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Adult oligodendrocyte progenitor cells - multifaceted regulators of the CNS in health and disease

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Abstract

Oligodendrocyte progenitor cells (OPCs) are the often-overlooked fourth glial cell type in the central nervous system (CNS), comprising about 5% of the CNS. For a long time, our vision of OPC function was limited to the generation of mature oligodendrocytes. However, new studies have highlighted the multifaceted nature of the OPCs. During homeostatic and pathological conditions, OPCs are the most proliferative cell type in the CNS, a property not consistent with the need to generate new oligodendrocytes. Indeed, OPCs modulate neuronal activity and OPC depletion in the brain can trigger depressive-like behavior. More importantly, OPCs are actively recruited to injury sites, where they orchestrate glial scar formation and contribute to the immune response. The following is a comprehensive analysis of the literature on OPC function beyond myelination, in the context of the healthy and diseased adult CNS.

Keywords

Oligodendrocyte progenitor cells; myelin; glial scar; inflammation; multiple sclerosis

1. Introduction

The central nervous system (CNS) is home to three major classes of glia: Astrocytes, microglia, and oligodendrocytes. In the last two decades, a fourth class of glia has emerged, called the oligodendrocyte progenitor cells (OPCs). OPCs have a stellate morphology and are present in both the gray and white matter. They belong to the same population of progenitors that give rise to oligodendrocytes during CNS development. However, a large fraction of OPCs do not differentiate and remain in a cycling state throughout adulthood. OPCs represent the largest dividing population among neural cells and are uniformly distributed, making up, on average, 5% of total CNS cells (Dawson et al., 2003). The first described function of adult OPCs was differentiation into oligodendrocytes (Gensert and Goldman, 1997). When myelin repair is needed after CNS injury, local OPC proliferation occurs, followed by OPC differentiation into oligodendrocytes (Lytle et al., 2009). OPC

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differentiation is accompanied by expression of mature oligodendrocyte markers such as proteolipid protein and myelin basic protein. Oligodendrocytes then generate a large amount of plasma membrane and begin to wrap around neuronal axons to form the myelin sheath in a process called myelination (Baron and Hoekstra, 2010; Snaidero et al., 2014). The mammalian brain undergoes myelination beyond postnatal stages and well into adulthood, highlighting the importance of adult OPCs in generating oligodendrocytes (Young et al., 2013). However, the differentiation rate of OPCs into myelinating oligodendrocytes decreases with age, with only a small percentage of OPCs giving rise to oligodendrocytes, suggesting that OPCs may have important functions beyond myelination (Psachoulia et al., 2009; Rivers et al., 2008; Zhu et al., 2011).

Adult OPCs are evenly dispersed throughout the CNS and *in vivo* imaging studies have shown that they are poised to detect perturbations within the CNS, by sending numerous filopodia to survey their surroundings (Hughes et al., 2013). For example, OPCs rapidly respond during CNS injury and disease by proliferating extensively and quickly populating the lesion site (Kang et al., 2013a; Simon et al., 2011). Although some OPCs in the lesion differentiate into oligodendrocytes, there is a burgeoning interest in other possible roles of OPCs in response to CNS injury. Furthermore, OPCs can influence neuronal activity by altering the composition of the extracellular matrix (Sakry et al., 2014). Recently, loss of OPCs in the prefrontal cortex has been shown to alter glutamatergic signaling and promote depressive-like behavior in mice (Birey et al., 2015). These studies highlight a novel role of OPCs in modulating neuronal network activity adding to our understanding of glia-neuron interactions. The multifunctional role of OPCs during CNS homeostasis and pathologies will be presented in the following chapters, keeping in mind the gaps that still exist in our knowledge about these fascinating cells.

