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Oligodendrocyte Progenitor Programming and Reprogramming: Toward Myelin Regeneration

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Abstract

Demyelinating diseases such as multiple sclerosis (MS) are among the most disabling and cost-intensive neurological disorders. The loss of myelin in the central nervous system, produced by oligodendrocytes (OLs), impairs saltatory nerve conduction, leading to motor and cognitive deficits. Immunosuppression therapy has a limited efficacy in MS patients, arguing for a paradigm shift to strategies that target OL lineage cells to achieve myelin repair. The inhibitory microenvironment in MS lesions abrogates the expansion and differentiation of resident OL precursor cells (OPCs) into mature myelin-forming OLs. Recent studies indicate that OPCs display a highly plastic ability to differentiate into alternative cell lineages under certain circumstances. Thus, understanding the mechanisms that maintain and control OPC fate and differentiation into mature OLs in a hostile, non-permissive lesion environment may open new opportunities for regenerative therapies. In this review, we will focus on 1) the plasticity of OPCs in terms of their developmental origins, distribution, and differentiation potentials in the normal and injured brain; 2) recent discoveries of extrinsic and intrinsic factors and small molecule compounds that control OPC specification and differentiation; and 3) therapeutic potential for motivation of neural progenitor cells and reprogramming of differentiated cells into OPCs and their likely impacts on remyelination. OL-based therapies through activating regenerative potentials of OPCs or cell replacement offer exciting opportunities for innovative strategies to promote remyelination and neuroprotection in devastating demyelinating diseases like MS.

Keywords

Oligodendrocyte; Progenitor; Plasticity; Myelination; Remyelination

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Introduction

Diseases that result in demyelination in the central nervous system (CNS) such as multiple sclerosis (MS), leukodystrophies, and cerebral palsy are major causes of neurological mortality and morbidity (Fancy et al., 2011; Franklin and Ffrench-Constant, 2008). In MS lesions, the myelin sheaths that wrap axons are damaged, resulting in impaired axonal conduction and neurological dysfunctions. Although MS is thought to be an autoimmune-mediated demyelinating disease, several immune-focused treatment methods for this disease show only partial benefits and do not result in lesion repair (Franklin and Ffrench-Constant, 2008; Zawadzka and Franklin, 2007). Loss of oligodendrocytes (OLs) that produce myelin is a hallmark of MS. Although neural stem cells are able to produce OLs in the adult brain (Alvarez-Buylla et al., 2000; Dimou et al., 2008; Rivers et al., 2008), their capacity to replenish OLs is limited. This has sparked considerable interest in treating demyelinating diseases in the CNS by enhancing the production of OLs and their precursors, OL precursor cells (OPCs). During development and adulthood, OPCs reside throughout the CNS and could be an important cell source for myelin regeneration in multifocal demyelinating lesions in MS.

OPCs are characterized by expression of platelet-derived growth factor receptor alpha (PDGFRα) and the proteoglycan NG2 (Levison et al., 1999; Nishiyama et al., 2002; Rivers et al., 2008; Zhu et al., 2008). OPCs produce differentiating and mature OLs in the CNS throughout the lifespan of the animals (Dawson et al., 2003). Moreover, in their undifferentiated state, OPCs exhibit specific electrophysiological properties and integrate into the cellular network that modulates neuronal activity and responds to pathological insults (Bergles et al., 2010). Recent studies indicate that OPCs may become multipotent and capable of adopting different cell fates under certain circumstances. For instance, a misguided differentiation of OPCs into astrocytes may exhaust the reparative cell pool, which contributes to remyelination failure in MS (Kotter et al., 2011).

In this review, we will discuss recent advances in OPC programming and reprogramming, including their developmental origins, plasticity, and the factors that direct OL lineage progression. We will also evaluate recently described strategies of mobilizing endogenous neural progenitor cells and reprograming of differentiated cells into OPCs, and their respective effectiveness in remyelination. Finally, we discuss how to harness current knowledge to develop effective therapeutic strategies to replace OL loss and promote myelin repair in MS patients.

Distribution, developmental origins, and heterogeneity of OPCs

OPCs are found throughout the CNS and reside in both the gray and white matter. Approximately 5–8% of the cells in the brain are OPCs (Dawson et al., 2003; Levine et al., 2001). OPCs represent a major proliferative population in the adult CNS of mammals, including humans (Alonso, 2000; Dawson et al., 2003; Geha et al., 2010; Peters, 2004; Smart, 1961; Tamura et al., 2007). Due to their distribution and abundance, it has been proposed that OPCs represent the fourth major glial cell classes in addition to astrocytes, OLs and microglia (Peters, 2004).

