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28 During the last decades, the production of myelin in the central nervous system (CNS)
29 has been the focus of a multitude of studies in the context of development or regeneration.
30 Oligodendrocytes, the cells synthesizing myelin in the CNS, were initially found in hind-jawed
31 fishes (Zalc and Colman, 2000;Hartline and Colman, 2007;Zalc, 2016). These cells derive from
32 oligodendrocyte progenitor cells (OPCs) occurring in several waves. In mice, the first wave
33 arises at embryonic day (E) 12.5 in the ventral domain of the ventricular wall in the developing
34 brain and spinal cord. The second one emerges more dorsally at E15.5 in both regions and the
35 last one arises specifically in the perinatal cortex around birth (Pringle and Richardson,
36 1993;Timsit et al., 1995;Trousse et al., 1995;Spassky et al., 1998;Olivier et al., 2001).
37 Unexpectedly, the destruction of one of these waves in the telencephalon induces the remaining
38 cells to compensate for the lost oligodendrocytes thus suggesting functional similarity. In
39 agreement with this observation, ventrally derived oligodendroglial cells strongly decline early
40 after birth in the postnatal dorsal forebrain and are replaced by dorsally derived cells, which
41 thus constitute more than 80% of oligodendroglial cells present in the adult corpus callosum
42 and cerebral cortex (Kessaris et al., 2006;Tripathi et al., 2011). Myelination itself progresses
43 according to typical sequences, which are spatially and temporally determined. In human, after
44 16 weeks of gestation, myelin can be detected in the fasciculus cuneatus, and shortly after
45 occurs in the cerebellar and pyramidal tracts. Then, myelination proceeds rapidly during the
46 first year from the occipital to the fronto-temporal lobes. Regions devoted to basic homeostasis
47 are proposed to be myelinated before areas involved in more intricate tasks like the frontal
48 cortex. Late myelinated areas are typically myelinated at a lower level than early myelinating
49 regions (Brody et al., 1987;Kinney et al., 1988). More recent data derived from serial
50 reconstructions of the adult mouse cortex showed that the degree of myelination can even vary
51 along a single axon. Thus, neurons located in superficial cortical layers exhibit both myelinated-
52 and large unmyelinated segments, contrasting with the pattern observed for instance in the
53 spinal cord or the optic nerve where myelinated axons display regular internodes (Tomassy et
54 al., 2014).

55 The finding that the CNS is able to regenerate myelin lost upon various types of insults
56 was observed much earlier than the characterization of oligodendrocyte and myelin generation.
57 Indeed, almost 60 years ago, occasional myelin sheaths was visualized a short time after
58 demyelination was induced into the subpial cord by repeated withdrawal and reinjection of
59 cerebrospinal fluid (Bunge et al., 1961). However, the demonstration that central remyelination
60 was able to restore secure conduction in the demyelinated spinal cord and to lead to functional
61 recovery was provided only two decades later (Smith et al., 1979). Since then, thousands of
62 publications were dedicated to this process notably in the aim to investigate how new OPCs are
63 recruited to the demyelinating area and differentiate into myelinating oligodendrocytes (Gallo
64 and Armstrong, 2008;Clemente et al., 2013;Domingues et al., 2016;Lloyd et al., 2017).

65 Although in both development and repair, the oligodendrocyte is the pivotal cell type
66 for myelin production, its function is widely influenced by the other glial cells, namely
67 astrocytes and microglia. This review is aimed at revisiting the present knowledge regarding
68 communication between oligodendroglial, astroglial and microglial cells in the context of
69 myelin development and regeneration with a specific focus on most recent advances.

70

71 **Astrocyte-oligodendrocyte communication in developmental myelin production**

72 In the mouse spinal cord and cerebral cortex, the first mature astrocytes expressing the
73 glial fibrillary acidic protein (GFAP) can be detected at the embryonic day (E) 12.5 and 16.5
74 respectively, thus before start of OPC maturation and axon myelination taking place during the
75 first three postnatal weeks (Miller et al., 1985; Qian et al., 2000). Like neurons and
76 oligodendrocytes, astrocytes are derived from the neuroepithelium from which they migrate
77 throughout the CNS along radial glia processes (Molofsky and Deneen, 2015).

78 **Astrocyte-derived trophic factors and cytokines control oligodendrogenesis**

79 The crucial role of astrocytes was initially related to the finding that these cells are the
80 main producers of platelet-derived growth factor (PDGF). Acting through its receptor PDGFR α ,
81 PDGF promotes OPC proliferation and mobility and, also inhibits OPC differentiation towards
82 mature oligodendrocytes, by generating a graded response requiring activation of the
83 phosphoinositide 3-kinase and/or phospholipase C γ pathways. Astrocyte-derived PDGF was
84 thus proposed to drive the clock that times oligodendrocyte development (Raff et al.,
85 1988; Richardson et al., 1988; McKinnon et al., 2005). Besides PDGF, astrocytes secrete other
86 growth factors. Brain-derived neurotrophic factor (BDNF) is namely required to potentiate
87 myelination during the early postnatal development as indicated by BDNF knockout
88 heterozygous mice, which exhibit delayed CNS myelination (Cellerino et al., 1997). In the same
89 line, under stress conditions such as those occurring during prolonged cerebral hypoperfusion
90 at birth, astrocyte-derived BDNF also supports OPC maturation in a TrkB-dependent manner
91 as shown *in vitro* in sublethal CoCl₂ exposition of OPC / astrocyte primary co-cultures and, *in*
92 *vivo*, in a transgenic mouse line in which BDNF expression was specifically downregulated in
93 astrocytes (Miyamoto et al., 2015). The observation that ciliary neurotrophic factor (CNTF)
94 synthesis by astrocytes starts at the onset of myelination in the rodent optic nerve (Stockli et
95 al., 1991; Dobra et al., 1992) led to suggest its physiological role on myelination, as well. The
96 strong pro-myelinating effects of CNTF and other members of the family such as leukemia
97 inhibitory factor (LIF) in myelinating co-cultures further supported this hypothesis. CNTF acts
98 on oligodendrocytes by favoring their final maturation via a mechanism involving the 130 kDa
99 glycoprotein receptor common to the CNTF family and transduced through the Janus kinase
100 (JAK) pathway (Stankoff et al., 2002). In contrast, other astrocyte-derived secreted proteins
101 negatively regulate oligodendrocyte biology. For instance, the chemokine CXCL1 transiently
102 expressed at a high level during spinal cord development signals through the chemokine
103 receptor CXCR2 expressed by immature OPCs. Migrating OPCs were proposed to enter the
104 presumptive white matter where they may encounter an environment in which astrocytes
105 transiently and locally express high CXCL1 levels. Through CXCR2, CXCL1 may inhibit
106 PDGF-stimulated OPC migration before subsequently increasing OPC proliferation in concert
107 with PDGF (Tsai et al., 2002).

108 **Astrocytes control the availability of cues regulating oligodendrocyte production**

109 Besides the secretion of trophic factors, astrocytes are also able to control the
110 bioavailability of oligodendrocyte-regulating cues (Fig. 1A). The best documented example
111 was provided by the capacity of astrocytes to control the concentration of the morphogen Sonic
112 Hedgehog (Shh) during OPC production in the optic nerve. Shh participates in the proliferation
113 and migration of OPCs during the colonization of this nerve (Merchan et al., 2007). The
114 multiligand receptor megalin, a member of the low density lipoprotein receptor family able to
115 bind Shh, was found to be exclusively expressed by astrocytes according to a dynamic pattern

116 paralleling optic nerve colonization by OPCs arising from the optic chiasm and migrating to
117 the retina. Indeed, when OPCs start their migration throughout the nerve at E14,5 in the mouse,
118 megalin is more widely distributed in the region close to the optic chiasm whereas the
119 distribution is reversed at E16.5 when the first OPCs reach the retina. Since, thereafter, megalin
120 was found to be weakly and uniformly expressed all along the nerve, this receptor was proposed
121 to control Shh internalization and its subsequent release at the suitable concentration during the
122 various steps leading to oligodendrogenesis (Ortega et al., 2012).

123 **Astrocyte integrity is required for proper myelination**

124 Consistent with the above findings, the requirement of astrocyte integrity for the normal
125 development of oligodendrocytes was shown by the analysis of transgenic mouse strains devoid
126 of GFAP expression. Although viable, GFAP knockout mice exhibit abnormal myelination
127 including the presence of actively myelinating oligodendrocytes in adults, nonmyelinated axons
128 in optic nerve, reduced myelin thickness in spinal cord and ultrastructural defects such as
129 loosening of myelin sheaths (Liedtke et al., 1996). More recently, the invalidation of the
130 transmembrane protein CD38, which possess ADP-ribosyl cyclase activity and is highly
131 expressed in astrocytes, was similarly reported to result in altered astrocyte maturation and
132 delayed oligodendrocyte differentiation during the postnatal development (Hattori et al., 2017).
133 Furthermore, physical interactions between oligodendrocytes and astrocytes appear to be also
134 required for myelination as shown by analysis of the role of connexins (Cx) 30 and Cx43 present
135 on astrocytes and forming gap junctions with Cx32 and Cx47 present on oligodendrocytes.
136 First, Cx47 mutants that cause the Pelizaeus–Merzbacher-like disease do not efficiently form
137 functional channels with Cx43 (Orthmann-Murphy et al., 2007). Second, the deletion of both
138 Cx47 and Cx30 in mice induces severe myelination defects including vacuole formation and
139 thin myelin sheaths as well as a decreased number of oligodendrocytes (Tress et al., 2012). A
140 mechanism possibly involved is proposed to be disruption of the metabolic support provided
141 by astrocytes to oligodendrocytes in agreement with the gap junction-mediated unidirectional
142 flux that transports the molecules preferentially from astrocytes to oligodendrocytes (Robinson
143 et al., 1993).

144 **Astrocytes are indispensable for axon myelination**

145 Accurate delineation of the molecular mechanisms supporting the role of astrocytes in
146 myelination itself has never ceased for the last decades. Among the most relevant findings, the
147 requirement of astrocytes for alignment and adherence of oligodendrocyte processes to axons
148 was shown by using cocultures of retinal ganglion cells and optic nerve oligodendrocytes that
149 led to propose a mechanism implicating neuroaminidase-mediated removal of polysialic acid
150 (PSA) from both cell types (Meyer-Franke et al., 1999). In agreement with this result, abolition
151 of the postnatal downregulation of PSA in oligodendrocytes from transgenic mice expressing
152 the polysialyltransferase ST8SiaIV under the control of the proteolipid protein promoter,
153 indicated that PSA downregulation is required for efficient differentiation of oligodendrocytes,
154 as well as for myelin formation and maintenance. However, *in vivo* implication of astrocytes is
155 still lacking (Fewou et al., 2007). Another link between astrocytes and myelination was
156 established by the demonstration that electrical activity in premyelinated axons increases
157 myelination after OPCs mature to a promyelinating stage via the activity-dependent release of
158 ATP from axons. ATP acts in a paracrine manner on astrocytes via the purinergic P2 receptor
159 and induces the release of the LIF cytokine that ultimately stimulates myelination (Ishibashi et

160 al., 2006). A specific myelinating CNS coculture system provided evidence that astrocytes are
161 implicated rather in promotion of rapid myelin growth than in initiation of myelination
162 (Watkins et al., 2008).