2. OPCs in the adult CNS

OPC development has been extensively studied and is beyond the scope of this review (Gallo and Deneen, 2014; Takebayashi and Ikenaka, 2015). In adults, OPCs are present across the CNS but their quantity varies between the white and gray matter (Dawson et al., 2003). In the white matter, such as the dorsal column of the spinal cord, OPCs can account for up to 8% of all cells, while in the dorsal horn gray matter OPCs account for only 3% of the cellular content (Dawson et al., 2003). With this difference in mind, adult OPCs remain uniformly distributed across the brain and the spinal cord. Live-imaging studies performed in the cortex reveal that OPCs have elegantly ramified processes that constantly survey the environment and maintain an even distribution using self-repulsion mechanisms (Hughes et al., 2013). In the superficial layers of the cortex, each OPC covers its own territory, with clear borders and no apparent overlap (Hughes et al., 2013). An important characteristic of OPCs is that they represent the major dividing cell population in the CNS. Using BrdU labeling methods, multiple studies have shown that OPCs account for more than 70% of CNS dividing cells, potentially outpacing the need for replacement of mature oligodendrocytes (Dawson et al., 2003; Gensert and Goldman, 2001). Yet, the principal role of adult OPCs was believed to be the generation of new myelinating oligodendrocytes. Myelination in white matter tracts of the mouse CNS occurs continuously after birth, even after 8 months of age (Psachoulia et al., 2009; Rivers et al., 2008). However, the rate at

which OPCs differentiate into oligodendrocytes decreases with age, suggesting that OPCs could have functions other than myelination. Given their uniform distribution and constant surveillance of the environment, OPCs are well positioned to sense changes in CNS homeostasis. Indeed, OPCs respond to primary demyelination and several types of CNS injury, with extensive proliferation, migration and morphological changes, but the utility of these actions in the context of CNS repair is not fully understood (Dimou and Gallo, 2015).

3. OPC heterogeneity

In development, OPCs have distinct spatial and temporal origins, raising the question of whether there is functional heterogeneity among the OPC populations (Takebayashi and Ikenaka, 2015). Ablation of any one OPC population during development results in compensation by neighboring OPCs of different origin, suggesting that spatial origin does not commit OPCs to a single function (Kessaris et al., 2006). Although no overt functional differences in OPCs across the CNS have yet been identified, region-specific environments can alter OPC behavior. In fact, fate-mapping studies have shown OPCs in white matter differentiate into oligodendrocytes more frequently than gray matter OPCs (Dimou et al., 2008). In addition, OPCs in white matter have a shorter cell division cycle (10 days in the corpus callosum at P60) compared to gray matter OPCs (36 days in the motor cortex at P60) (Young et al., 2013). Hill *et al.* also demonstrated that white matter perinatal OPCs have a greater proliferative response to PDGFα than gray matter OPCs and that this difference was not due to differential expression of the PDGFα receptor (PDGFRα) (Hill et al., 2013). This suggests that regional differences in environment might affect OPC properties and account for dissimilarities between OPC populations. Furthermore, transplantation of white matter OPCs into gray or white matter results in comparable amounts of oligodendrocyte differentiation (Vigano et al., 2013). On the other hand, gray matter OPCs only exhibited greater oligodendrocyte differentiation when transplanted into white matter. Therefore, it appears that the white matter environment supports oligodendrocyte maturation, and that this effect is preserved in OPCs even after they have been taken out of the white matter environment (Vigano et al., 2013). These differences highlight the long-term effects that the extracellular environment could have on OPC function. However, OPC functional heterogeneity remains a matter of debate, and identification of OPC subtypes characterized by expression of specific markers is warranted. It is possible that a subtype of OPCs specializes in remyelination and repair, while others have a role in CNS homeostasis. The recent improvement in single cell RNA sequencing methods could aid in answering these open questions about OPC biology.