Diverse developmental origins of OPCs have been proposed (Richardson et al., 2006); however, definitive cell sources in the specific region of the CNS have not been fully defined. In the early stages of spinal cord development, the precursors in the motor neuron progenitor domain of the ventral ventricular zone can give rise to motor neurons and OLs sequentially. These precursor cells are defined by the expression of the basic helix-loop-helix transcription factor Olig2 (Lu et al., 2002; Takebayashi et al., 2002; Zhou and Anderson, 2002). Expression of Olig2 precedes that of OPC markers PDGFRα and NG2 and defines a primitive OPC state (Pri-OPC) beginning at embryonic day 8.5 (Lu et al., 2002; Takebayashi et al., 2002; Zhou and Anderson, 2002) (Figure 1). Cell fate mapping analyses suggest three waves of OL production in the developing forebrain (Kessaris et al., 2006): The first wave originates from Nkx2.1^{+} progenitors in the ventral telencephalon; the second wave originates from Gsx2^{+} precursors in the lateral ganglionic eminences (LGE) and/or caudal ganglionic eminences; and the third results from Emx1^{+} cortical progenitor cells (Figure 1). Interestingly, the experimental depletion of either the Nkx2.1^{+} or Gsx2^{+} OPC populations does not cause significant myelination defects, suggesting that remaining populations compensate each other (Kessaris et al., 2006). In fact, Nkx2.1 progenitors-derived OPCs are almost completely eliminated under normal conditions during postnatal development (Kessaris et al., 2006). In contrast, genetic ablation of *Olig2* in the dorsal progenitor cells of the developing cortex leads to myelination deficits; these defects cannot be fully compensated by ventrally-derived OPCs at postnatal stages (Yue et al., 2006), suggesting that the dorsal progenitors contribute significantly to cortical myelination. Consistently, genetic fate mapping analysis, combined with BrdU birth-dating labeling, indicates that the majority of myelinating OLs in the brain are derived from progenitors that originate in the neonatal subventricular zone (SVZ) (Tsoa et al., 2014). Overall, these studies indicate that OPCs arise from diverse spatiotemporally-restricted origins, and that subpopulations of OPCs from a particular niche may contribute to the regional diversity of OL myelination in the CNS (Bercury and Macklin, 2015).

Adult OPC generation and functions

A population of OPCs generated during development are maintained as an immature slowly proliferative or quiescent state in the adult CNS (Dawson et al., 2003). Studies have demonstrated that NG2+ OPCs in the adult brain display a very long cell cycle length with a prolonged G1-phase (Simon et al., 2011). In line with this, analysis of the integration of nuclear bomb test-derived C^{14} reveals that OLs in the white matter are remarkably stable during adult life of humans and have low turnover rates, which contribute minimally to myelin modulation or remodeling (Yeung et al., 2014). Adult NG2^{+} OPCs appear to maintain unique territories through self-avoidance. A balance between OPC expansion and self-repulsion likely controls the homeostasis of OPC cell density in the adult brain (Hughes et al., 2013). Strikingly, newly formed adult OLs appear to participate in myelin remodeling by either replacing dying OLs or adding new myelin sheaths along existing myelinating axons (Young et al., 2013). The adult-born OLs, although small in number, are required for acquiring motor learning skills (McKenzie et al., 2014), suggesting a critical role of newly formed adult OLs in learning acquisition. Upon injury, however, adult parenchymal NG2+ OPCs can become re-reactivated and re-enter cell cycle following demyelination (Hughes et al., 2013; Simon et al., 2011) and contribute to OL regeneration and myelin repair (Xing et al., 2014).

Several lines of evidence indicate that OPCs exhibit regional and temporal differences in their frequency of differentiation into OLs. In adult mice, fate mapping analysis of PDGFRα^{+} cells suggests that OPCs generate 20% of myelinating OLs in the corpus callosum, but only around 5% in the cortex (Rivers et al., 2008). Similarly Olig2^{+} progenitors generate myelinating OLs in the adult white matter; however, only few Olig2^{+} fate-mapped cells generate OLs in the gray matter, even after 6 months (Dimou et al., 2008; Rivers et al., 2008; Tatsumi et al., 2008). Olig2^{+} adult neural progenitors (type C cells) generate a small population of OPCs destined for the corpus callosum and striatum (Menn et al., 2006). These studies established that, although OPCs continuously differentiate into OLs during development and in adulthood, the signals available in specific niches are critical for the control of the oligodendrogenesis rate. Recently, cell-type specific transcriptome profiling and single-cell transcriptome analyses revealed previously unrecognized cell subclasses of OL lineage cells in the brain (Zeisel et al., 2015; Zhang et al., 2014), indicating that OPC populations are spatially and temporally heterogeneous in the brain.

OPCs exhibit cell-fate plasticity

The developmental process of OPCs is highly plastic. OPCs have the potential to differentiate into astrocytes and even neurons depending on the signals available within a given niche. The ability of OPCs to form OLs and type 2 astrocytes *in vitro* has been well established (Raff et al., 1983); however, whether this plasticity of OPCs is a cell-culture artifact or actually occurs during normal development has been a matter of intense debate. Cultured OPCs can differentiate into astrocytes in response to certain factors in serum, such as bone morphogenetic proteins (BMPs), which activate OL differentiation inhibitors ID2 and ID4 (Kondo and Raff, 2000a; Kondo and Raff, 2004; Raff et al., 1983; Samanta and Kessler, 2004). Lineage tracing of the fate of NG2^{+} OPCs with the use of NG2-CreBAC transgenic mice carrying a Cre reporter Z/EG suggests that OPCs produce protoplasmic astrocytes in a region-dependent manner, such as in the posterior-ventral cortex, in addition to OL lineage cells during development (Zhu et al., 2008). In contrast, low or no production of OPC-derived astrocytes was detected in the adult brain (Dimou et al., 2008; Rivers et al., 2008).