163 **Astrocytes provide lipids for myelin sheath production**

164 Still consistent with their implication in myelination, astrocytes were also proposed to
165 supply lactate to oligodendrocytes. Lactate constitutes a source of energy and a precursor of
166 lipid synthesis including cholesterol altogether necessary for myelin production. Although
167 astrocytes and oligodendrocytes are both in direct contact with blood vessels and may thus take
168 up lactate from blood, the hypothesis is that lactate released from astrocytes through the
169 monocarboxylate transporter (MCT) 4 may be supplied to oligodendrocytes possibly importing
170 the molecule through MCT1 (Sanchez-Abarca et al., 2001; Rinholm et al., 2011). The
171 requirement for local synthesis of cholesterol is consistent with the fact that myelin comprises
172 about 80% of the brain cholesterol content and that peripheral cholesterol entry into the brain
173 is largely precluded by the blood-brain barrier. During postnatal myelination, *de novo* synthesis
174 of cholesterol is carried out by both astrocytes and oligodendrocytes. Astrocyte-derived
175 cholesterol is then distributed to oligodendrocytes via lipoproteins contained in apolipoproteins,
176 mostly the apolipoprotein E (ApoE) in the CNS, and secreted via the ATP-binding cassette
177 transporter ABCA1 (Saher and Stumpf, 2015). Astrocytes provide a substantial fraction of the
178 lipids incorporated into CNS myelin and in the absence of astrocyte lipid synthesis,
179 oligodendrocytes are unable to finalize CNS myelination, leading to hypomyelinated and
180 slower-conducting fibers in adulthood. Indeed, the specific inactivation of an essential co-
181 activator of the transcription factor SREBP, the SREB cleavage activating protein (SCAP) in
182 oligodendrocytes, resulted in lipid biosynthesis and myelination delay nevertheless recovering
183 in adulthood. In contrast, when the enzyme was deleted in astrocytes or in both astrocytes and
184 oligodendrocytes, a persistent hypomyelination was observed. Thus, extracellular lipids seem
185 to be supplied by astrocytes under conditions of compromised oligodendrocyte lipid synthesis.
186 Moreover, full myelin synthesis requires an astrocyte lipid supply in addition to endogenous
187 oligodendrocyte lipid synthesis (Camargo et al., 2017).

188 Besides providing lipids for synthesis of myelin sheaths during development, astrocytes,
189 namely those contacting the nodes of Ranvier, were also reported to reversibly modify myelin
190 thickness and nodal gap length thus appropriately regulating conduction velocity in individual
191 axons. In support of this observation, the reduction of exocytosis induced in transgenic mice
192 expressing a dominant-negative fragment of the vesicle-associated membrane protein 2
193 (VAMP2) in astrocytes, exhibited detachment of adjacent paranodal loops of myelin from the
194 axon, increased nodal gap length, thinning of myelin sheath in the optic nerve and finally
195 decrease in visual acuity. These data led to propose that thrombin-dependent proteolysis of the
196 cell adhesion molecule neurofascin 155 that attaches myelin to the axon, is inhibited by
197 vesicular release of thrombin protease inhibitors from perinodal astrocytes, which likely
198 involves these cells in myelin remodeling necessary for optimal electrical conduction (Dutta et
199 al., 2018).

200 A last evidence of the remarkable and specific relationship between astrocytes and
201 myelination is finally provided in a model of neuromyelitis optica, a chronic inflammatory
202 demyelinating disease characterized by the destruction of astrocytes and their foot processes in
203 early lesions. Indeed, in a model of this disease, the death of oligodendrocytes was found to

204 occur before granulocyte or macrophage / microglia infiltration, but only a few hours after the
205 death of astrocytes induced in a complement-dependent manner (Wrzos et al., 2014).

206

207 **Microglia-oligodendrocyte communication in developmental myelin production**

208 Considered as resident myeloid cells of the CNS, microglia have been only recently
209 characterized as the progeny of yolk sac-derived macrophages that start to enter the CNS at E9
210 through the blood vasculature before closure of the blood-brain barrier that occurs by E13 in
211 mice (Ginhoux et al., 2010;Schulz et al., 2012;Kierdorf et al., 2013). Thereafter, at least under
212 non-pathological conditions, microglia cells are autonomously maintained through proliferation
213 (Askew et al., 2017). Microglia is crucial during neurodevelopment namely via its interaction
214 with neuronal cells for wiring and neural circuit regulation (Thion et al., 2018).

215 **Distinct patterns of secreted molecules for microglia and astrocyte-mediated** 216 **control of OPC generation**

217 The first arguments supporting a role for microglia in developmental myelination were
218 mainly derived from microglia-oligodendrocyte cocultures. They showed that microglia was
219 able to stimulate the synthesis of sulfatide, a myelin-specific galactolipid, and to increase
220 myelin-specific proteins, MBP and PLP in oligodendrocytes (Hamilton and Rome, 1994).
221 Microglia activity was mimicked by conditioned medium derived from microglia cultures
222 suggesting that the cells acted via the secretion of appropriate molecules. Together with
223 promoting cell maturation, microglia was found to prevent OPC apoptosis by upregulating
224 nuclear factor-kappa B (NF- κ B) p65 subunit via the recruitment of PI-3 kinase to the PDGFR α
225 thus leading to a synergism with PDGF (Nicholas et al., 2001).

226 Although both microglia- and astrocyte-conditioned media were able to prevent OPC
227 degeneration induced by growth factor deprivation in the culture medium during a short time,
228 microglia-derived medium was unable to support OPC survival in the long-term compared to
229 astrocytes. These differential effects were supported by distinct patterns of cytokine/growth
230 factors correlated with differentially activated intracellular signaling pathways in OPCs (Pang
231 et al., 2013). More specifically, mechanisms underlying enhanced microglia-induced
232 oligodendrocyte differentiation were proposed to be related to IGF-1. IGF-1 levels were more
233 than six-fold higher in microglia- than in astrocyte-derived medium and its expression was
234 consistently detected in amoeboid microglial cells located in the corpus callosum until the
235 seventh postnatal day, which corresponds to the time of morphological change of microglia
236 towards the ramified phenotype present in adulthood unless microglia become activated. In a
237 consistent manner, exposure of microglia cultures to lipopolysaccharide leading to microglia
238 activation, increased IGF-1 secretion (Kaur et al., 2006) and IGF-1 knockout mice display
239 reduced oligodendrocyte survival, differentiation and maturation (Ye et al., 2002). Moreover,
240 IGF-2 also derived from microglia was found to prevent TNF α -induced death of mature
241 oligodendrocytes *in vitro* (Nicholas et al., 2002).

242 **Unique phenotype of neonatal microglia implicated in developmental myelination**

243 As soon as the end of 1970's, the existence of a specific subpopulation of microglial
244 cells had been proposed in the early postnatal corpus callosum (Imamoto and Leblond, 1978).
245 Unexpectedly, the pharmacological suppression of microglia activation by using the anti-

246 inflammatory drug minocycline, was reported to significantly inhibit oligodendrogenesis both
247 *in vitro* in neurosphere culture and *in vivo* in the subventricular zone (SVZ) of the dorsal
248 forebrain. This inhibition was mediated by the blockade of several proinflammatory cytokines
249 including IL-1 β , IL-6, TNF- α , and IFN- γ . In addition, the observation that activated microglia
250 significantly increased O4⁺ cells but decreased PDGFR α ⁺ OPCs (Fig. 1B) again confirmed
251 microglia activity on oligodendrocyte maturation (Shigemoto-Mogami et al., 2014).

252 More recent data provided by two independent groups led to a major advance in the
253 understanding of the identity and role of this microglial subpopulation that appeared to highly
254 proliferate and display a rhomboid shape in contrast to microglia detected at the same time in
255 the neighboring cortex and exhibiting small processes comparable to adult microglia
256 (Hagemeyer et al., 2017; Włodarczyk et al., 2017). Presently, neonatal microglia implicated in
257 developmental oligodendrogenesis appear as a cell population with a dramatically different
258 gene expression profile compared to the one from adult healthy mice. Based on the observation
259 that during neuroinflammation, microglia expressing the integrin complement receptor CD11c
260 are a major source of IGF-1, Włodarczyk and collaborators detected a substantial increase of
261 CD11c⁺ microglia during the first days after birth before a sharp decrease mainly in highly
262 myelinating areas such as the developing corpus callosum and cerebellum. IGF-1 depletion in
263 this subset led to a reduction in brain weight, a decrease in the expression of myelin proteins
264 including PLP, MBP, MAG and MOG, and was finally associated with higher frequency of less
265 myelinated fibers in the corpus callosum. Thus, as the major source of IGF-1, the CD11c⁺
266 microglia subset was proposed to play a critical role in primary myelination and neuronal
267 support in the neonatal CNS (Włodarczyk et al., 2017). Interestingly, the comparison of
268 transcriptomes from sorted CD11c⁺ and CD11c⁻ microglia revealed that neonatal microglia,
269 naive adult microglia and microglia derived from the experimental autoimmune
270 encephalomyelitis (EAE) model of demyelination formed distinct global expression clusters.
271 Unexpectedly, CD11c⁺ and CD11c⁻ subpopulations were relatively close together indicating
272 that the major difference was related to developmental age rather than subpopulation
273 phenotype. The identification of gene expression profiles associated with microglia from the
274 different conditions showed that under demyelinating conditions, microglia cells were enriched
275 for immune system genes consistent with their activated state. On the contrary, in the neonatal
276 brain, microglia gene profile included genes involved in nervous system development
277 displaying a neurogenic phenotype. Remarkably, upon a quite total ablation of microglia in the
278 adult brain by using an inducible mouse strain, clusters of highly proliferating microglia were
279 detectable throughout the CNS. Although expressing CD11c and nestin, the proliferating cells
280 did not display a neurogenic gene expression profile confirming that the myelinogenic CD11c⁺
281 subset of microglia is unique to neonatal CNS (Włodarczyk et al., 2017).

