelination and axonal loss. Astrocytes observed in these lesions typically have small somata with long filamentous processes forming an astrocytic scar and are transcriptionally inactive [30, 38]. NMO is another demyelinating disease characterized by antibodies against the aquaporin 4 water channel present on astrocytes [41]. This disease is characterized by astrocyte loss, immune cell infiltration, demyelination, and axonal degeneration. Loss of astrocytic endfeet on blood vessels leads to vascular permeability. In addition to MS and NMO, astrocytes have also been implicated in a variety of leukodystrophies, as has been extensively reviewed elsewhere [42].

Beneficial roles of astrocytes in remyelination

Several studies over the last three decades have explored the role astrocytes play in models of remyelination and have shown that astrocytes can be both beneficial and detrimental to the remyelination process (Table 1; Figure 1). One of the first studies to show a pro-remyelinating role for astrocytes was one in which astrocytes were transplanted into an ethidium bromide-induced model of CNS demyelination in rats characterised by loss of astrocytes and extensive Schwann cell remyelination [43]. Following astrocyte transplantation, a significant increase in host oligodendrocyte remyelination was observed, suggesting the ability of astrocytes to

promote remyelination by these cells. Subsequent to this study, it was found that the astrocytic expression of GFAP correlated with the expression of growth factors implicated in OPC maturation. Astrocytes responding to demyelination in the rat spinal cord displayed a similar spatial and temporal profile as platelet-derived growth factor-A, fibroblast growth factor 2, transforming growth factor- β , and insulin-like growth factor-1 [44]. In this study, GFAP mRNA was associated with these growth factors in the recruitment phase of remyelination, whereas at later stages growth factor expression was coupled to areas with low GFAP mRNA expression. In a more recent study using dietary cuprizone to induce demyelination in the mouse corpus callosum, it was found that astrocyte-derived tissue inhibitor of metalloproteinases-1 promoted remyelination [45].

In addition to the secretion of favourable factors for remyelination, astrocytes may also play a role in recruiting phagocytic microglia in areas of demyelination [46]. Myelin debris inhibits remyelination, and the clearance of myelin debris by phagocytic macrophages/microglia is essential for remyelination to proceed efficiently [47-49]. Inactivation of astrocytes in mice led to reduced myelin clearance following demyelination and a subsequent reduction in remyelination efficiency [46].

Although not definitively shown in the context of remyelination, astrocytes are critical components of cholesterol metabolism and provide cholesterol to neurons. As astrocytes are the major source of cholesterol and its CNS carrier, apolipoprotein E, it is feasible that astrocytes may also transfer cholesterol to maturing OPCs during a phase of remyelination where cholesterol would be critical for myelin synthesis [50]. Indeed, a recent study in mice examining the role of reverse cholesterol transport in macrophages/microglia implicates a role for cholesterol mobilisation within the demyelinated lesion [51].

Astrocytes and Schwann cell remyelination of the CNS

In some regenerative contexts, CNS remyelination can also be performed by Schwann cells in addition to oligodendrocytes [52]. It was long thought that Schwann cells within CNS lesions were

derived from the adjacent peripheral nerve roots after a loss in the integrity of the *glia limitans*. However, genetic fate mapping **in mice** showed that the majority of remyelinating Schwann cells are derived from OPCs residing in the CNS [11, 52]. Although Schwann cell remyelination re-establishes conduction velocity within axons in the CNS, it is not known whether Schwann cells can offer the metabolic support that oligodendrocytes normally provide to CNS axons [53]. It is also not well understood what molecular cues dictate the fate choice of OPCs. There is evidence to suggest that astrocytes can influence whether OPCs differentiate into oligodendrocytes or Schwann cells in the context of injury (Table 1, Figure 1). Transplantation of OPCs into X-irradiated ethidium bromide lesions **in rats** that are devoid of astrocytes results in Schwann cell remyelination [54]. When OPCs are transplanted together with astrocytes, the appearance of Schwann cells is greatly reduced. Similarly, engraftment of OPCs overexpressing an inhibitor of bone morphogenetic proteins (BMP) reduced Schwann cell differentiation, suggesting that astrocytes may be influencing fate choice partially through BMP inhibition. Another study made use of a conditional astrocyte-specific pStat3 knockout mouse to prevent the formation of reactive astrocytes following demyelination [55]. Inactivation of reactive astrocytes resulted **ed** in a significantly greater degree of Schwann cell remyelination, supporting the hypothesis that astrocytes favour oligodendrocyte remyelination over Schwann cell remyelination [55]. Furthermore, it was recently shown that OPCs in proximity to the vasculature in the absence of astrocytes are more likely to differentiate into Schwann cells [56]. This study found that astrocytes express the dual BMP/Wnt antagonist *Socsd1* and the lack thereof favours a Schwann cell fate choice by OPCs. Revealing the molecular cues that lead to Schwann cell remyelination and its functional significance may lead to new therapeutic strategies to harness this cell type for CNS remyelination.