OPCs may exhibit neurogenic potential. It has been reported that OPCs isolated from CNP-GFP^{+} reporter mice differentiate into functional neurons (Belachew et al., 2003). Fate-mapping analysis of OPCs during development suggests that OPCs are the source of specific neuronal populations *in vivo*. Based on BrdU labeling analysis and immunodetection of NG2, a subpopulation of OPCs expresses the neuroblast markers, doublecortin and TUC-4, in the adult rat neocortex (Tamura et al., 2007). Fate-mapping analysis of PDGFRα^{+} cells, based on *PDGFRα*-creERT2/Rosa26-YFP double-transgenic mice, indicates that OPCs may also give rise to a population of projection neurons in the forebrain piriform cortex (Rivers et al., 2008). In addition, the progeny of *Plp*$^{+}$ OPCs in the postnatal stage of a *Plp*-CreER transgenic line express doublecortin, Sox2, and Pax6, indicating that OPCs may generate pyramidal glutamatergic neurons in the adult piriform cortex (Guo et al., 2010). Similarly, a subset of immature, but functional, neurons are derived from Sox2$^+$/NG2$^+$ OPCs in the hypothalamus (Robins et al., 2013). Moreover, a population of medial ganglion eminence-derived OPCs appears to migrate tangentially and gives rise to interneurons in deep layers of the dorsal cerebral cortex (Tsoa et al., 2014).

In contrast to observed neurogenic potential of OL lineage cells in some studies, the fate mapping analysis of Olig2$^+$ or NG2$^+$ cells using *Olig2*-CreER knock-in and NG2CreER transgenic lines indicates no production of neurons from OPCs in the postnatal and adult brain (Dimou et al., 2008; Zhu et al., 2008). Recently, fate-mapping analysis of a new BAC transgenic line of *PDGFRα*-CreER mice in the developing and adult CNS show that PDGFRα/NG2$^+$ OPCs develop into postnatal myelinating OLs but not astrocytes or neurons (Kang et al., 2010). The discrepancies in studies of the fates of PDGFRα$^+$ or NG2$^+$ cells are likely due to the intrinsic properties of different transgenic lines. In the NG2-Cre BAC transgenic line (Zhu et al., 2008), the constitutive NG2-promoter driven-Cre may be active in astrocyte lineage cells at a specific time-point during embryonic development. In the *Plp*-CreER mice (Doerflinger et al., 2003), the 2.4 kb *Plp* promoter segment may not fully recapitulate endogenous *Plp* gene expression and the *Plp*-Cre transgene expression is not restricted to OL lineage cells but is also expressed in subpopulations of astrocytes and neurons, as observed in fate-mapping studies (Guo et al., 2010). Similarly, these *PDGFRα*-CreER reporter-positive neurons are likely derived from direct expression of CreER in neurons, rather than through evolution or trans-differentiation of NG2$^+$ cells (Kang et al., 2010; Rivers et al., 2008). Currently, it is not clear whether chromosomal integration sites of CreER transgenes in different transgenic lines impact the outcome of fate-mapping experiments. Even though accumulating genetic fate mapping evidence supporting that OPCs might represent a disseminated pool of progenitor cells that can potentially be steered into a range of neural lineages, those results derived from Cre-mediated fate-mapping might have alternative interpretations. For example, OLs are able to secrete exosomes that can be internalized by neurons, raising the possibility that genetic information (e.g. Cre mRNA or protein) may be transferred from OLs to neurons by exosomes or microvesicles, and therefore leading to reporter expression in neurons due to Cre-mediated recombination (Fruhbeis et al., 2013; Ridder et al., 2014).

OPCs could potentially adopt alternative cell fates under pathological conditions or upon injury. Fate switch control is clinically significant, since most approaches for myelin repair in MS lesions do not take into consideration that OPCs can be directed towards alternative fates or lineages. For example, a misguided fate switch of OPCs into astrocytes may cause depletion of OPC cell pools, leading to remyelination failure in MS lesions, which consist of demyelinated axons surrounded by a dense astroglial milieu. Several studies, unfortunately lacking stringent fate-mapping data, suggest that OPCs give rise to astrocytes following injury. A population of Olig2$^+$/GFAP$^+$ cells with astrocyte identity is detected after cortical injury (Tatsumi et al., 2008). In experimental autoimmune encephalomyelitis, GFAP$^+$ cells in lesions were co-labeled with Nkx2.2 and Olig2, suggestive of intermediate stages of OPC conversion into astrocyte-lineage cells (Cassiani-Ingoni et al., 2006). A proportion of OPCs appear to become committed to astrocyte differentiation based on cytoplasmic expression of Olig2 following cortical stab injury (Magnus et al., 2007).

A recent study, however, showed that Olig2 is upregulated in the majority of GFAP+ cells after traumatic brain injury. The fate of OPCs traced by the PDGFRα-H2b-GFP reporter does not express GFAP, suggesting that reactive astrocytes are derived from astrocytes in which Olig2 is re-expressed or activated, but not from PDGFRα+ OPCs (Chen et al., 2008). Consistently, after stab wound injury, the progeny of OPCs remains positive for the proteoglycan NG2 (Dimou et al., 2008). In addition, the fate mapping analysis of OPCs in *PDGFRα*-creERT2:Rosa26-YFP mice found that OPCs produce, at most, a very small proportion of astrocytes following toxin-mediated demyelination (Zawadzka et al., 2010). In fact, a great majority of reactive astrocytes in the vicinity of the lesions are derived from preexisting FGFR3-expressing cells (Zawadzka et al., 2010). It should be noted that these experimental findings do not formally preclude the formation of astrocytes from OPCs in multiple sclerosis patients. The misguided adoption of astrocyte fates by OPCs or pri-OPCs may occur in the presence of certain genetic alterations. For instance, the loss of Olig2 (Zhu et al., 2012) or its upstream epigenetic regulators such as Hdac3 (X. He and R. Lu, unpublished) or certain chronic disease settings (Nishiyama et al., 2009) could convert OPCs into astrocytes in vivo. In addition, OPCs may adopt the neuronal fate following traumatic injury as well. Elevation of Sox2 alone, or in combination with Ascl1/Mash1, can induce the conversion of NG2 glia into doublecortin (DCX)+ neurons in the adult mouse cerebral cortex following stab wound injury (Heinrich et al., 2014). Intriguingly, such cell fate conversion requires prior injury, suggesting that unidentified signals present in the lesion contribute to the directed programing of OPCs into neurons.