282 Independently, Hagemeyer and collaborators similarly identified this amoeboid
283 microglia subset that they called ‘the fountain of microglia’ specifically located in myelinating
284 regions from postnatal day (P)1 to P8, displaying a high expression of the activation marker
285 Mac3 and dramatically collapsing at P9. Microglia found in the postnatal subcortical (with an
286 amoeboid shape) and cortical regions (with multiple cellular processes) were found to share
287 their early origin from the same CX3CR1⁺ CNS endogenous precursors without any
288 contribution from circulating blood monocytes. The pharmacological blockade of the receptor
289 for the secreted cytokine, colony stimulating factor 1 (CSF1), known to efficiently deplete
290 microglia (Elmore et al., 2014), showed that early postnatal microglia is required for the proper
291 induction of oligodendrocyte progenitors and subsequent myelination. Transcriptomic analysis

292 of the studied subpopulation revealed genes also detected in disease models such as CLEC7a,
293 SPP1, IGF-1, ANXA5, ITGAX, and GPNMB. An additional RNA sequencing analysis led to
294 identify change in gene expression profile between P7 and P10, the former being related to
295 phagocytosis, migration, priming of microglia more particularly described during aging and
296 disease while the latter was associated with apoptosis and necrosis according to a profile further
297 increased in adulthood. Thus, a specificity of neonatal microglia in P7 corpus callosum was the
298 expression of SPP1, CLEC7A and CD206 since none of them could be detected in cortical
299 microglia (Staszewski and Hagemeyer, 2019). Importantly, functional microglia is also
300 required for OPC homeostasis in the adult brain in agreement with the severe white matter
301 abnormalities observed in patients suffering from microgliopathies (Hagemeyer et al., 2017).

302 **The extracellular matrix at the crossroads of microglia and OPC activity**

303 The investigation of how OPCs integrate signals from the matrix and other glial cells
304 led to a growing interest for the adhesion G protein-coupled receptor (aGPCR) family, the
305 second largest class of GPCRs playing crucial roles in developmental processes (Mehta and
306 Piao, 2017). The finding that the genetic loss of one of its members, GPR56, was phenocopied
307 by the specific deletion of the enzyme microglia-derived transglutaminase 2 (TG2) in microglia
308 both resulting in the decrease of OPC cell division and number of mature oligodendrocytes, as
309 well as to hypomyelination during postnatal CNS development, led to identify GPR56 as the
310 receptor of TG2. In agreement with the ability of TG2 to bind ECM proteins to exert its
311 crosslinking activity, the activation of GPR56 by TG2 was found to require the ECM protein
312 laminin to promote OPC proliferation according to a mechanism leading to the dissociation of
313 GPR56 N- and C-terminal fragments allowing the agonist to initiate G-protein signaling and
314 subsequently RhoA activation. Thus, microglia TG2, extracellular laminin and OPC GPR56
315 provide an additional evidence of the critical role of microglia / oligodendrocyte
316 communication for developmental oligodendrogenesis (Giera et al., 2015). Remarkably,
317 laminin is also involved in OPC proliferation via promoting the metalloproteinase-mediated
318 cleavage of dystroglycan, one of its OPC surface receptors (Leiton et al., 2015). Moreover,
319 other ECM glycoproteins play a crucial role in myelination as, for instance, anosmin-1
320 characterized as an important modulator of oligodendrocyte progenitor lineage progression
321 likely via FGFR1/ERK1/2 signaling activation, which results in the control of MBP expression,
322 myelin formation and conduction velocity (Murcia-Belmonte et al., 2016). The enhanced
323 differentiation of induced pluripotent stem cells into myelin-expressing oligodendrocytes
324 promoted by the functionalization of culture substrates using brain ECM prepared from
325 decellularized human brain tissue further supports the critical activity of ECM in myelination
326 (Cho et al., 2019).

327

328 **Influence of astrocytes during remyelination**

329 **Reactive astrocytes provide pro-regenerative trophic factors**

330 As in other diseases, astrocytes become reactive after CNS demyelination. Astrocyte
331 reactivity includes hypertrophy of the cells and upregulation of intermediate filament proteins
332 such as GFAP and vimentin. The requirement of astrocytes for oligodendrocyte-mediated
333 remyelination has been established more than 15 years ago (Blakemore et al., 2003; Talbott et
334 al., 2005) and more recently reported to depend on the presence of androgen hormones in male

335 mice (Bielecki et al., 2016). The delay in astrocyte activation in mice lacking IL-1 β and the
336 finding that activated microglia release IL-1 β , were the first arguments supporting the idea that
337 microglia activation is a pre-requisite for astrocyte activation. In a consistent manner,
338 microglia-derived IL-1 β is able to upregulate CNTF. Added to astrocyte cultures, CNTF
339 induces astrocyte activation (Herx et al., 2000;Albrecht et al., 2003), which promotes fibre
340 myelination *in vitro* (Nash et al., 2011). *In vivo*, astrocytes derived from mice infected with the
341 mouse hepatitis virus, a model for multiple sclerosis (MS), secrete high levels of CNTF during
342 the remyelination phase while CNTF injection in the spinal cord upregulates the transcripts
343 encoding FGF2, a potent OPC mitogen (Albrecht et al., 2003). The loss of astrocytic gp130
344 receptor, the ubiquitous signal transducer for CNTF, consistently exacerbates both
345 demyelination and the proinflammatory T cell infiltration in the EAE model via apoptosis of
346 astrocytes, decrease of CNS regulatory Foxp3-expressing T cells and increase of IL-17-, IFN γ -
347 and TNF-producing T cells. The SHP2/Ras/ERK pathway was then identified as the involved
348 intracellular mechanism (Haroon et al., 2011).

349 IL-1 β also stimulates the astroglial production of LIF promoting survival of
350 oligodendrocytes and thus decreasing disease severity in EAE mice (Butzkueven et al., 2002).
351 In a pathological context where tumor necrosis factor (TNF) is a key component of the
352 inflammatory response, LIF can alternatively be released upon TNFR2-mediated activation of
353 the PI3K-PKB/Akt pathway in primary astrocytes. The selective stimulation of TNFR2 on
354 astrocytes cocultured with OPCs promoted OPC differentiation into mature oligodendrocytes
355 while the process was blocked in the presence of LIF neutralizing antibodies (Fischer et al.,
356 2014). Reactive astrocytes also produce BDNF supporting oligodendrogenesis and regeneration
357 after white matter damage. *In vitro*, conditioned medium from astrocytes restored the process
358 of OPC maturation even under an hypoxic stress known to block OPC differentiation unless the
359 medium was specifically treated in order to remove BDNF. Similarly, *in vivo*, the conditional
360 astroglial deletion of BDNF led to a highly reduced number of newly generated
361 oligodendrocytes and thus to larger white matter damage in animals subjected to prolonged
362 cerebral hypoperfusion (Miyamoto et al., 2015).

363 The multitude of factors secreted by astrocytes are proposed to induce a rapid change in
364 the lesion environment sensed by OPCs, which thereby become activated. Upon demyelination,
365 OPC activation is associated with a reversion of gene expression profile of adult OPCs towards
366 a profile more closely resembling that of neonatal OPCs. A notable increase in the expression
367 of genes associated with innate immune system functions (including IL1 β and CCL2) was
368 identified, as well, together with an increased ability of activated OPCs to migrate and
369 differentiate compared with non-activated ones. Activated OPCs finally express transcription
370 factors such as TCF4 and Sox2, which serve to maintain OPC in the cell cycle and to prime
371 these cells for further differentiation (Moyon et al., 2015;Franklin and ffrench-Constant, 2017).

372 **Pro-inflammatory secreted molecules associated with reactive astrocytes**

373 All the above activities derived from reactive astrocytes are likely involved in the
374 spontaneous regenerative process of remyelination that can occur with a remarkable efficiency,
375 not only in experimental models of demyelination but also in humans suffering from MS
376 (Prineas et al., 1993;Patrikios et al., 2006;Patani et al., 2007;Franklin and ffrench-Constant,
377 2017). However, in chronic lesions, remyelination mostly fails or occurs only in the periphery
378 of the plaques (Prineas and Connell, 1979;Barkhof et al., 2003;Bramow et al., 2010), where

379 OPC migration and / or differentiation are likely impaired (de Castro et al., 2013;Franklin and
380 ffrench-Constant, 2017). Such failure has been associated with deleterious activities of
381 astrocytes classically related to a more severe level of reactivity and the secretion of damaging
382 molecules (Fig. 2). One of these molecules, TNF- α , was mainly detected in fibrous astrocytes
383 at the periphery of chronic active MS lesions and mostly transcribed in highly demyelinated
384 plaques (Hofman et al., 1989;Selmaj et al., 1991;Bitsch et al., 2000). Although it is not yet clear
385 whether TNF- α is internalized or produced by astrocytes (Selmaj et al., 1991;Aranguéz et al.,
386 1995), the direct physical contact between astrocytes and oligodendrocytes was proposed to be
387 necessary for oligodendrocyte apoptosis by TNF- α in glial cell cultures. One possibility for
388 contact-dependent cell killing is through gap junctions known to couple astrocytes and OLs
389 (Nagy and Rash, 2000;Orthmann-Murphy et al., 2007) and previously suggested for
390 propagation of cell injury (Lin et al., 1998;Farahani et al., 2005;Froger et al., 2010;Kim et al.,
391 2011).

392 In the same manner, the knockout of IFN- γ receptor in astrocytes was found to decrease
393 chemokine expression and inflammatory cell infiltration thus preventing demyelination and
394 consequently lowering clinical signs, namely by alleviating both Th1- and Th17-mediated
395 adoptive EAE (Ding et al., 2015). Together with suggesting an important role for IFN- γ
396 signaling in astrocytes during autoimmune CNS inflammation, this phenotype was consistent
397 with the delay in disease recovery observed in transgenic EAE mice ectopically expressing IFN-
398 γ in astrocytes during the recovery stage and also with the dramatic reduction of
399 oligodendroglial repopulation in the demyelinated lesions of the cuprizone model upon CNS
400 delivery of IFN- γ (Lin et al., 2006). The detection of IFN- γ in astrocytes of active chronic MS
401 plaques and its ability to induce class II major histocompatibility antigen HLA-DR-Ia in
402 astrocytes *in vivo* suggested that IFN- γ may play an important role in the development of MS
403 lesions (Traugott and Lebon, 1988;Hashioka et al., 2009).