4. CNS Myelination in Adulthood

When they were first phenotypically characterized, adult OPCs were shown to express the same markers as embryonic OPCs. However, questions were raised about whether these cells shared the same lineage and whether they also generated oligodendrocytes. With advances in transgenic reporter mice, it became possible to conduct fate-mapping studies using specific Cre reporter lines, and the functions of adult OPCs began to emerge. Zhu *et al.* used NG2-Cre stop-flox-EGFP reporter mice to examine the fate of postnatal OPCs. In this system, NG2-expressing OPCs express the Cre recombinase and excise the stop-flox

sequence, and are labeled with EGFP. As expected, 78% of oligodendrocytes in the corpus callosum and striatum are $EGFP^+$, indicating that OPCs gave rise to those oligodendrocytes (Zhu et al., 2008). This study, however, was conducted at the peak of myelination (P14) in the mouse CNS, and hence OPCs examined here likely belong to the last wave of the progenitors that occurs at birth. Therefore, a P14 OPC is likely not the same as an OPC from, for example, a three- or an eight-month old mouse. Surprisingly, $EGFP^+$ astrocytes were also found in the ventral gray matter, implying that either OPCs can also generate astrocytes *in vivo,* or that astrocyte precursors also express NG2 (Zhu et al., 2008). Rivers *et al.* used an inducible PDGFRα-driven Cre YFP reporter line to label OPCs at P45 and examine their progeny 240 days later (Rivers et al., 2008). The authors found that an astonishing 29% of oligodendrocytes in the corpus callosum were generated by OPCs between P45 and P255 (Rivers et al., 2008). Interestingly, the authors found no evidence to support the fact that OPCs also generate astrocytes, but did report a small population of reporter positive neurons in the piriform cortex (Rivers et al., 2008). Subsequently, three independent fate-mapping studies concluded that adult OPCs produce oligodendrocytes exclusively throughout life (Dimou et al., 2008; Kang et al., 2010; Zhu et al., 2011). It is unclear whether imperfections in the reporter systems used contributed to the conclusions that OPCs are multipotent progenitors that can give rise to astrocytes and neurons, in addition to oligodendrocytes (Richardson et al., 2011).

Oligodendrocyte generation in gray matter occurs less frequently than in white matter (Dimou et al., 2008). Studies using *in vivo* two-photon imaging of superficial cortical layers in adult mice reported that less than 1% of OPCs mature into oligodendrocytes, while 96% remain stable over a 40-day timespan (Hughes et al., 2013). Though one might expect higher OPC turnover in highly myelinated regions, the overall oligodendrocyte production does not differ between adult structures with varying degrees of myelination (Young et al., 2013). Young *et al.* compared the robustly myelinated optic nerve to the partially myelinated corpus callosum in adult mice and found no long-term change in the number of new oligodendrocytes integrating in those tracts (Young et al., 2013). Whether newly differentiated OPCs replace dying oligodendrocytes to stabilize a circuit or integrate to improve network function is still not known. Evidence to support the latter comes from observations that newly generated oligodendrocytes have significantly shorter internodes compared to neonatal oligodendrocytes, suggesting integration into already myelinated axons (Young et al., 2013). At odds with this explanation is the fact that myelinated axons are not encapsulated with myelin uniformly. For example, myelinated axons from pyramidal neurons in the neocortex have lengthy unmyelinated tracts in which newly generated oligodendrocytes can integrate without restrictions on internode length (Tomassy et al., 2014).

The factors responsible for inducing continuous oligodendrocyte generation in adulthood are also incompletely understood. In mice, physical exercise can cause cortical OPCs to exit the cell cycle and generate oligodendrocytes (Simon et al., 2011). In humans, structural changes associated with white matter can be detected by magnetic resonance imaging after performing complex tasks such as practicing piano (Bengtsson et al., 2005). In rodents, it has been demonstrated that motor skill learning induces myelination (Sampaio-Baptista et al., 2013). More importantly, blocking the differentiation of OPCs into myelinating

oligodendrocytes impairs motor skill learning (McKenzie et al., 2014). These findings are consistent with the role of myelin in improving the stability and function of neuronal circuits that are involved in learning. As discussed in more detail below, neuronal activity is implicated in OPC differentiation and proliferation, but myelination is not exclusively activity-dependent (Gibson et al., 2014; Hines et al., 2015). Elucidation of the specific molecular and behavioral trigger mechanisms that control myelination is a fascinating area of future research.