Diverse extrinsic factors regulate OPC specification and plasticity

Distinct and opposing extrinsic factors modulate and balance OPC fate specification (Figure 1). In the developing neural tube, OPCs originate in the ventral neural epithelium under the influence of extracellular ligands such as sonic hedgehog (Shh) and BMP, which exert opposing effects on OPC specification. Shh secreted from the ventral neural tube and floor plate induces OPC specification, whereas BMP signaling inhibits the process (Orentas et al., 1999; Poncet et al., 1996; Pringle et al., 1996) (Figure 1). A recent study indicates that Indian Shh is also involved in the specification of OPCs in zebrafish (Chung et al., 2013). Studies using pharmacological blocking of FGF2 and Shh signaling suggest that the function of Shh on OPC specification is facilitated through the activation of FGF signaling (Kessaris et al., 2004). On the other hand, BMP signals from the dorsal neural tube inhibit OPC generation by activating negative regulators of OL differentiation, such as ID2 and ID4 (Feigenson et al., 2011; Miller et al., 2004). Indeed, cultured OPCs treated with BMP2, BMP4, or BMP7 differentiate into type-2 astrocytes rather than OLs (Mabie et al., 1997).

Modulation of BMP signaling can regulate fate determination and plasticity of glial cells. *In vitro*, OPCs can be reprogramed into multipotent neural stem-like cells, capable of generating both neurons and glial cells in response to BMPs (Kondo and Raff, 2000b). Elevation of levels of endogenous BMPs, unmasked by noggin antagonism with a function-blocking antibody (noggin-FbAb), appears to convert a population of OPCs to type 2 astrocyte-like cells following adult CNS injury (Hampton et al., 2007). BMP4 signaling may activate histone acetylation to inhibit OPC differentiation and favor expression of astrocytic genes (Wu et al., 2012).

In the adult CNS, Wnt/β-catenin signaling has been shown to have an instructive role in specification of neural stem cells from subependymal zone (SEZ) or SVZ into OPCs. Activation of canonical Wnt signaling using pharmacological GSK3β inhibitor ARA-014418 or by in vivo genetic approaches stimulates the generation and expansion of OPCs from the dorsal SVZ microdomain (Azim et al., 2014a; Azim et al., 2014b; Ortega et al., 2013a). Intriguingly, in the cuprizone-challenged demyelination model, adult OPCs specified from the SVZ could migrate into the demyelinated lesions and contribute significantly to OL regeneration and remyelination (Xing et al., 2014). These studies suggest that Wnt pathway activation contributes to oligodendrogenesis from the SEZ/SVZ progenitors in adult mice and subsequent OL regeneration in demyelinating lesions.

It has been proposed that there are two components of the intrinsic clock for OPC differentiation: a “mitogenic counting component” controlling cell proliferation, and an “effector component” controlling the differentiation process (Raff et al., 1983) (Figure 1). In the presence of mitogens and absence of thyroid hormone, glucocorticoids, or retinoic acid, OPCs appear to divide indefinitely and do not differentiate into mature OLs. Conversely, in the absence of the counting component, OPCs stop dividing and differentiate prematurely (Barres et al., 1994). Several mitogens involved in the proliferative response of OPCs have been identified in *in vitro* experiments; these include PDGF, bFGF, and EGF. bFGF and PDGF cooperate to promote rapid division of OPCs, but inhibit their differentiation and maturation (Wolswijk and Noble, 1992). Overexpression of PDGF increases the proliferation of OPCs (Calver et al., 1998; Woodruff et al., 2004); however, OPCs generated in excess undergo cell death, suggesting that multiple survival and differentiation signals determine the final number of mature OLs. Consistently, in the developing optic nerve, approximately 50% of OLs die, possibly in response to the absence of neuron-derived factors such as the ciliary neurotrophic factor or insulin-like growth factor I (Barres et al., 1992; Barres et al., 1993). The response of OPCs to PDGF may also depend on spatiotemporal cues. Studies with *ex vivo* transplant and explant culture models indicate that OPCs from the postnatal white matter region exhibit greater proliferative responses to PDGF than OPCs from the gray matter region (Hill et al., 2013). A recent *in vivo* transplantation study shows that white matter-derived adult OPCs differentiate into mature OLs in gray and white matter regions with equal efficiency; however, OPCs derived from the gray matter differentiate with lower efficiency, especially in the gray matter niches (Vigano et al., 2013). These observations suggest an intrinsic difference among regionally-specific adult OPCs, which could be due to extended residency in different environmental niches, factors expressed in these niches, or the presence of the early phase of OPCs in the white matter niche.