404 Another cytokine secreted by astrocytes is CXCL10 that is namely detectable around
405 active MS lesions (Ransohoff et al., 1993;Omari et al., 2005;Carter et al., 2007). Its production
406 increases before the onset of clinical symptoms, maintains at high levels during the peak of the
407 disease and decreases during remission in the EAE model (Glabinski et al., 1997;Fife et al.,
408 2001). *In vitro*, CXCL10 is upregulated in an astrocyte phenotype endowed with an inhibitory
409 role in glial/axonal ensheathment without impairment of OPC proliferation / differentiation or
410 process extension (Nash et al., 2011).

411 Among the other molecules highly expressed by reactive astrocytes, endothelin-1 also
412 stands as a strong inhibitor of remyelination. This neuropeptide acts by promoting Notch
413 activation in OPCs through induction of Jagged1 expression in reactive astrocytes (Hammond
414 et al., 2014). In the same line, lesion formation was reported to be associated with increased
415 expression of fibroblast growth factor 9 (FGF9) by astrocytes acting not via a direct effect on
416 the oligodendroglial lineage, but via an off target effect mediated by soluble astrocyte-derived
417 factors inhibiting terminal differentiation of myelinating oligodendrocytes. *In vitro*, this activity
418 is associated with the appearance of multi-branched ‘pre-myelinating’ oligodendrocytes that
419 extend processes able to interact with axons without forming any myelin sheaths, reminiscent
420 of the oligodendrocyte phenotype observed in chronically demyelinated MS lesions. Astrocyte-
421 derived factors included metalloproteases associated with ECM remodelling and the pro-
422 inflammatory chemokines CCL2 and CCL7 that contribute to the development of inflammatory
423 responses in the CNS (Lindner et al., 2015).

424

Reactive astrocytes secrete extracellular matrix deleterious for remyelination

425 Apart from cytokines, growth factors and neuropeptides, ECM molecules are also
426 secreted by reactive astrocytes and highly modify the lesion environment in MS, consequently
427 influencing the behavior of OPCs (Maier et al., 2005;van Horssen et al., 2005;van Horssen et
428 al., 2006;Clemente et al., 2011;Pu et al., 2018). Both the receptors present at the surface of
429 OPCs and the ECM molecules secreted by reactive astrocytes are susceptible to change the
430 environment from permissive to inhibitory for remyelination (de Castro et al., 2013). Indeed,
431 except the interaction reported between astroglial laminin and oligodendroglial $\alpha 6 \beta 1$ integrin
432 shown to attenuate oligodendrocyte death *in vitro* (Corley et al., 2001), ECM accumulation
433 appears as an important factor in tissue regeneration failure. For instance, the expression of N-
434 cadherin on the surface of both oligodendrocytes and astrocytes led to the first *in vitro* evidence
435 that this molecule was in part responsible for the poor migration-promoting properties induced
436 by astrocytes on oligodendrocytes suggesting that the inhibition of cell-cell adhesion could
437 improve repopulation of MS lesions by OPCs. Indeed, the blocking of cadherin function by
438 specific peptides reduced adhesion of oligodendroglia to astrocyte monolayers, diminished the
439 duration of the contact between oligodendrocyte processes and individual astrocytes, and
440 increased the migration of oligodendrocytes on astrocyte monolayers (Schnadelbach et al.,
441 2000). In the same line, astrocytes in culture produce fibronectin as fibril-like structures in
442 inflammatory conditions, known to inhibit myelin formation in different experimental
443 paradigms (Siskova et al., 2009). In agreement with this hypothesis, fibronectin rapidly
444 accumulates as an acute response to demyelination in MS and disappears during remyelination,
445 whereas astrocyte-released aggregated fibronectin persists in chronic lesions (Stoffels et al.,
446 2013). Similarly, the ECM-associated glycoprotein anosmin-1 can also be detected in the core
447 of chronic active and inactive MS plaques where it is suggested to prevent OPC colonization
448 rather than inhibit their differentiation via a mechanism possibly involving the FGF-2 receptor
449 FGFR1 consistently detected in the periplaque of chronic lesions (Bribian et al., 2006;Bribian
450 et al., 2008;Clemente et al., 2011).

451 Major CNS ECM proteoglycans have also been characterized in MS lesions. In active
452 plaque edges, the chondroitin sulfate proteoglycans (CSPG) versican, aggrecan, neurocan and
453 the dermatan sulfate proteoglycan increase in correlation with astrocytosis. In contrast, these
454 molecules accumulate in foamy macrophages in active plaque centers, suggesting their
455 engulfment together with myelin. In inactive lesions and normal-appearing white matter,
456 proteoglycans are decreased and display undetectable abnormal heterogeneous aggregation,
457 respectively (Sobel and Ahmed, 2001). The roles of CSPG during development in particular in
458 myelination and the different localizations of CSPG according to the type of MS lesions both
459 support the idea that these molecules comprising part of the astrogliotic scar, are critical in
460 inhibition of OPC processes outgrowth and OPC differentiation (Siebert and Osterhout, 2011).
461 The hypothesis is consistent with the recent design of a novel CSPG synthesis inhibitor reducing
462 CSPG deposition into the lesion microenvironment and found to rescue OPC process outgrowth
463 *in vitro* and to accelerate remyelination following focal demyelination in mice (Keough et al.,
464 2016). Moreover, the glycosaminoglycan hyaluronan characterized by its ability to bind CSPG
465 is deposited in early MS lesions in a low molecular weight form by lymphocytes and microglia /
466 macrophages whereas it is deposited by astrocytes in a higher molecular weight form in chronic
467 lesions. There, hyaluronan degraded by hyaluronidases expressed by OPCs inhibits OPC
468 maturation and thus remyelination (Back et al., 2005) through a mechanism requiring the Toll-
469 like receptor 2 expressed by oligodendrocytes and upregulated in MS lesions (Sloane et al.,

470 2010). Evaluated in the Theiler's murine encephalomyelitis model, the spatio-temporal course
471 of ECM alterations confirmed the correlation of matrix accumulation with astrogliosis still
472 supporting a mainly astrocytic origin of ECM deposits. The data led to propose disturbed
473 aggregation or post-translational modifications of matrix molecules leading to impairment of
474 their regular degradation rather than changes in their transcription level (Haist et al., 2012).

475 **The dual activity of astrocytes in the demyelinated tissue**

476 The dual activity of astrocytes described above not only reflects more or less severe
477 levels of astrocyte reactivity, but also clearly reminds the duality that characterizes the glial
478 scar itself, which is considered as a rearrangement of tissue structure, astrocyte proliferation,
479 and pronounced overlap of astrocyte processes resulting in the disruption of individual astrocyte
480 domains (Zamanian et al., 2012;Anderson et al., 2016;Adams and Gallo, 2018). While
481 traditionally viewed as a barrier to axon regeneration, the glial scar has been nevertheless
482 reported to be beneficial for restricting leukocyte migration outside the damaged tissue
483 (Faulkner et al., 2004;Okada et al., 2006;Herrmann et al., 2008;Voskuhl et al., 2009). Moreover,
484 in contrast to the initial dogma, its deleterious effect on axon regeneration was recently
485 questioned. Indeed, genetically targeted loss-of-function approaches leading to prevention of
486 astrocyte scar formation, attenuation of scar forming astrocytes or deletion of chronic astrocyte
487 scars, failed to result in spontaneous regrowth of transected CNS axons following spinal cord
488 injury lesions. These data were corroborated by results of RNA sequencing revealing the
489 expression of multiple axon-growth supporting molecules namely in astrocytes (Anderson et
490 al., 2016).

491 Astrocyte ability to exhibit different phenotypes obviously participates in this
492 heterogeneity (Zamanian et al., 2012;Liddelw and Barres, 2017). Indeed, despite a core set of
493 genes up-regulated in different injury models such as ischemic stroke and neuroinflammation,
494 50% of altered gene expression is specific to a given injury. The first transcriptomic analyses
495 provided evidence for the existence of two subtypes of reactive astrocytes (Zamanian et al.,
496 2012) afterwards named 'A1' and 'A2'. A1 astrocytes induced by classically activated
497 neuroinflammatory microglia following exposure to lipopolysaccharide have been described as
498 harmful by inhibiting OPC proliferation and differentiation. A2 astrocytes identified during the
499 regeneration stage in an ischemia model, were found to up-regulate genes thought to be
500 protective. In line with this observation, analysis of MS lesions reported the detection of A1
501 mostly in active lesions whereas A2 were found during remyelination (Haindl et al., 2019).
502 However, it may be more likely that the occurrence of different astrocytic phenotypes and the
503 existence of suitable levels of various factors expressed at particular time points may achieve
504 successful repair. In agreement with this hypothesis, investigation of the astrocytic reaction at
505 various steps of lesion progression in the rat EAE model led to detect simultaneously in shadow
506 plaques all features of a glial scar and densities of OPCs and mature oligodendrocytes, which
507 were quite comparable to the densities observed in unaffected white matter (Haindl et al., 2019).

508 The first line response of astrocytes to myelin injury consisting in myelin phagocytosis
509 was similarly considered to be either beneficial or detrimental on the lesion pathology,
510 depending on the inflammatory context. Indeed, although myelin debris phagocytosis was
511 mainly reported to be performed by microglia/macrophages, myelin-positive hypertrophic
512 astrocytes can be observed at sites of acute myelin breakdown. The uptake was proposed to rely
513 on receptor-mediated endocytosis and to result in astroglial NF- κ B activation and secretion of

514 specific chemokines. The latter leads to recruitment of immune cells shown *in vitro* in rodent
515 and validated in human disease. Although microglia and monocyte recruitment may be
516 beneficial for myelin clearance in a non-inflammatory environment, it increases tissue damage
517 in demyelinating conditions driven by inflammation such as MS since additional recruitment of
518 lymphocytes and microglia/macrophages exacerbates the inflammatory process (Ponath et al.,
519 2017).

520 Finally, the finding that transplanted immature astrocytes are unable to become reactive
521 after CNS injury (Jiang et al., 2013) and that only immature (but not mature) astrocytes are
522 neuroprotective and suppress endogenous astrocyte activation and glial scar formation
523 presently stands as an interesting novel concept (Chen et al., 2015). Thus, transplanted human
524 pluripotent stem cell-derived astrocytes at a defined immature stage were shown to regulate the
525 differentiation of endogenous OPCs, to promote myelinogenesis and to improve behavioral
526 outcome in the model of periventricular leukomalacia in neonate mice via a mechanism
527 depending on the tissue inhibitor of metalloproteinases TIMP-1 (Jiang et al., 2016).