Another intriguing question is whether the myelination dynamics observed in rodent models are also a feature of human myelination. While in mice new oligodendrocytes appear to be generated throughout adulthood, emerging studies challenge our rodent-based perception of oligodendrocyte dynamics in the adult CNS. In the human corpus callosum, the oligodendrocyte number is established early in childhood and remains stable throughout life, such that an annual oligodendrocyte generation rate is estimated at 0.3% (Yeung et al., 2014). This number is strikingly low even when compared to a conservatively calculated rate in mice of 36% (Yeung et al., 2014). Of note, however, is that although oligodendrocytes are established early in life, the myelin sheath is continuously renewed, suggesting that it is a highly dynamic structure (Yeung et al., 2014). An attractive hypothesis is that human oligodendrocytes have evolved to remodel the myelin sheath without requiring generation of a new oligodendrocyte from an OPC (Yeung et al., 2014). Thereby, oligodendrocyte turnover could result in segments of axons temporarily demyelinated, not conducive for efficient neuronal activity. The discrepancies in adult myelination and OPC function between species remain to be reconciled. It is an essential problem warranting further studies, as much of our understanding of human demyelinating diseases comes from non-human vertebrate models.

5. Neuron-OPC bidirectional crosstalk

Recently, neuronal activity has been studied as a regulator of myelination in the CNS (Gibson et al., 2014; Hines et al., 2015). OPCs were first reported to receive excitatory glutamatergic synaptic input via OPC-expressed AMPA receptors (Bergles et al., 2000). Subsequently, Lin and Bergles showed that OPC also express $GABA_A$ receptors and are responsive to GABAergic input (Lin and Bergles, 2004). These seminal works established the notion of a bona fide neuron-OPC synapse, but little is known about its significance. Gibson *et al.* recently used optogenetic technology to stimulate the mouse premotor cortex and showed that neuronal activity promotes OPC proliferation, differentiation and myelination (Gibson et al., 2014). OPC proliferation in the premotor cortex was detectable with three hours of optogenetic stimulation. Four weeks following a seven-day optogenetic stimulation paradigm, there was also an increase in newly generated oligodendrocytes. The authors also noted a mild but significant increase in myelin thickness in the premotor cortex, which correlated with increased limb swing speed (Gibson et al., 2014). Follow up studies demonstrated that activity-dependent synaptic vesicle release is necessary to induce myelination during zebrafish development, confirming the hypothesis that endogenous neuronal activity can affect myelination in the CNS (Hines et al., 2015; Mensch et al., 2015). There are many questions left unanswered regarding the effects of neuronal activity on OPCs. It is important to note that suppressing neuronal activity by blocking voltage-gated sodium channels did not completely prevent myelination during zebrafish development

(Hines et al., 2015). Specific deletion of NMDA receptor subunit NR1 in OPCs also does not affect myelination in the developing rodent CNS (De Biase et al., 2011). Yet, NR1 deletion in OPCs results in their upregulation of calcium-permeable AMPA receptors, another avenue by which glutamate signaling might modulate OPC biology. Activation of AMPA receptors has been shown to inhibit OPC differentiation *in vitro* and stimulate OPC migration *in vivo*, but OPC-specific deletion of AMPA receptor signaling is needed to fully elucidate their contribution to OPC biology (Gallo et al., 1996; Harlow et al., 2015). In addition, the magnitude of OPC proliferation and the newly derived oligodendrocyte number after optogenetic stimulation did not translate into a robust increase in myelin thickness. In fact, only a surprisingly low increase in g-ratio was observed between stimulated and unstimulated mice, suggesting a potential unconventional fate for these newly generated cells (Gibson et al., 2014).