Inhibitory roles of astrocytes in remyelination

Some of the detrimental roles described for astrocytes is through secretion of inhibitory molecules and extracellular matrix components (Table 1; Figure 1). After injury to the CNS, several cells including reactive astrocytes, microglia/macrophages and pericytes secrete extracellular matrix components [57]. Members of this extracellular matrix include the

chondroitin sulphate proteoglycans, hyaluronan, tenascin-C and fibronectin, all of which have been shown to inhibit remyelination and are present in lesions from MS patients [58]. Inhibiting the synthesis of chondroitin sulphate proteoglycans accelerates remyelination in a mouse model of demyelination [59]. Furthermore, a recent study conducted in both mice and rats described that the stiffness of the CNS increases with age and that this causes decreased OPC proliferation and differentiation [60]. In this study, when ageing OPCs were transplanted into young brains, they proliferated to a comparable extent as neonatal OPCs, while when young OPCs were transplanted into aged brains, their proliferation was significantly reduced. It was further found that the mechanosensitive ion channel Piezo1 was a critical mediator of OPC response to substrate stiffness: silencing of the mechanosensitive channel Piezo1 in ageing OPCs resulted in the restoration of OPC proliferation and differentiation in the context of a stiffer substrate. Importantly, this study established that the age-related decline in OPC function is highly influenced by the extrinsic microenvironment. Although not addressed in this study, the ageing astrocyte phenotype may be a critical contributor to the age-related increase in mechanical stiffness. Indeed, some groups have reported an increase in astrocyte-associated extracellular matrix molecules with ageing in nonhuman primates, rats, and mice, such as hyaluronan and aggrecan, as well as reporting an increase in the expression of certain protease inhibitors [61-64]. In addition to influencing the extracellular matrix, astrocytes express endothelin-1, a molecule which has been shown to be inhibitory to remyelination through notch activation in mice [65]. Astrocytes responding to endothelin-1 upregulate the Notch1 receptor ligand, jagged 1, resulting in an inhibitory interaction between astrocytes and OPCs [65, 66].

Beneficial or detrimental?

It has been the convention to assign roles for astrocytes (and indeed other cells types) as being either beneficial or harmful. However, this is a rather binary view of what is likely to be a much subtler and complex reality that depends on the temporal and dynamic interplay between cells involved in remyelination. So, is it really helpful terminology? As remyelination is a tightly orchestrated sequence of events contingent on a multitude of cell types, astrocytes likely serve different functions at different stages of remyelination in synchrony with the other cell types.

Astrocytes potentially become detrimental when the timing and precision of this sequence of events is knocked out of synchrony, a concept we originally proposed as the 'dysregulation hypothesis' of remyelination failure (Box 1) [67]. Thus, what may appear to be detrimental may only be so in certain contexts. One such context where this precise control of remyelination could be dysregulated is ageing. The following section will discuss the effect of ageing on remyelination and how the balance may be tipped towards a detrimental astrocytic phenotype.