Specification, proliferation, and differentiation of OPCs in the adult injured brain seem to be influenced by signals similar to those active during development; for example, Shh, FGF, EGF, and PDGF are expressed during development and post injury (Figure 1). FGF receptors FGFR1/2 are enriched in the dorsal SVZ, from which OLs are largely derived, and the administration of FGF2 into the lateral ventricle increases the specification and proliferation of OPCs and disrupts myelination in the adjacent white matter and cortex (Azim et al., 2012). Additionally, it has been described that, upon EGF stimulation, a subpopulation of type-B cells are converted into OPCs, and, upon removal of EGF, these cells differentiate into myelinating OLs in the corpus callosum, fimbria fornix, and striatum (Gonzalez-Perez and Alvarez-Buylla, 2011).

Shh signaling is upregulated in the oligodendroglial lineage in a model of focal demyelination, and adenovirus-mediated expression Shh in the injured brain results in an increase of the number of OPCs (Ferent et al., 2013). However, inhibition of endogenous Shh did not reduce the density of Olig2^{+} cells, suggesting an additional Shh-independent mechanism for OL generation (Ortega et al., 2013b). Currently, it is not known whether extrinsic factors impact OPC development and regeneration in regional- or stage-specific manners.

It is worth noting that OPC proliferation can be also regulated by neuronal activity. Blockade of axonal activity by axotomy or tetrodotoxin reduces OPC proliferation in the developing optic nerve (Barres and Raff, 1993). Similarly, stimulation of neuronal activity via an optogenetic approach induces a mitogenic response of neural progenitor cells and OPCs, promotes oligodendrogenesis, and increases adaptive myelination within the premotor cortex and subcortical white matter (Gibson et al., 2014). Conversely, blocking new OL production through Myrf deletion in OPCs in adult mice resulted in a deficit in motor learning (McKenzie et al., 2014), suggesting that generation of new OLs and myelin is critical for neuronal activity and function. To what extent neuronal activity contributes to OPC proliferation and differentiation *in vivo*, or vice versa, remains to be determined.

Control of OPC specification and plasticity by intrinsic factors

OPC fate specification and their lineage plasticity are coordinated and fine-tuned by a series of cell-intrinsic regulators (Figure 1). During development, the basic helix-loop-helix transcription factor Olig2 is not only necessary for OPC specification and their differentiation, but also, in some contexts, sufficient for OPC generation (Liu et al., 2007; Lu et al., 2002; Takebayashi et al., 2002; Zhou et al., 2001; Zhou and Anderson, 2002). *Olig2* deletion leads to a loss of the majority of OL lineage cells in *Olig2* null mice (Lu et al., 2002; Takebayashi et al., 2002), deletion of both *Olig2* and *Olig1* causes complete absence of OPCs in the CNS, suggesting that Olig2 and Olig1 cooperate for OPC specification (Lu et al., 2002; Zhou et al., 2001; Zhou and Anderson, 2002). Olig2 can interact with transcriptional co-regulators Nkx2.2 or Zfp448 to further promote OPC differentiation in ovo (Wang et al., 2006; Zhou et al., 2001). The initial analysis of the function of Olig1, a close homolog of Olig2, indicates a developmental delay in OL differentiation in the spinal cord of an *Olig1*-null mouse strain (Lu et al., 2002), while a recent study of the mutant line indicates persistent impairment of OPC commitment and OL differentiation in the corpus callosum from early postnatal stages to adulthood (Dai et al., 2015). This observation indicates a primary role of Olig1 in OL development and subsequent myelination in brain, but not spinal cord, suggesting a region-specific Olig1 function OL development in the CNS. Intriguingly, a modified *Olig1* deletion mouse line with neomycin targeting cassette removal develops a more severe hypomyelination defect in both brain and spinal cord than the original line (Xin et al., 2005). In contrast, two additional *Olig1*-deficient mouse lines exhibit only mild developmental delay in myelination in the spinal cord (de Faria et al., 2014). The phenotypic discrepancy of *Olig1* mutant mice has not yet fully understood, perhaps in part due to different strain backgrounds and the impact of the neomycin cassette on expression of neighboring genes, Cre or noncoding RNAs.

The proneural factor Ascl1 is detected in neural progenitors and OPCs, and is required for oligodendrogenesis in the developing CNS (Nakatani et al., 2013; Parras et al., 2007). Ascl1 interacts with Olig2 and regulates the specification, proliferation, and differentiation of OPCs. In remyelinating lesions, Ascl1 is upregulated and promotes the production of new OLs, suggesting that Ascl1 modulates normal development and regeneration of OPCs (Nakatani et al., 2013; Parras et al., 2007).

SoxE family transcription factors (e.g. Sox10) regulate in OL lineage differentiation. Elevated Olig2 levels induce the expression of Sox10 and Nkx2.2, leading to OL differentiation in the chick neural tube (Figure 1) (Liu et al., 2007). Sox10 is expressed in OPCs, persists in mature OLs, and promotes OPC differentiation (Stolt et al., 2004). Sox9 shares a similar function in normal OPC development, but not OL differentiation. The SoxD family (Sox5 and Sox6) are highly expressed in OPCs and down-regulated in differentiating OLs, resembling the Sox9 expression pattern; Sox9 and the SoxD factors have repressive roles in OL differentiation (Stolt et al., 2006).