OPCs are well positioned in the CNS to directly modulate neuronal function. At the synapse, OPCs have been shown to make contact with pre and post-synaptic terminals (Bergles et al., 2000; Ong and Levine, 1999). Furthermore, OPCs are known to contact axons at the nodes of Ranvier, suggesting that OPCs could maintain node function (Butt et al., 1999). Because OPCs receive GABAergic and glutamatergic synaptic input, they could be capable of sensing and modulating network activity. Birey *et al.* have now demonstrated that OPC deletion in the prefrontal cortex (PFC) compromises glutamatergic signaling in pyramidal neurons (Birey et al., 2015). This perturbation in neurotransmission is accompanied by a decrease in astrocytic gluatamate uptake following OPC ablation. Aberrations in glutamatergic signaling translate into a behavioral phenotype, as loss of OPCs triggered depressive-like behavior, which was rescued after endogenous OPC repopulation. Likewise, mice susceptible to a social defeat stress paradigm had reduced numbers of OPCs in the PFC, a feature shared by patients with major depressive disorder (Birey et al., 2015). This study is the first to demonstrate a robust physiological and behavioral change after OPC ablation, elucidating a novel role of OPCs in regulating CNS homeostasis. However, as this OPC ablation model does not delete OPCs uniformly across the CNS, novel roles for OPCs outside the PFC remain unknown.

Sakry *et al.* have demonstrated that ectodomain cleavage of NG2, a proteoglycan highly expressed by OPCs, can also modulate neuronal networks (Sakry et al., 2014). Cleavage of NG2 in OPCs was activity dependent, and its blockade with protease inhibitors resulted in the impairment of NMDAR-dependent long-term potentiation (Sakry et al., 2014). This loss of long-term potentiation was recapitulated using the global NG2 knockout mouse, which also had diminished AMPAR- and NMDAR-mediated neuronal currents but did not present with learning and memory deficits (Sakry et al., 2014). Finally, bath application of the NG2 ectodomain onto brain slices results in more c-Fos positive neurons compared to controls after glutamate stimulation (Sakry et al., 2014). The lack of an OPC-specific NG2 knockout model questions whether these findings are mediated exclusively by OPCs. A follow up study found that OPCs express neuromodulatory factor neuronal Pentraxin 2 (Nptx2), which affects AMPAR stability and trafficking at the cell surface (Sakry and Trotter, 2015). Taken together, the data suggests that OPC-derived factors can affect neuronal network activity, but the importance of this bidirectional OPC-neuron communication requires further investigation.

Oligodendrocytes also participate in a novel mode of bidirectional crosstalk using the transfer of exosomes from oligodendrocytes to neurons (Fruhbeis et al., 2013). Neuronal activity mediates exosome secretion from oligodendrocytes, which are then endocytosed by the neurons and promote survival under oxidative stress or nutrient deprivation conditions (Fruhbeis et al., 2013). Neurons can also endocytose exosomes from oligodendrocytes during the resting state, but the contents of the exosome cargo and how they impact neurons under these conditions is not known. Exosome secretion is further triggered by the Ca^{2+} influx that results from the glutamate binding NMDA and AMPA receptors on oligodendrocytes (Fruhbeis et al., 2013). Given that OPCs express NMDAR and AMPAR and are part of the oligodendroglial lineage, it is possible that similar modes of communication exist in OPCs (Sakry et al., 2015).