The effect of ageing on remyelination and astrocytes

As with most other regenerative processes, remyelination efficiency declines with age [3, 68]; however, the endogenous mechanisms within glial cells which lead to this decline are still not well understood. Failure of remyelination is characteristic of the later stages of chronic demyelinating diseases, such as MS [69]. Indeed, lesions from chronic stages of MS often contain cells of the oligodendrocyte lineage which have failed to differentiate [70, 71]. Depending on age of onset, the progression of MS can involve a significant period of subclinical disease and a subsequent relapse remitting phase characterised by bouts of symptoms followed by recovery, reflecting the intrinsic ability of the younger brain to effectively regenerate lost myelin [69]. However, regardless of the age of onset, most patients transition to the progressive stage at 40-45 years of age [72], which may reflect the remyelination efficiency declining below a critical point beyond which myelin is no longer being regenerated fast enough to prevent axon degeneration.

Mouse and rat studies have shown that both OPC proliferation and differentiation become less efficient with age [73-75]. However, enhancing proliferation of OPCs does not lead to increased remyelination of lesions [76]. This led to the suggestion that the main bottleneck for OPCs in the remyelination response of the aged brain is their impaired ability to differentiate into functional oligodendrocytes [3]. Indeed, this reduced capacity of OPCs to differentiate and produce myelin is also observed during normal ageing [77, 78]. But non-cell autonomous mechanisms are also involved. For example, macrophages exhibit an age-dependent decline in their ability to effectively clear myelin debris, both via phagocytosis [79, 80] and lysosomal degradation [81],

and ageing macrophages and microglia exhibit defective cytokine secretion following demyelinating injury [82].

There are currently no studies (to our knowledge) which have directly investigated the ageing astrocyte response in the context of demyelination and remyelination. However, several studies examining tissue from rodents, rhesus macaques, and humans have assessed the effects of normal ageing on the astrocyte population. Most notably, ageing astrocytes appear more reactive, displaying an upregulation in cytoskeletal proteins associated with astrocytes responding to injury, in addition to displaying hypertrophic cell bodies with shorter processes [83-86]. In addition to these studies, recent investigations in mice have used RNA sequencing to examine the genetic changes that occur in astrocytes with ageing [87, 88]. Corroborating the morphological studies, these gene expression studies also show a shift in the astrocyte signature to a more reactive state, albeit with heterogeneity dependent on the CNS region analysed [87, 88]. In addition to an upregulation in cytoskeletal protein genes such as GFAP, these studies noted an increase in genes associated with the complement components C3 and C4b. These complement components are important for processes such as synapse elimination and have been implicated in age-related neuronal loss and several neurodegenerative diseases [89]. Ageing astrocytes were also found to have a decrease in transcripts encoding cholesterol synthesis enzymes [87, 88] (Figure 2). Given that cholesterol is important for myelin synthesis during remyelination, the decrease in enzymes regulating cholesterol synthesis would be predicted to have a negative effect during this regenerative process. Overall, these studies suggest that like ageing microglia, ageing astrocytes may become more inflammatory, a state that has been termed “inflammaging” [82]. As mentioned above, however, future studies should examine the astrocyte secretome over the lifespan of the organism to validate many of the transcriptomic changes identified in these studies. As astrocytes significantly modulate the various niches they occupy within the CNS through the secretion of various classes of molecules, identifying how these secreted products change with age will undoubtedly uncover new targets that might be harnessed to provide new therapeutic avenues. Future studies using models of demyelination and remyelination are required to directly examine how the ageing astrocyte

response influences this regenerative process. Given that ageing microglia are primed to be more pro-inflammatory after demyelination, it seems plausible that astrocytes may undergo a similar process, potentially contributing to greater tissue injury and reduced repair.

Harnessing astrocytes to promote remyelination

Several groups have conducted drug screens to identify clinically-approved medications that can directly enhance OPC differentiation to promote remyelination [90-92]. Although such screens have resulted in several promising compounds, the approach does not take into account the inhibitory nature of the lesion microenvironment or the effect of ageing. In fact, when several of these medications are added to ageing OPCs or to OPCs plated on CSPGs, they are unable to enhance OPC maturation [59, 74]. It is, therefore, critical to take the ageing microenvironment into account when attempting to enhance remyelination. As astrocytes are essential components of the lesion microenvironment, therapeutic strategies which target astrocyte function offer additional opportunities to promote remyelination. Since astrocytes are secretory cells, one approach may be to target various aspects of the astrocytic secretome. For instance, pharmacological inhibition of CSPG synthesis accelerated remyelination in a focal demyelination model in young adult mice [59]. Another approach is to neutralise the effect of astrocyte-derived endothelin-1 by administering a pharmacological antagonist against the endothelin receptor [65]. This strategy also resulted in accelerated remyelination in young adult mice subject to lysolecithin demyelination. As Stat3 signalling in astrocytes promotes trophic support, targeting this pathway may be a feasible approach in the ageing context, where it was shown in rats a delay in growth factor production [22, 68, 93]. A deeper understanding of the ageing astrocyte response in remyelination will most likely reveal further therapeutic targets to enhance remyelination.