Expression of neurogenic homeodomain transcription factors modulates the neuronal versus oligodendroglial cell fate choice in the ventral telencephalon. In the ventral telencephalon, progenitors in the LGE and medial ganglion eminence can generate GABAergic neurons and OLs. Transcription factors like Dlx1/Dlx2 control neuronal versus oligodendroglial cell fate acquisition by repressing Olig2-dependent OPC formation in the developing forebrain (Petryniak et al., 2007). Similarly, the absence of Gsx2 in the LGE leads to an increase of OPCs in the dorsal LGE, whereas overexpression of Gsx2 decreases the number of OPCs, suggesting a repressive role of Gsx2 in OPC specification (Chapman et al., 2013).

In the developing cortex, Olig2 plays a key role in OL specification and differentiation from dorsal cortical progenitor cells (Yue et al., 2006). Constitutive or conditional deletion of *Olig2* in $NG2^+$ cells in the developing neocortex also results in astrocyte generation from neocortical $NG2^+$ glia (Zhu et al., 2012), suggesting that Olig2 controls the switch of glial subtypes. Transcription factors could also serve as nexus that connect extracellular signaling pathways to intracellular transcriptional programs for OL differentiation. For example, a Smad-interacting protein-1 (Sip1/Zeb2) was found to antagonize BMP signaling to repress differentiation inhibitory signals, while activating I-Smad, Smad7, further blocked BMP receptor signaling to promote OL differentiation (Weng et al., 2012).

Several lines of evidence indicate that chromatin modifications, such as histone modifications and ATP-dependent chromatin remodeling, control oligodendrocyte specification and mediate developmental plasticity. *In vitro*, treatment with pan histone deacetylase (HDAC) inhibitors induces programming of OPCs to acquire neural progenitor properties. HDAC inhibitor treatment activates Sox2 and other stem cell associated genes while suppressing OL lineage-specific genes (Lyssiotis et al., 2007). Consistently, genetic ablation of both *HDAC1/2*, but not either of the single genes alone, in the OL lineage cells blocks OPC proliferation and differentiation, at least in part by inhibiting Wnt signaling activation in the progenitor cells (Ye et al., 2009). *HDAC1/2*-deficient OPCs do not appear to adopt alternative cell fates, suggesting that other HDAC family members inhibited by pan HDAC inhibitors may also contribute to directed programming of OPCs and their developmental plasticity.

Expression of three transcription factors – Sox10, Olig2, and either Zfp536 or Nkx6.2 – induces rat fibroblasts or mouse embryonic or lung fibroblasts to reprogram into OPCs (Najm et al., 2013; Yang et al., 2013). The cell morphologies and gene expression profiles of these transcription factor-induced OPCs (iOPCs) are similar to those of primary OPCs. Importantly, iOPCs generate myelinating OLs and compact myelin sheaths around axons when transplanted into myelin-deficit Shiverer mice, which lack expression of MBP (Najm et al., 2013; Yang et al., 2013). SoxE transcription factors induce neural precursor cells from the early postnatal SVZ to become OPCs. Sox10 can restrict differentiation of neural precursor cells into the OL lineage, in part by regulating the expression of the Shh signaling pathway (Pozniak et al., 2010). Overexpression of Sox10 alone is sufficient to promote the commitment of neural precursor cells toward the OL lineage to form mature OLs (Wang et al., 2014).

Chromatin remodeling regulated by ATP-dependent remodelers is critical for programming of transcriptional states required for lineage specification during development. ATP-dependent SWI/SNF chromatin-remodeling enzyme Smarca4/Brg1 is activated at the onset of OPC differentiation (Yu et al., 2013). Deletion of *Brg1* alleles in neural progenitors or *Olig1*$^{+}$ early OL progenitors leads to severe defects in OPC differentiation, indicating that Brg1 is necessary and sufficient to initiate and promote OL lineage progression (Bischof et al., 2015; Yu et al., 2013). Olig2 can recruit the SWI-SNF chromatin remodeling complex Brg1 to the enhancers of OL-specification genes such as *Sox10*, *Zfp191*, and *Myrf*, the key regulators of OL differentiation (Emery, 2010), to activate their expression (Figure 1) (Yu et al., 2013). How chromatin remodelers, transcription factors, and histone-modifying enzymes coordinate to control OPC specification and developmental plasticity remains to be further elucidated.

Repair of myelin damage by OPC programming and reprogramming

At least two main approaches have been proposed to enhance the production of mature OLs (Vishwakarma et al., 2014). The first is through the transplantation of OPCs, and the second involves mobilization of endogenous OPCs to form mature myelinating OLs (Figure 2). Transplantation of OPCs into lesions in the injured or diseased CNS is a promising therapeutic strategy; however, generation of OPCs from stem cells or from other somatic sources has proven challenging. A series of strategies have been employed to induce human embryonic stem cells (ESC) to differentiate into OPCs (iOPC) by sequential exposures to hESC growth media, bFGF- and EGF-containing glial restriction media, and all-trans retinoic acid (Erceg et al., 2010; Keirstead et al., 2005). iOPCs transplanted into rats with spinal cord transection, can differentiate into mature OLs and improve motor function of animals (Erceg et al., 2010; Keirstead et al., 2005). Similarly, OPCs derived from Olig2-positive mouse ESCs can differentiate into myelinating OLs after transplanted into rats with spinal cord injury induced by irradiation an (Sun et al., 2013). Furthermore, human CNS stem cells (hNSC) expanded from the fetal brain have been used to treat patients with the leukodystrophy Pelizaeus-Merzbacher disease (Gupta et al., 2012). Transplantation of HuCNS-SC into the human frontal lobe resulted in durable cell engraftment, signs of myelination, and modest gains in neurological function with no obvious adverse effects upon immunosuppression (Gupta et al., 2012).