6. OPCs respond to CNS Injury

One of the most unique qualities of OPCs is their ability to respond to several types of CNS injury. OPCs respond to secondary demyelinating insults, even when oligodendrocytes are not primarily targeted, for example in mechanical lesions, spinal cord injury, ischemia, and neurodegeneration (Kang et al., 2010; Levine, 1994; McTigue et al., 2001; Zhang et al., 2013). Increased levels of OPCs have also been documented in the prefrontal cortex after acute methamphetamine exposure, perhaps as a part of the alterations to addiction circuitry that needs to be examined further (Somkuwar et al., 2014). OPCs, along with microglia, respond within a day after traumatic brain injury by migrating to and occupying the lesion site, where they become hypertrophic and highly proliferative (Dimou and Gallo, 2015). Surprisingly, *in vivo* imaging of CNS stab wound injuries showed that at 5 days post-injury astrocytes have a low proliferation rate, and do not exhibit migration to the lesion site (Bardehle et al., 2013). Reactive OPCs are also found in models of CNS neurodegeneration, such as the SOD1 (G93A) mutant mouse that recapitulates features of human amyotrophic lateral sclerosis (ALS) (Kang et al., 2010). Progressive motor neuron death in the spinal cord of these mice is accompanied by a robust increase in OPC proliferation and differentiation (Kang et al., 2010). This suggests that OPCs and microglia, but not astrocytes, are playing an immediate role in the CNS injury response that remains to be fully explored.

7. OPCs contribute to glial scar formation

After any kind of CNS injury, glial cells become activated and orchestrate the formation of the glial scar. The glial scar is characterized by a high content of ECM molecules forming an environment known to block axonal regeneration and remyelination (Cregg et al., 2014; Silver and Miller, 2004). Chondroitin sulfate proteoglycans (CSPGs) are a key component of the inhibitory glial scar (Davies et al., 1997; Lau et al., 2012). While reactive astrocytes are the principal cells present within the glial scar, it is now clear that OPC are not bystanders during the scar formation. Following spinal cord injury, OPCs proliferate and upregulate NG2 expression, thereby inhibiting axonal regeneration (Tan et al., 2005). Rhodes *et al.* reported that treatment with antimitotic drugs, aimed at diminishing glial scar formation by eliminating OPC proliferation in knife wound injuries, results in a slight improvement in axonal regeneration (Rhodes et al., 2003). This result suggests that OPC proliferation and upregulation of NG2 can be detrimental to axon regrowth. Conversely, OPC expression of

NG2 has also been shown to support axon growth *in vitro*, even when NG2 was overexpressed in OPCs (Yang et al., 2006). The contribution of the OPC to the glial scar is not limited to only one type of CSPG (Jones et al., 2003). OPC have been show to also produce keratan sulfate proteoglycan after injury, and can also produce neurocan and versican, CSPGs known to impair CNS repair (Asher et al., 2000; Asher et al., 2002; Jones and Tuszynski, 2002). In conclusion, OPC clearly participate in the formation of the glial scar and produce CSPGs that impair CNS repair and their differentiation into mature myelinating oligodendrocytes. This apparent duality in function clearly highlights the multi-functionality of OPC in the CNS.