528 **Key studies supporting detrimental roles of astrocytes on oligodendrocytes and** 529 **myelin**

530 Several publications using astrocyte ablation have improved our knowledge about the
531 main detrimental roles of reactive astrocytes in the context of CNS demyelination. For instance,
532 OPC transplantation in ethidium bromide-demyelinated animals in the presence or absence of
533 astrocytes indicated that astrocyte-free regions favour Schwann cell differentiation whereas the
534 presence of astrocytes delayed the interaction of OPCs with the demyelinated axons (Blakemore
535 et al., 2003). Similarly, the depletion of astrocytes via intracallosal injection of La-aminoadipate
536 in cuprizone-treated animals revealed a notable increase in the percentage of myelinated areas,
537 decrease in Iba-1⁺ microglia staining and collapse in the expression of genes related to either
538 recruitment of microglia classically triggered by astrocytes or suppression of OPC
539 differentiation (Madadi et al., 2019). The considerable amount of fibronectin produced by
540 astrocytes and the ability of astrocytic fibronectin to become aggregated after treatment with
541 lipopolysaccharide led to conclude to the deleterious effects of such aggregates on
542 oligodendrocyte differentiation and myelin regeneration *in vivo*, in agreement with the detection
543 of a low level of fibronectin aggregates in remyelinated MS lesions (Stoffels et al., 2013). The
544 signaling molecule endothelin-1 (ET-1) expressed by reactive astrocytes in MS and murine
545 demyelinated lesions is a negative regulator of OPC differentiation and remyelination acting by
546 promoting Notch activation in OPCs during remyelination (Hammond et al., 2014).

547 Moreover, the CCL2 chemokine produced by astrocytes plays an important role in the
548 continued recruitment of immune cells and activation of glial cells in the CNS during chronic
549 EAE (Kim et al., 2014). Similarly, the adhesion molecule VCAM-1 expressed by astrocytes is
550 essential for T cell entry into the CNS parenchyma from EAE animals (Gimenez et al., 2004).
551 As previously mentioned, myelin uptake is an early response of astrocytes in diseases with
552 prominent myelin injury that results in recruitment of immune cells possibly increasing tissue
553 damage in demyelinating conditions driven by inflammation (Ponath et al., 2017). In the same
554 line, astrocytes constitute one of the cell types that have the capacity to express molecules
555 required for antigen presentation under inflammatory conditions required for T cell reactivation
556 targeting the myelin sheath-forming oligodendrocytes (Waisman and Johann, 2018). Finally,
557 although in the healthy brain, perivascular astrocyte end-feet closely ensheath the

558 microvasculature, activation of perivascular astrocytes may alter their involvement in the blood-
559 brain barrier formation as suggested by the damage of perivascular end-feet reported in MS
560 patients. The revisit of this observation in the EAE model showed that reactive astrocytes detach
561 from the blood vessels and lose their contacts with both blood vessels and neuronal synapses,
562 which was proposed to contribute to the neurological impairment and the cognitive decline
563 occurring in EAE/MS as well as to the neurodegenerative disease progression (Eilam et al.,
564 2018).

565

566 **Microglia in remyelination**

567 In the context of myelin repair, microglia and their hematopoietic cell-derived
568 counterparts, macrophages, both contribute to the regenerative process through key effects
569 including the phagocytosis of myelin debris, the secretion of cytokines, chemokines, growth
570 factors or soluble mediators and the recruitment/differentiation of progenitors at the lesion site.
571 Although microglia and macrophages can now be distinguished by using a few specific markers
572 (Bennett et al., 2018), they have been indistinguishable for a long time. Therefore,
573 ‘microglia/macrophages’ will be used for most presently available data.

574 **Microglia/macrophage phenotypes upon CNS demyelination**

575 As resident immune cells of the CNS, microglia/macrophages become activated as soon
576 as they detect any insult. This activation implicates changes in morphology and transcriptional
577 profiles of the cells. The failure of microglia to convert from a ‘resting state’ with a branched-
578 like morphology to an ‘activated state’ with an amoeboid-like morphology was namely
579 observed upon knocking down either the β -galactoside-binding lectin Galectin-3 (Reichert and
580 Rotshenker, 2019) or one of the receptors of the secreted proteins Sonic hedgehog, the protein
581 Boc (Zakaria et al., 2019).

582 Like astrocytes, microglia/macrophages are endowed with a dual activity supported by
583 the existence of different phenotypes observed under various *in vitro* conditions and that have
584 been named, respectively the classical activated state (M1) associated with pro-inflammatory
585 activities and the alternative polarized state (M2) involved in OPC recruitment and
586 differentiation associated with anti-inflammatory activities (Fig. 3A). The characterization of
587 these phenotypes performed in the model of focal demyelination induced by stereotaxic
588 injection of lysolecithin into the corpus callosum led to the identification of a few specific
589 markers namely including iNos, TNF, CD16/CD32 for the classical activated state and Arg1,
590 IGF1 and CD206 for the alternative state. The switch from an M1- to an M2-dominant response
591 was detected in microglia/macrophages at initiation of remyelination (Miron et al., 2013). It
592 was more recently characterized as a process requiring necroptosis of pro-inflammatory
593 microglia and subsequent repopulation to a pro-regenerative state (Lloyd et al., 2019). *In vitro*
594 experiments revealed the ability of M2 cell conditioned media to promote OPC differentiation
595 whereas the depletion of M2 cells in focal demyelinating lesions prevented OPC differentiation.
596 In addition, parabiosis experiments detected a higher number of M2 cells in lesions of aged
597 mice in which remyelination was increased by coupling to a younger mouse. Finally, the
598 blockade of activin-A secreted by M2 cells fully prevented OPC differentiation in demyelinated
599 cerebellar slice cultures (Miron et al., 2013).

600 Microglia/macrophage activation cannot be nevertheless regarded as a simple
601 dichotomy of M1 or M2, but undoubtedly as a much broader reactive phenotype spectrum. In
602 agreement with this observation, in the Theiler's induced demyelinating disease model, the
603 endogenous cannabinoid 2-AG induces pro-phagocytic response of microglia and OPC
604 differentiation, without any detectable regulation of the main markers used to identify classic
605 and alternatively activated microglia, respectively (Mecha et al., 2019). In the same line, myelin
606 debris were consistently proposed to promote the emergence of a novel phenotype that differs
607 from conventional M1 and M2. Indeed, myelin-induced macrophages appear foamy, displaying
608 a striking deficiency of the expression of the ATP-binding cassette transporter ABCA1 required
609 for lipid efflux in response to myelin debris loading, thus suggesting that this homeostatic
610 mechanism characterizing non myelin-induced macrophages is overwhelmed. The impaired
611 capacity of foamy macrophages for apoptotic and necrotic cell clearance is consistent with this
612 hypothesis and likely contributes to the development of secondary injury (Wang et al., 2015b).

613 In agreement with this observation, a growing number of recent publications support the
614 existence of a wide spectrum of microglia activation states evidenced by single cell and bulk
615 RNA sequencing approaches characterizing this process not as a simple phenotypical change
616 but as a dynamic response involving spatially and transcriptionally distinct subpopulations.
617 High-dimensional single-cell mapping in EAE mouse CNS led to a unique activation profile
618 comprising universal markers of microglia/macrophage activation including CD44, CD86,
619 programmed death-ligand 1 (PDL1) as well as a decreased CD14 expression and increased
620 major histocompatibility complex II (MHC II) and stem cell antigen-1 (Sca-1) expressions
621 notably not detected in old mice or Alzheimer's disease models (Mrdjen et al., 2018). Single-
622 cell RNA sequencing of microglia from LPC-mediated lesions revealed multiple gene
623 expression profile clusters of activated microglia/macrophages sharing common genes such as
624 apoE and unique genes such as Ccl4 or Cxcl10 according to the clusters (Hammond et al.,
625 2019). Multiple activation states specifically reflecting microglia (and not macrophages) was
626 also identified upon LPC-mediated demyelination suggesting that microglia can have multiple
627 forms of activation likely identified by common or selective transcriptional programs (Plemel
628 et al., 2020). Similarly, a specific ApoE-dependent molecular signature was identified in
629 microglia/macrophages from different models of neurodegenerative diseases including EAE
630 (Krasemann et al., 2017). Strikingly, one of these subsets displayed an expression profile
631 comparable to the one found in MS microglia (Zrzavy et al., 2017). Real-time in vivo imaging
632 of microglia/macrophages in EAE mice visualized the expected switch from pro-inflammatory
633 to immuno-regulatory markers mostly in initial lesions with an increase during lesion resolution
634 (Locatelli et al., 2018). In a consistent manner, in actively demyelinating lesions from MS
635 patients, some microglia/macrophages express pro-inflammatory markers while active lesions
636 prone to remyelinate comprise microglia/macrophages expressing anti-inflammatory markers
637 at a higher level than chronic inactive lesions (Miron et al., 2013;Zrzavy et al., 2017).

638 **Factors controlling the pro-regenerative microglia/macrophages**

639 Recently, the subpopulation of CD11c-expressing microglia previously reported to be
640 transiently expanded soon after birth and critical for primary myelination, was found to be
641 remarkably increased in EAE and cuprizone models of demyelination. The expansion of this
642 subpopulation is induced by the stimulation of CSF1R, the key transducer of CSF1 and
643 interleukin (IL)-34 signals, essential in myeloid cell development. CSF1R activation induces
644 the expression of the chemokine CCL2, itself leading to a dramatic increase of CD11c⁺

645 microglia, finally resulting in improvement of EAE symptoms and lower level of demyelination
646 (Wlodarczyk et al., 2018). Among factors implicated in promotion of the remyelinating
647 phenotype of microglia, the homeobox gene Msh-like homeobox-3 (MSX3) is a pivotal
648 regulator for microglial polarization that is induced and repressed in M2 and M1 cells,
649 respectively. This finding is supported by the dynamic regulation of MSX3 in the EAE model
650 as well as by the beneficial and deleterious effects observed after MSX3 gain- and loss-of
651 function experiments in different demyelination models. Pparg, Stat6 and Jak3 are key genes
652 regulated by MSX3 (Yu et al., 2015). In the same line, pro-regenerative microglia express a
653 high level of the purinergic receptor P2X4R at the peak of recovery in the EAE model. P2X4R
654 activation increases and decreases pro-regenerative and pro-inflammatory genes, respectively,
655 whereas its blockade prevents myelin debris clearance (Zabala et al., 2018).