Direct programming of OPCs has the potential to provide enormous benefits to patients with demyelinating diseases and spinal cord injury; however, a number of challenges remain for cell-replacement based therapies. Some of the main concerns of using allogenic ESCs or NSCs are possible immune responses, genomic alterations due to prolonged protocols of *in vitro* OPC generation, the intrinsic capability of embryonic stem cells to form teratomas after implantation, and non-targeted lineage differentiation that might be induced by environmental signals at the site of implantation. The use of autologous cell sources of induced pluripotent stem cells (iPSCs) for the generation of implantable OPCs would help to overcome the immune responses. Engraftment of human iPSC-iOPCs into neonatal myelin-deficient Shiverer mice resulted in brain myelination without evident generation of tumors up to 9 months after transplant (Wang et al., 2013). Since the engraftment of iPSC-iOPCs has been performed in the corpus callosum of neonatal mice, a region where the endogenous signals for oligodendrogenesis are highly enriched, it will be of interest to analyze graft efficiency in the injured adult CNS such as a spinal cord transection model. Factors such as genomic instability/epigenetic memory and the impact of cell propagation in culture represent significant concerns derived from reprogramming technologies (de Lazaro et al., 2014). In addition, whether endogenous or induced OPCs produce non-OL cell types has not been fully investigated.

Adult SVZ neural progenitors are an important source for remyelinating OLs (Xing et al., 2014). Activation of EGF receptor signaling by EGF stimulates generation and expansion of OPCs from endogenous SVZ progenitors, and promotes new myelinating OL formation and behavioral recovery in the developing brain with diffuse white matter injury (Scafidi et al., 2014). Similarly, mobilization of endogenous neural progenitors e.g. by genetic deletion and pharmacological inhibition through GANT61 of Gli1, a transcriptional effector of the Shh pathway, also promotes neural progenitor differentiation into OPCs (Samanta et al., 2015). This process promotes subsequent myelination in demyelinated lesions and improves the functional recovery in demyelinating animal model of experimental autoimmune encephalomyelitis (Samanta et al., 2015). Recently, a series of bioactive small molecules have been identified through high-throughput screening that promote differentiation and maturation of rat OPCs (Deshmukh et al., 2013; Mei et al., 2014) and mouse epiblast stem cell-derived OPCs (Najm et al., 2015). These small molecule compounds such as benztropine, clemastine, miconazole, and clobetasol promote precocious myelination in early postnatal mouse pups, and enhance remyelination in mouse models of demyelination induced by lysolecithin-mediated injury and experimental autoimmune encephalomyelitis. Benztropine and clemastine appear to act through muscarinic acetylcholine receptor signaling (Deshmukh et al., 2013; Mei et al., 2014), whereas miconazole and clobetasol may activate mitogen-activated protein kinase and glucocorticoid receptor signaling, respectively (Najm et al., 2015). In addition to small molecule drugs that promote OL differentiation, targeted inhibition with an antibody against a Nogo receptor-interacting protein Lingo-1, which negatively regulates OL myelination (Mi et al., 2005), has been shown to promote OL remyelination and functional recovery in animal models of MS (Mi et al., 2007). Currently, several small molecules and Lingo-1 antagonists are in clinical trials in MS. The exciting preclinical evidence of these OL-promoting compounds and reagents presents novel therapeutic strategies for treating patients with demyelinating diseases or other neurodegenerative diseases in the CNS.

Challenges and future directions

The limited self-repair potential of the brain has encouraged the exploration of strategies to replace OLs lost to demyelinating diseases. Direct programming or reprogramming of diverse cell types (from autologous and even endogenous cell sources) toward OPC fate is a promising therapeutic strategy. OPC differentiation and reprogramming are dynamic processes, and the interplay of sustained and transient expression of key regulators controls the ultimate cell fate. During OL lineage progression, the expression and subsequent repression of specific genes or networks are critical for continuity of the differentiation process. Although the sustained expression of transcriptional regulators such as Sox10 and Olig2, together with other factors, induces reprograming of differentiated cells toward OPC identity, how the transcriptional regulators selectively activate expression of the differentiation network while simultaneously repressing inhibitory genes is not fully understood.

A better grasp of the differentiation process of OPCs is critical as misguided OPC differentiation into alternative fates may block myelination and remyelination, and OPCs can be source of gliomas upon genetic alterations such as *p53* and *NF1* mutations (Liu et al., 2011). The understanding of possible repercussion of the OPC fate switch will be essential before cell replacement or endogenous activation therapies can be used to treat neurodegenerative diseases such as MS. Small non-coding microRNAs and long noncoding RNAs may play critical roles in regulating OPC plasticity and differentiation (Dugas et al., 2010; Zhao et al., 2010); however, their roles in re/myelination remain unknown. Transcriptome profiling analysis at the single cell level in different brain regions, developmental stages, and disease conditions will offer new targets and avenues to design strategies of OPC differentiation and reprograming. Currently, the potential therapeutic agents including small molecule compounds and anti-Lingo antibody, which promote OPC differentiation, have been entered (or are about to enter) clinical trials aiming at promoting remyelination (Kremer et al., 2015). As reflected by the high efficiency and long-term myelination effects observed in animal models, programming and reprograming toward OPC production by intrinsic or extrinsic factors or small-molecule compounds has enormous potential for the treatment of demyelinating diseases.