8. OPC as innate immune cells

Microglia and astrocytes are considered to be the classic innate immune cells of the CNS because of their response to pathogens or tissue damage and their ability to recruit peripheral immune cells (Ransohoff and Brown, 2012). However, the literature contains evidence that OPCs are not simple spectators of the CNS immune response. In a mouse model of cerebral prolonged hypoperfusion, OPCs are the initial producers of MMP9, an enzyme necessary for degradation of the extracellular matrix, prior to the appearance of white matter damage (Seo et al., 2013). Furthermore, authors demonstrated that OPC derived MMP9 could mediate the opening of the BBB and the infiltration of neutrophils that ultimately damage the myelin sheath in this model (Seo et al., 2013). Moyon *et al.* have recently demonstrated that OPCs isolated from the brain of mice undergoing cuprizone-induced demyelination express high levels of CCL-2 and IL-1β (Moyon et al., 2015). CCL-2 has a critical role in recruiting monocytes (Deshmane et al., 2009) while IL-1β is a powerful inflammatory cytokine involved in many aspects of the immune response (Sims and Smith, 2010). While authors did not explore the role of these mediators on immune cell recruitment/activation, they discovered that CCL-2 promotes OPC migration *in vivo* and is also expressed by OPCs present in active multiple sclerosis (MS) lesions (Moyon et al., 2015). Recent work by Gadani *et al.* also highlights the role that myelinating glia play in repair after spinal cord injury. Oligodendrocytes release IL-33, a nuclear alarmin implicated in orchestrating the recruitment of peripheral immune cells necessary for CNS repair (Gadani et al., 2015b). Although predominantly expressed by oligodendrocytes, OPCs also express IL-33 and participate in promoting CNS repair (Gadani et al., 2015b). Beyond producing inflammatory mediators, OPC can respond to cytokines and chemokines, such as TNF-α, IL-1β and IFN-γ (Arnett et al., 2001; Vela et al., 2002). The impact of these molecules on OPCs remains controversial, with reports suggesting both a beneficial outcome on myelination and induction of OPC death. For example, TNFα is highly expressed in demyelinating MS lesions and has been shown to potentiate IFN-γ-induced cell death *in vitro* (Andrews et al., 1998; Watzlawik et al., 2010). Arnett *et al.* showed a modest delay in cuprizone-induced oligodendrocyte death in TNF-α knockout mice, implicating it as a potentially harmful cytokine (Arnett et al., 2001). Unexpectedly, the study also showed that TNF-α knockout mice suffered from impaired remyelination (Arnett et al., 2001). Mice lacking TNF-α showed decreased OPC proliferation and, as a result, less oligodendrocytes were ultimately generated, accounting for decreased remyelination (Arnett et al., 2001). This data implies that TNF-α has a dual role in both demyelination and remyelination. Furthermore, a recent

study demonstrated that OPCs respond to the T cell produced cytokine, IL-17, and actively participate in the amplification of pathology in experimental autoimmune encephalomyelitis, an animal model of MS (Kang et al., 2013b). Finally, OPCs have been shown to be phagocytic *in vitro*, as isolated cultures of OPCs can efficiently engulf myelin debris (Gaultier et al., 2009). More work needs to be performed *in vivo* to determine if OPC could participate in the clearance of cellular debris in the context of CNS pathology, especially considering their rapid recruitment at the injury site. In conclusion, OPCs contribute to the immune response in the CNS by producing and responding to inflammatory mediators in a multitude of pathologies.

9. Conclusion

Over the past decade, we have greatly expanded our knowledge of OPC biology and function within the CNS. We now appreciate that adult OPCs are responsible for generating myelinating oligodendrocytes throughout life. Yet, myelination is not their only role within the CNS, as presented in this review (Figure 1). Recent studies have provided compelling evidence that OPCs are capable of modulating neuronal and astrocytic functions that can ultimately affect behavior (Birey et al., 2015; Sakry et al., 2014), providing a new perspective on adult OPC function. After all, adult OPCs are uniformly distributed across the CNS, giving them the ability to survey widespread network activity. However, questions remain regarding adult OPC function. Despite their unique developmental origins within the CNS, no functional differences have been found regarding their myelination potential. It is possible that differences in function might arise in their ability to regulate neuronal activity in distinct regions of the CNS. As the field continues to examine the OPC-neuron synapse, other roles of adult OPCs might become clearer.

OPCs also respond to several types of CNS injury. As microglia and astrocytes have traditionally held the spotlight in CNS injury, the contribution of OPCs to tissue repair would be interesting to explore. Recent work has shown that OPCs upregulate expression of immune signaling molecules CCL-2 and IL-1β to promote their migration into demyelinating lesions (Moyon et al., 2015). These immune molecules were shown to be important for OPC migration, but they could also be involved in orchestrating an inflammatory response. CCL-2 produced by astrocytes and IL-1β produced by microglia has been shown to amplify the immune response following CNS injury, which can be beneficial to tissue repair (Gadani et al., 2015a). Although it is clear that OPCs can produce immune molecules during CNS injury, their contribution to the inflammatory response needs to be further elucidated.