Concluding remarks

Astrocytes play a critical role in supporting remyelination. Activated astrocytes secrete several growth factors important for OPC proliferation and differentiation, and they signal to microglia to clear myelin debris. As astrocytes provide cholesterol to neurons, they may also be an important source of cholesterol for maturing OPCs. Despite these benefits, astrocytes have also

been associated with the secretion of factors which inhibit remyelination such as several extracellular matrix molecules. As remyelination is a tightly regulated process influenced by several cell types, astrocytes likely serve different roles at different stages to allow remyelination to proceed efficiently. Dysregulation of this sequence of events leads to remyelination failure and is likely influenced by an astrocyte phenotype that is more detrimental than beneficial. The ageing CNS is an example where remyelination becomes dysregulated. Addressing how the ageing astrocyte responds to demyelination may reveal new therapeutic targets to enhance remyelination in this context (see Outstanding Questions).

Box 1 – Reconciling the differing roles of astrocytes in remyelination

Astrocytes have been shown to be both beneficial and detrimental in remyelination. What determines when these cells are permissive or inhibitory? One hypothesis is the ‘dysregulation hypothesis’ [67]. As remyelination proceeds efficiently in the young CNS, reactive astrocytes are presumably beneficial to the process through the secretion of both permissive and inhibitory factors at different stages in a tightly regulated sequence of events. Moreover, the timely interaction of reactive astrocytes with other cells such as microglia and infiltrating macrophages is critical in establishing a microenvironment that is conducive for OPC proliferation and differentiation. As remyelination starts with the sufficient proliferation of OPCs to provide enough oligodendrocytes for myelin regeneration, it is important that mitogens and differentiation inhibitors would be upregulated in this first stage. Indeed, reactive astrocytes and macrophages/microglia are a major source of these molecules. Once enough OPCs have proliferated to allow for a sufficient number of oligodendrocytes to be produced, differentiation inhibitors are suppressed and instead molecules that promote differentiation are upregulated. An example of such a factor is activin-A, a molecule secreted by immunoregulatory microglia at the onset of differentiation following the initial peak of pro-inflammatory cells [15]. Furthermore, as both pro- and anti-inflammatory microglial factors such as tumour necrosis factor- α , complement component 1q (C1q), interleukin-1 α , nitric oxide, extracellular vesicles, and other molecules influence astrocyte polarization as well as survival, it is conceivable that the

astrocytic phenotypic state may change as a consequence of microglia polarization [33, 94-98]. Remyelination likely fails when this tightly regulated process and intercellular interaction becomes dysregulated. Such an instance where this occurs is during ageing, where several cells in the microenvironment become senescent and dysfunctional. The age-related delay in macrophage/microglia recruitment, growth factor secretion, and phagocytosis not only delays the OPC response, but also likely alters the reactive astrocyte response [48, 80, 93, 99, 100]. Furthermore, as ageing microglia have a propensity to be more pro-inflammatory, they likely also promote a reactive astrocyte phenotype that is more pro-inflammatory, tipping the balance of when astrocytes are toxic rather than regenerative [87, 101]. According to the dysregulation hypothesis, it is in this context when normal permissive or inhibitory cues important for efficient remyelination become unsynchronised, resulting in cells appearing more detrimental than beneficial.

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Figure Legends

Figure 1. Astrocytes secrete several factors that either promote or inhibit remyelination.