656 **The critical role of microglia/macrophages in myelin phagocytosis**

657 The ability of microglia/macrophages to phagocyte myelin debris is critical for
658 promoting OPC recruitment and differentiation into myelinating cells (Triarhou and Herndon,
659 1985;Kotter et al., 2001;Kotter et al., 2005;Kotter et al., 2006;Neumann et al., 2009). The main
660 phagocytic receptor in microglia/macrophages is the complement receptor-3 (CR3). Binding of
661 myelin to CR3 initiates structural changes characteristic of phagocytosis mostly reflected by
662 filopodia-like membrane protrusions that engulf myelin as they extend and then pull myelin
663 into phagocytes as they retract. Filopodia production depends on F-actin remodeling, which is
664 promoted by active unphosphorylated cofilin and impeded by inactive phosphorylated cofilin.
665 Spleen tyrosine kinase (Syk), the non-receptor tyrosine kinase known to be recruited by
666 phagocytic receptors including CR3, downregulates CR3-mediated myelin phagocytosis by
667 increasing the inactive state of cofilin. This self-negative control of phagocytosis is useful in
668 protecting phagocytes from excessive phagocytosis during prolonged exposure to particles that
669 are fated to ingestion (Hadas et al., 2012). Remarkably, myelin debris are able to inhibit their
670 own clearance by using a protective mechanism whereby CD47 protein expressed by myelin
671 debris binds the immune inhibitory receptor signal regulatory protein- α (SIRP α) on the surface
672 of phagocytes (Fig. 3B). The mechanism supporting such detrimental protection involves the
673 regulators of cytoskeleton function paxilin and cofilin, which are both either activated by
674 phagocytic receptors or inactivated by the immune inhibitory SIRP α (Gitik et al., 2014). The
675 finding that expression of Galectin-3 correlates with myelin-debris phagocytosis in microglia
676 led to show its implication in phagocytosis activation first by advancing cofilin activation,
677 causing filopodia/lamellipodia to extend/engulf myelin-debris and, second, by advancing
678 actin/myosin-based contraction through K-Ras.GTP/PI3K signaling, causing
679 filopodia/lamellipodia to retract and thus internalize myelin debris (Reichert and Rotshenker,
680 2019).

681 The retinoid X receptor (RXR) plays an important role in monocyte/macrophage
682 phagocytosis of myelin as suggested by pioglitazone-induced activation of peroxisome
683 proliferator-activated receptor γ , one of the permissive binding partners of RXR, shown to
684 inhibit pro-inflammatory differentiation of MS patient-derived monocytes/macrophages and to
685 enhance myelin phagocytosis (Natrajan et al., 2015b). Moreover, the blockade of myelin debris
686 clearance by microglia/macrophages in cuprizone-demyelinated CX3CR1-deficient mice,
687 revealed the critical role played by CX3CR1, the receptor controlling microglial physiology
688 and orchestrating the crosstalk between microglia and neurons (Lampron et al., 2015).
689 Moreover, macrophages lacking miR-223 expression have impaired ability to polarize towards

690 the M2 phenotype thus altering myelin debris clearance and remyelination in the lysolecithin-
691 demyelinated corpus callosum (Galloway et al., 2019). Interestingly, the use of human
692 monocyte-derived macrophages and microglia led to demonstrate that myelin phagocytosis is
693 significantly enhanced in cells exposed to TGF- β compared with resting basal conditions
694 whereas it is markedly reduced in classically activated polarized cells. The transcriptional
695 analysis of TGF- β -treated microglia revealed the tyrosine kinase receptor MerTK as one of the
696 most upregulated among differentially expressed genes. In contrast, the enzyme and its ligands
697 (growth arrest-specific 6 and Protein S) are down-regulated in classically activated cells (Healy
698 et al., 2016).

699 Recent publications identified novel signaling pathways aimed at restoring homeostatic
700 microglial phagocytosis in aging CNS. Indeed, old mice fail to resolve the inflammatory
701 response initiated after myelin damage. This observation was related to accumulation of
702 excessive amounts of myelin debris by aged phagocytes, which trigger cholesterol crystal
703 formation and phagolysosomal membrane rupture, thus stimulating inflammasomes. However,
704 stimulation of cholesterol efflux and solubility by administering 2-hydroxypropyl- β -
705 cyclodextrine in old demyelinated mice knockout for the major cholesterol transporter ApoE
706 was sufficient to restore the capacity to remyelinate lesioned tissue (Cantuti-Castelvetri et al.,
707 2018).

708 Combined CRISPR-Cas9 knockout screens together with RNA-seq led to discover age-
709 related genetic modifiers of microglial phagocytosis such as the canonical B-cell receptor
710 CD22, a negative regulator of phagocytosis that is upregulated on aged microglia. CD22
711 mediates the anti-phagocytic effect of α 2-6-linked sialic acid. Its inhibition promotes the
712 clearance of myelin debris *in vivo* and reprograms microglia towards a homeostatic
713 transcriptional state leading to improvement of cognitive function in aged mice (Pluinage et
714 al., 2019). By up-regulating the expression of the scavenger receptor CD36, niacin (also called
715 vitamin B3) induces myelin phagocytosis through binding its receptor, hydroxycarboxylic acid
716 receptor 2, both *in vitro* and *in vivo* (Rawji et al., 2020).

717 **Pro-regenerative microglia/macrophage-derived factors**

718 Many cytokines, growth factors and soluble factors are known to be secreted by
719 microglia/macrophages (Fig. 3C). Although induced by IL1 β characterized as a pro-
720 inflammatory cytokine (Mason et al., 2001), microglia/macrophage-derived IGF-1 enhances
721 remyelination as suggested by EAE rats receiving IGF-1 subcutaneously (Yao et al., 1996) and
722 in lysolecithin-demyelinated spinal cord of young and aged rats intrathecally infused with the
723 growth factor (Hlavica et al., 2017). TNF α through its TNFR2 receptor promotes remyelination
724 by increasing OPC proliferation as shown by using mouse strains knockout for the ligand or its
725 receptor as well as by their up-regulation during the remyelination stage in the cuprizone model
726 (Arnett et al., 2001). T helper cell-derived TGF- β induces the secretion of microglial hepatocyte
727 growth factor (HGF), which drives OPC chemotaxis and differentiation. In agreement with this
728 finding, spinal cord lesions from relapsing-remitting EAE mice contain both OPC and HGF-
729 producing microglia/macrophages in the recovery-, but not in the acute phase (Lalivie et al.,
730 2005). Highly expressed in microglia, the β -galactoside-binding lectin, galectin-3, has a critical
731 role in driving OPC differentiation and myelination in agreement with the oligodendrocyte
732 maturation effects displayed by supernatants derived from galectin-3-expressing- but not
733 galectin-3-deficient microglia (Pasquini et al., 2011).

734 Microglia/macrophages also express activin-A at onset of remyelination of focally-
735 induced demyelination. This growth factor regulates oligodendrocyte differentiation and
736 myelin compaction via the activin receptor subtype Acvr2a up-regulated during efficient myelin
737 regeneration, in contrast to the other receptor subtype Acvr2b, which has to be down-regulated
738 for allowing oligodendrocyte differentiation. In actively remyelinating areas of MS tissue,
739 oligodendrocyte lineage cells expressing Acvr2a consistently outnumber cells expressing
740 Acvr2b suggesting that increase in Acvr2b expression may impair oligodendrocyte
741 differentiation and myelin formation induced by Acvr2a (Dillenburg et al., 2018).

742 Finally, microglia is a main iron source in the form of ferritin. The latter is required for
743 OPC proliferation and differentiation and stands as an essential cofactor for enzymes involved
744 in myelin cholesterol and fatty acid synthesis (Schonberg et al., 2012). The cellular iron level
745 in microglia/macrophages is controlled by hepcidin and ferroportin. The transcription of the
746 former is regulated by the BMP/Smad and IL-6/Jak-STAT3 signaling pathways during
747 inflammation resulting in the degradation of the only known iron exporter ferroportin,
748 subsequently increasing intracellular iron level. Recently, the infusion of the BMP antagonist
749 noggin in a model of ischemic stroke decreased the induction of hepcidin and ferritin proteins
750 whereas it increased the number of myelinated axons and myelin thickness (Shin et al., 2018).

751 Several microglial enzymes are also clearly implicated in remyelination. As shown in
752 development, microglia-derived TG2 signals to GPR56 on OPCs in the presence of the ECM
753 protein laminin, promotes OPC proliferation and improves remyelination *in vivo* in the
754 cuprizone model and *ex vivo* in cerebellar slices exposed to lysolecithin (Giera et al., 2015).
755 Lipoprotein-lipase involved in lipid-processing, which plays an important role during initiation
756 of remyelination and is considered as a feature of alternatively-activated microglia, is
757 significantly increased in the EAE model when clinical symptoms start to decrease (Bruce et
758 al., 2018; Kamermans et al., 2019). Finally, CD38 that catalyzes the synthesis of cyclic
759 adenosine diphosphate-ribose (cADPR) from nicotinamide adenine dinucleotide (NAD⁺), is
760 increased in the cuprizone model of demyelination in both astrocytes and microglia and may be
761 required for myelin clearance and oligodendrocyte repopulation (Roboon et al., 2019).

762 Recently, extracellular vesicles produced *in vitro* by either pro-inflammatory- or pro-
763 regenerative microglia were proposed to be one of the mechanisms used to promote or block
764 myelin repair. Remarkably, exposure of cultured OPCs to inflammatory vesicles blocked OPC
765 maturation only in the presence of astrocytes, thus implicating the latter in remyelination failure
766 via a mechanism involving astrocyte conversion into deleterious cells. Moreover, biochemical
767 fractionation revealed that the inflammatory cargo of the pro-inflammatory vesicles mainly
768 contribute to the blockade of OPC maturation whereas surface lipid components may be mostly
769 involved in extracellular vesicle-mediated migration and/or differentiation of OPCs likely
770 implicating sphingosine 1 phosphate at least for OPC migration (Lombardi et al., 2019).

771 **Therapeutic modulation of microglia/macrophages**

772 Major improvement of our knowledge of the role of microglia/macrophages during
773 remyelination recently led to new therapeutic perspectives. One of the first papers providing
774 evidences that increased recruitment of microglia/macrophages can support remyelination,
775 regarded the anti-fungal amphotericin B and its association with macrophage colony-
776 stimulating factor (M-CSF). Although using amphotericin B is precluded by its ability to
777 stimulate TNF secretion and its toxic properties (Doring et al., 2015), the increased uptake of

778 myelin debris induced by M-CSF in the cuprizone model remains interesting (Laflamme et al.,
779 2018). The adoptive transfer of bone-marrow-derived M2 macrophages results in a shift of the
780 immunological response from helper T1 to helper T2 lymphocytes through the production of
781 anti-inflammatory cytokines, which in turn induces the polarization of microglia/macrophages
782 to the M2 phenotype in a model of spinal cord injury (Ma et al., 2015). Preventive IL-13 gene
783 therapy in the cuprizone model directs the polarization of microglia and infiltrating
784 macrophages towards an alternatively activated phenotype, thereby limiting lesion severity and
785 improving disease outcome (Guglielmetti et al., 2016).