The need to target OPCs to promote remyelination in demyelinating diseases such as MS, is an important therapeutic goal. Although much of the research has been focused on identifying the factors implicated in inhibition of OPC differentiation and remyelination, acknowledgement that OPC can exert a multitude of function might accelerate the discovery of novel treatment option for demyelinating disorders. Given the evidence presented in this review, it is highly possible that the multi-functionality of OPCs during CNS disease might steer OPCs away from repair and towards the immune response and/or the glial scar

formation. A deeper understanding of OPC function in the CNS is warranted before we can truly begin to explore their therapeutic potential.

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Highlights

- Oligodendrocyte progenitor cells comprise about 5% of the CNS cellular content.
- OPC are continuously renewed, with rates increasing during pathologies.
- Beyond myelination, oligodendrocyte precursor cells can modulate neuronal activity.
- Oligodendrocyte precursor cells are recruited to injury sites
- OPC contribute to the immune response and the formation of the glial scar.

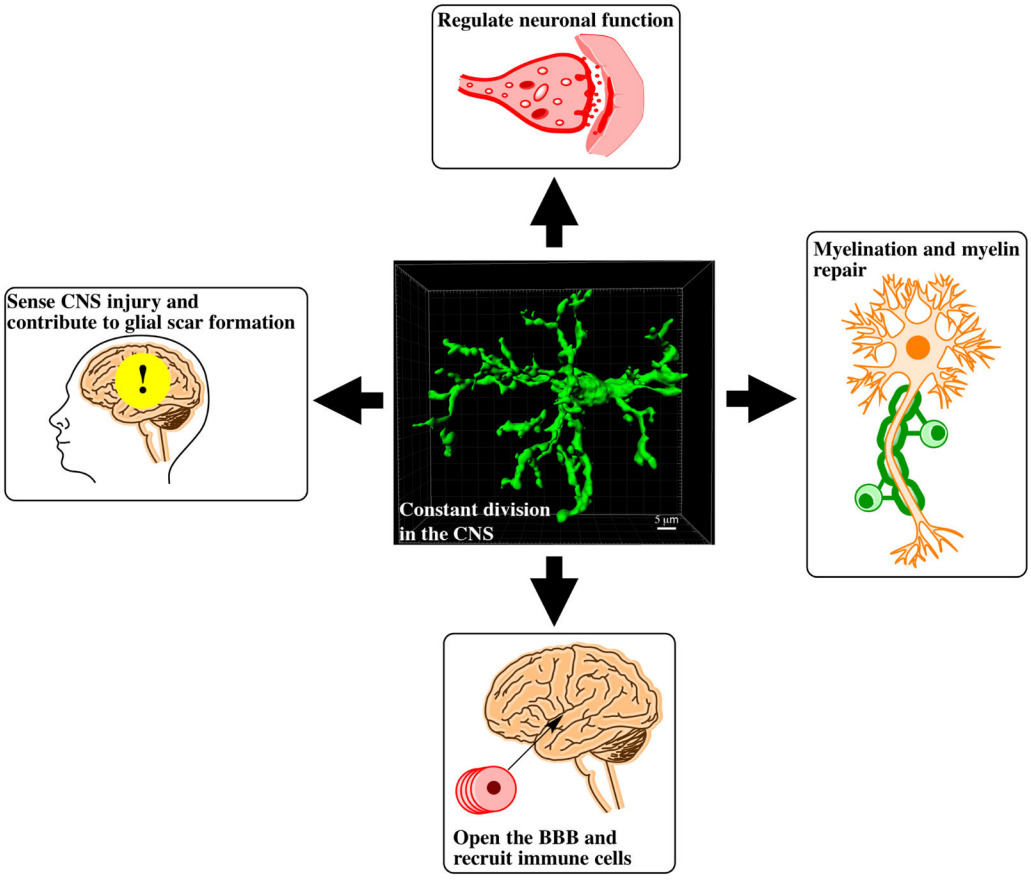

Figure 1.
The multiple functions of oligodendrocyte progenitor cells in the central nervous system. Central panel represents a 3D rendering of an OPC in the cortex.