Astrocytes have been characterized to secrete several factors that are important for the proliferation of oligodendrocyte progenitor cells (OPCs), including the growth factors platelet-derived growth factor-AA (PDGF-AA) and fibroblast growth factor 2 (FGF2), as well as the cytokines interleukin-1 β (IL-1 β) and tumor necrosis factor (TNF). Astrocytes also promote OPC differentiation by producing ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), insulin-like growth factor-1 (IGF-1), CXCL1, and tissue inhibitor of metalloprotease-1 (TIMP-1). Astrocytes are known to be involved in cholesterol metabolism of neurons and other CNS cell types, but it remains to be tested whether astrocytic production of cholesterol positively impacts myelin synthesis in remyelinating oligodendrocytes. Astrocytes also produce inhibitory molecules such as chondroitin sulphate proteoglycans (CSPGs), hyaluronan, endothelin-1 (ET-1), fibronectin, tenascin-c, and jagged-1. Furthermore, astrocytes suppress Schwann cell differentiation from OPCs through the production of Socstdc1. Astrocytes also recruit monocytes through the production of CCL2 and microglia through the secretion of CXCL10.

Figure 2. Ageing modulates the astrocyte phenotype and may contribute to the age-related decrease in remyelination efficiency.

Ageing has been shown to modulate the astrocyte phenotype in various ways. Ageing astrocytes display an altered morphology (top schematic). Genomic analyses of ageing astrocytes display an upregulation of several markers characteristic of a pro-inflammatory astrocyte phenotype, including glial fibrillary acidic protein (GFAP), serine protease inhibitor 3n (Serpina3n), complement components C3 and C4b, the chemokine Cxcl10, and molecules involved in antigen presentation (H2-D1, H2-K1). Ageing astrocytes display a downregulation of genes associated with mitochondrial function and energy production (Ucp2, Cox8b, Atp5g1), antioxidant defence-related genes (Gpx8, Atox1), as well as cholesterol synthesis genes (Hmgcr). Furthermore, ageing decreases the efficiency of remyelination, and it is possible

660 that a detrimental ageing astrocyte phenotype contributes to this reduction in remyelination
661 capacity.

<i>Permissive roles of astrocytes in remyelination</i>		
<i>Function</i>	<i>Experiment</i>	<i>Reference</i>
Provide a conducive microenvironment for oligodendrocyte remyelination	Transplantation of astrocytes into ethidium bromide-induced lesions in the rat spinal cord	[43]
Source of PDGF-A, FGF-2, TGF-B, and IGF-1 to promote OPC maturation	Spatial and temporal examination of mRNA expression of growth factors following focal lysolecithin demyelination in the rat spinal cord	[44]
Recruit microglia to clear inhibitory myelin debris	Astrocyte ablation using GFAP-TK mice in cuprizone-induced demyelination of the corpus callosum	[46]
Source of TIMP-1 to promote remyelination	TIMP-1 KO mice in cuprizone-induced demyelination of the corpus callosum	[45]
<i>Inhibitory roles of astrocytes in remyelination</i>		
<i>Function</i>	<i>Experiment</i>	<i>Reference</i>
Source of ET-1 to inhibit remyelination	Astrocyte-specific knockout of ET-1 in the spinal cord of mice injected with lysolecithin	[65]
Secretion of inhibitory CSPGs	Pharmacological inhibition of CSPG synthesis in lysolecithin-induced demyelination of the mouse spinal cord	[59]
Production of fibronectin aggregates	Injection of astrocyte-derived fibronectin aggregates into lysolecithin-induced lesions of the rat	[102]
Source of inhibitory HMW hyaluronan	Injection of HMW hyaluronan into lysolecithin-induced lesions of the mouse corpus callosum	[103]
Secretion of molecules which are toxic to oligodendrocytes	Conditioned media taken from astrocytes stimulated by LPS-activated microglia	[33]
Abbreviations: PDGF-A, platelet-derived growth factor-A; FGF-2, fibroblast growth factor-2; TGF-B, transforming growth factor-B; IGF-1, insulin-like growth factor-1; GFAP, glial fibrillary acidic protein; TK, thymidine kinase; TIMP-1, tissue inhibitor of metalloproteinases-1; KO, knock-out; ET-1, endothelin-1; CSPGs, chondroitin sulphate proteoglycans; HMW, high molecular weight; LPS, lipopolysaccharide		

Table 1. Permissive and inhibitory roles of astrocytes in remyelination