786 Several molecules modulating microglia/macrophages are presently trialled in patients.
787 For instance, the anti-muscarinic molecule Clemastine, modulates macrophage inflammatory
788 responses *in vitro* and microglia/macrophage activation *in vivo* (Mei et al., 2014). Bexarotene,
789 an agonist of the retinoid X receptor pathway, has been identified as a positive regulator of
790 myelin debris clearance and a key player in the age-related decline in remyelination acting via
791 a yet undetermined direct or indirect effect (Natrajan et al., 2015a). The anti-psychotic
792 quetiapine fumarate promotes remyelination *in vivo* together with attenuating microglial
793 responses to inflammatory stimuli by decreasing TNF and nitric oxide secretion and preventing
794 activation of NF- κ B (Wang et al., 2015a).

795 New molecules are continuously being identified. Among them, a recombinant version
796 of a naturally occurring human IgM, rHIgM22, has been shown to promote remyelination in
797 Theiler's virus infection and cuprizone animal models and to stimulate myelin phagocytosis in
798 a dose-dependent manner (Zorina et al., 2018). The CSF1R kinase inhibitor BLZ945
799 prophylactically and therapeutically prevents demyelination in the cuprizone model, namely in
800 the corpus callosum, but however increase myelin debris and axonal damage in other fiber tracts
801 reminding the phenotype observed in cuprizone-treated TREM2 knock-out mice (Beckmann et
802 al., 2018; Wies Mancini et al., 2019). Although TNF is a master proinflammatory product of
803 activated microglia/macrophages implicated in CNS demyelination, the blockade of its soluble
804 form did not prevent cuprizone-induced oligodendrocyte loss and demyelination, but led to
805 efficient early remyelination due to improved phagocytosis of myelin debris and resolution of
806 microglia/macrophage activation (Karamita et al., 2017). Finally, the allosteric modulator of
807 P2X4R, Ivermectin, mimics P2X4R activation and improved motor function, electrical nerve
808 conductance, myelin debris phagocytosis and remyelination in the EAE model (Zabala et al.,
809 2018).

810 **Key studies supporting detrimental roles of microglia/macrophages on** 811 **oligodendrocytes and myelin**

812 Besides the growing number of data supporting the beneficial consequences of
813 promoting the pro-regenerative phenotype of microglia/macrophages, several critical works
814 support the deleterious effects of microglia activated through the classical way. First, activated
815 microglia synthesize a multitude of cytokines, chemokines, cell adhesion glycoproteins or
816 reactive oxygen radicals able to damage axons, myelin, oligodendrocytes (Minghetti and Levi,
817 1998; Raivich and Banati, 2004) and therefore involved in the initiation and propagation of the
818 inflammatory cascade, which promotes demyelination in neural disorders (Perry et al., 2010).
819 In a consistent manner, LPS-activated microglia, polarized to pro-inflammatory status secrete
820 tumor necrosis factor alpha (TNF α) and interleukin-1beta (IL-1 β), both known to be cytotoxic
821 for oligodendrocytes (Selmaj and Raine, 1988). TNF α and cuprizone supplementation to rat

822 primary cultures of oligodendrocytes consistently decreased cell viability (Pasquini et al.,
823 2007). Moreover, minocycline-mediated blockade of microglial activation in cuprizone-treated
824 mice prevented demyelination while a positive correlation was shown between the production
825 of nitric oxide and oligodendrocyte death (Merrill et al., 1993). Finally, LPS-induced secretion
826 of the stress chaperone protein, heat shock protein 60 (HSP60), was found to initiate OPC
827 apoptosis (Li et al., 2017).

828 As competent presenters of antigen, microglia activated in the classical way express
829 molecules for antigen presentation such as MHC II and its co-stimulatory factors CD40 and
830 CD86, characterized as classical markers of microglia activation in MS and Alzheimer's disease
831 patients (Gobin et al., 2001;Lehmann et al., 2001;Hoftberger et al., 2004). Remarkably,
832 activated microglia/macrophage is also highly proliferative in both MS and animal models of
833 demyelination mostly in actively demyelinating areas at the early stages of the disease but not
834 in remyelinating lesions again attesting the major role of classically activated
835 microglia/macrophages during the early stages of demyelinating diseases (Matsumoto et al.,
836 1992;Schonrock et al., 1998;Ponomarev et al., 2005). Early activation of microglia is similarly
837 observed in ischemic dementia models as shown by the increased expression of MHC-I/II or
838 matrix metalloprotease-2 (MMP-2) 3 days after hypoperfusion whereas administration of the
839 natural dipeptide carnosine (β -alanyl-L-histidine) able to decrease microglial activation
840 improved cognitive function and white matter lesions (Wakita et al., 1994;Ihara et al., 2001).
841 Finally, as previously mentioned, extracellular vesicles released by pro-inflammatory
842 microglia block remyelination via a mechanism depending on the presence of astrocytes
843 apparently converted into harmful cells by the inflammatory extracellular vesicle cargo
844 (Lombardi et al., 2019).

845 In summary, the majority of experimental evidence reported in this review, points to
846 astrocytes and microglia/macrophages as being crucial in both developmental and repairing
847 oligodendrogenesis and myelination. During development, astrocytes and a unique phenotype
848 of neonatal microglia secrete different patterns of molecules controlling oligodendrocyte
849 development and myelination. Although both cell types shape the number of OPCs with
850 consequences for subsequent myelinogenesis, astrocytes are also implicated in a tight crosstalk
851 between OPCs and axons making them indispensable for myelination. In addition, by providing
852 a substantial fraction of lipids incorporated into CNS myelin, astrocytes are also required for
853 the proper generation of the myelin sheath. Under pathological and demyelinating conditions,
854 reactive astrocytes and activated microglia/macrophages both exhibit a dual activity inducing
855 detrimental or beneficial effects, the balance of which appears to be critical for tissue
856 regeneration. Besides the secretion of a wide range of molecules, both cell types are able to
857 phagocyte myelin debris. However, in contrast to the beneficial role of microglia/macrophages-
858 induced phagocytosis, myelin uptake occurring as an early response of astrocytes results in
859 recruitment of immune cells possibly increasing tissue damage in demyelinating conditions
860 driven by inflammation. As a whole, the review indicate that beyond the secretion of a multitude
861 of cues directly controlling diverse facets of OPC biology, astrocytes and
862 microglia/macrophages strongly modify the lesion microenvironment. Further delineation of
863 this crosstalk should open the way towards novel therapeutic approaches aimed at recovering
864 proper developmental myelination and relieving the obstacles on failure of regeneration of
865 damaged myelin characterizing CNS demyelinating diseases.

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1499 **Figure legends**

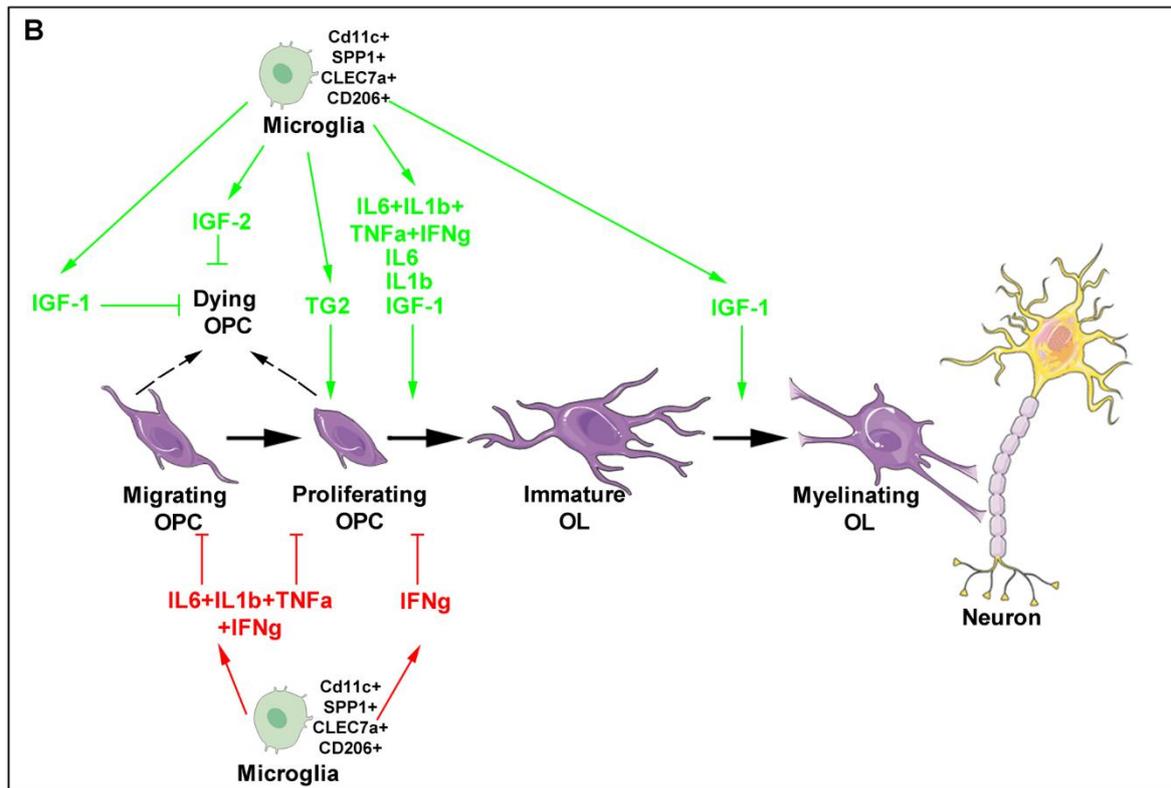
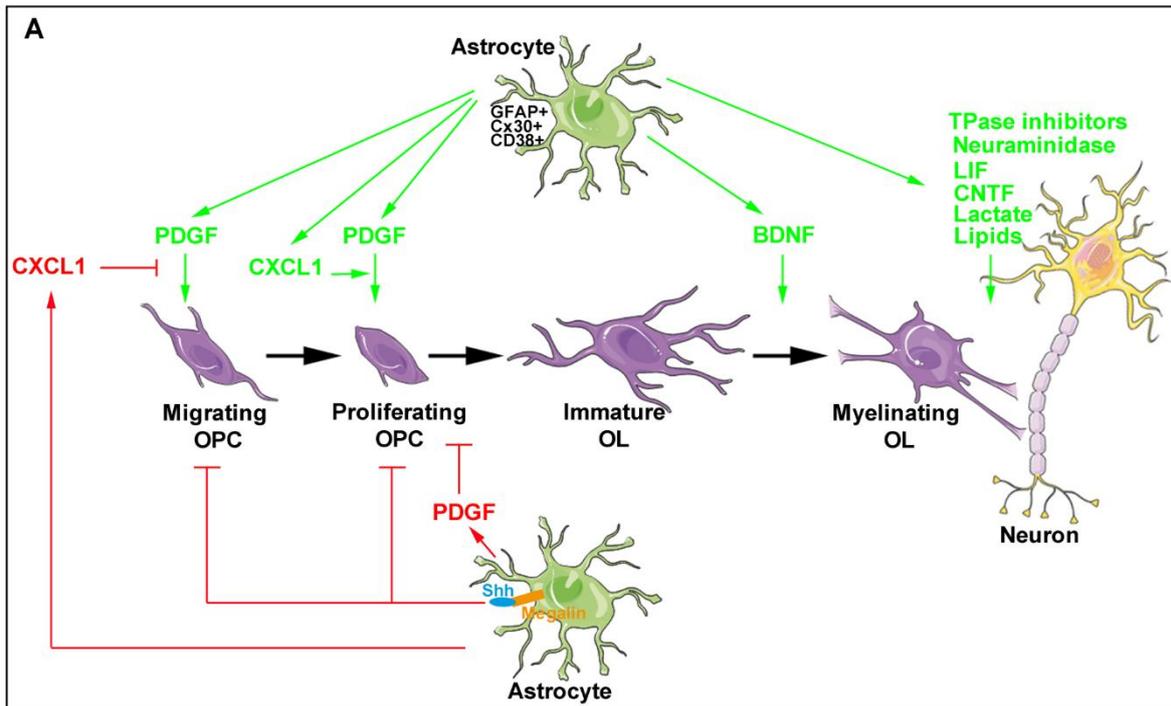
1500 **Figure 1 : Major roles of astrocytes and microglia during developmental**
1501 **oligodendrogenesis and myelination.** The different steps of oligodendroglial cell production
1502 (purple) are shown and include OPC migration, proliferation, differentiation as well as the
1503 maturation of immature oligodendrocytes into cells able to myelinate neuronal axons.
1504 Astrocyte- (A) and microglia- (B) derived molecules are indicated. The green arrows indicate
1505 molecules exhibiting a positive activity on oligodendrocyte lineage and myelin production (top
1506 in each panel) whereas the red arrows and blocking symbols indicate molecules displaying an
1507 inhibiting activity on oligodendroglial lineage production (bottom in each panel).

1508 **Figure 2 : Reactive astrocyte-derived secretion products during myelin repair.** The
1509 oligodendroglial lineage is shown in purple. Reactive astrocytes generate molecules promoting
1510 (top, green arrows) or blocking (bottom, red arrows and blocking symbols) myelin regeneration.
1511 Besides reactive astrocytes, two additional forms of astrocytes are indicated including myelin-
1512 laden astrocytes endowed with a deleterious effect under inflammatory conditions and
1513 transplanted immature astrocytes which promote OPC proliferation / differentiation and
1514 additionally prevent glial scar formation.

1515 **Figure 3 : Key effects of microglia/macrophages during myelin repair.** (A) Illustration of
1516 morphological modifications of ramified microglia/macrophages, which adopt a rhomboid
1517 shape in the presence of any insult and become activated into a classical or alternative manner
1518 giving rise to a range of cell phenotypes expressing mostly pro- (red) or anti-inflammatory
1519 (green) molecules, respectively. (B) Phagocytosis of myelin debris is a critical activity of
1520 microglia/macrophages for promoting myelin regeneration. Phagocytic receptors such as CR3
1521 advance phagocytosis by promoting the activation of paxillin and cofilin whereas the immune
1522 inhibitory receptor SIRP α , inhibits phagocytosis by promoting the inactivation of the two.
1523 Recruited by CR3, Syk downregulates CR3-mediated myelin phagocytosis protecting
1524 phagocytes from excessive phagocytosis during prolonged exposure to debris. (C) Pro-
1525 regenerative microglia secrete a range of molecules intervening at various steps of myelin
1526 repair.

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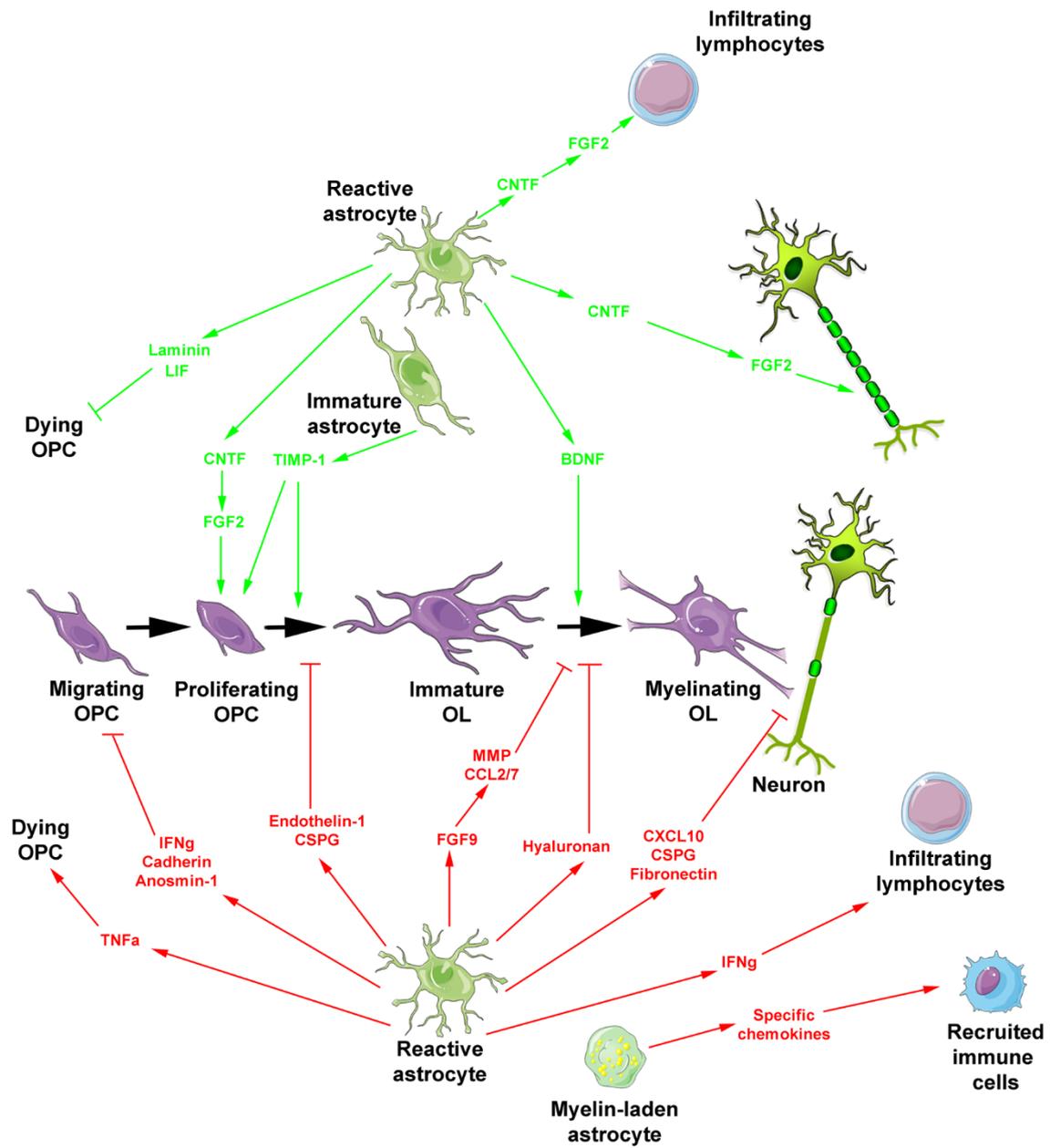
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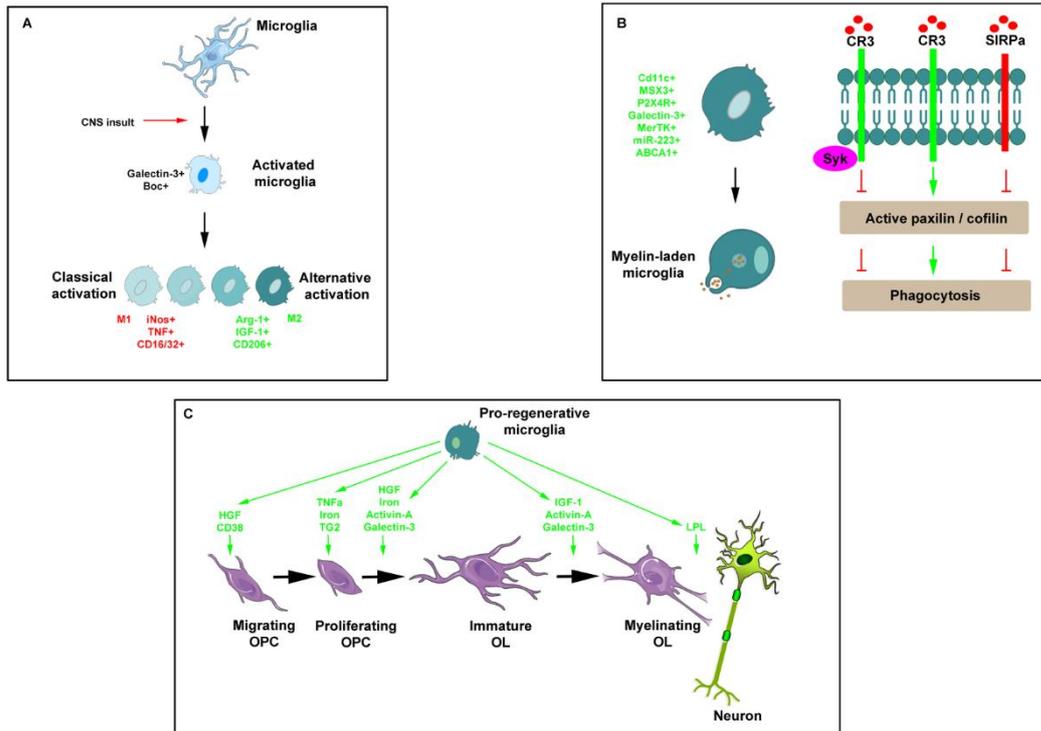
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1531 Figure 1

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 1534 Figure 2.
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1537 Figure 3.