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Highlights

- Distribution, developmental origins, and heterogeneity of OPCs
- OPCs exhibit cell-fate plasticity
- Diverse extrinsic factors regulate OPC specification and plasticity
- Control of OPC specification and plasticity by intrinsic factors
- Repair of myelin damage by OPC programming and reprogramming

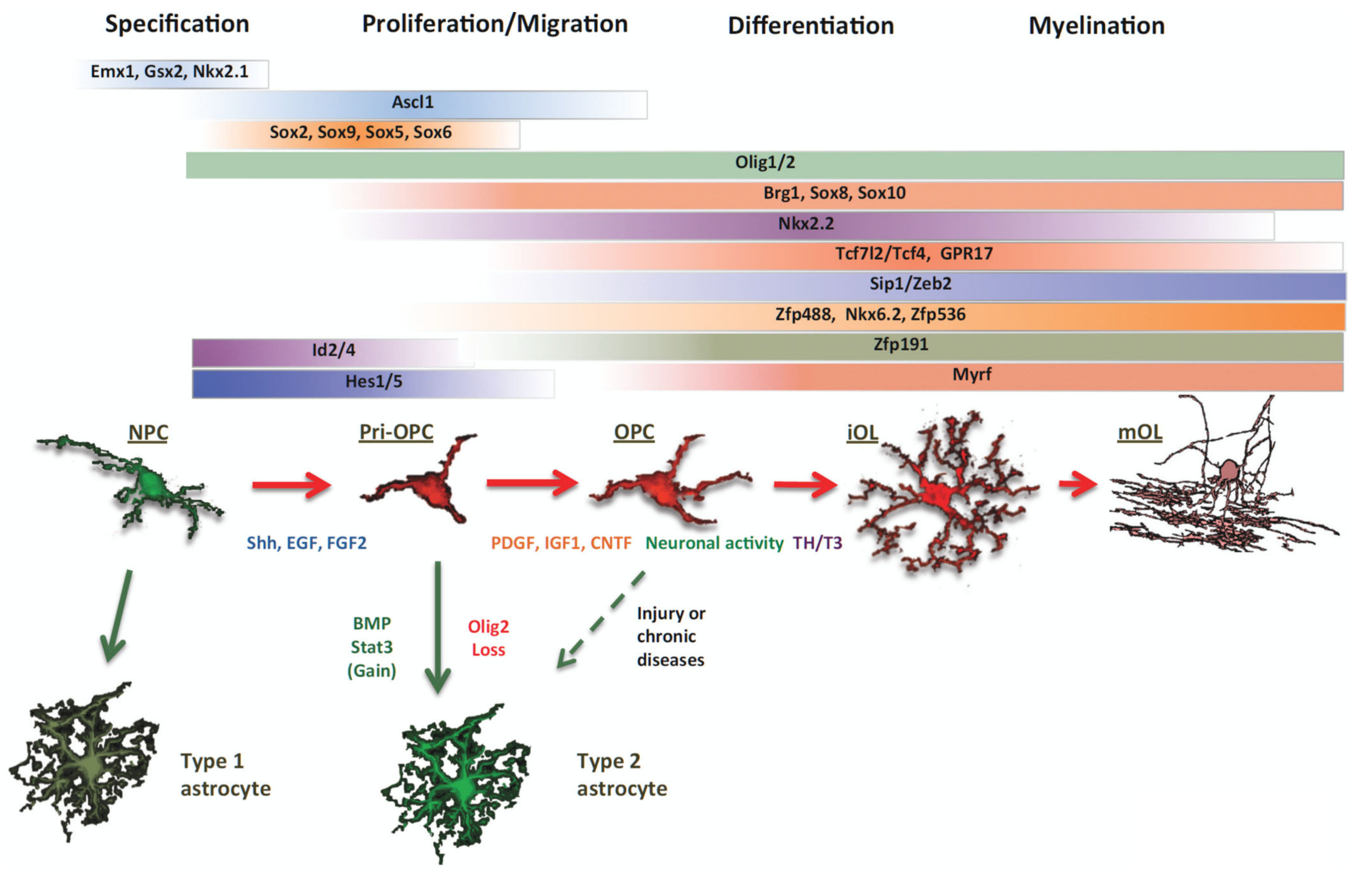

Figure 1. Molecular and signaling control of OL lineage progression and astrocyte differentiation

The interplay of a series of extrinsic factors and intrinsic transcriptional regulators and their targets controls each transition steps during OL lineage progression. Neural precursor cells are specified toward the OL lineage (red arrows) or toward type 1 astrocytes (green arrows) upon activation of defined factors. The potential plasticity of OPCs is depicted by the production of type 2 astrocytes induced under certain circumstances, including activation of BMP signaling or Jak-Stat3 activity, or loss of Olig2, or injury conditions, or chronic diseases like MS. NP, neural precursors; pri-OPC, primitive OPC ($Olig2^+$, $PDGFR\alpha^-$/ $NG2^-$); iOL, immature OL; mOL, mature OL; TH, thyroid hormone.

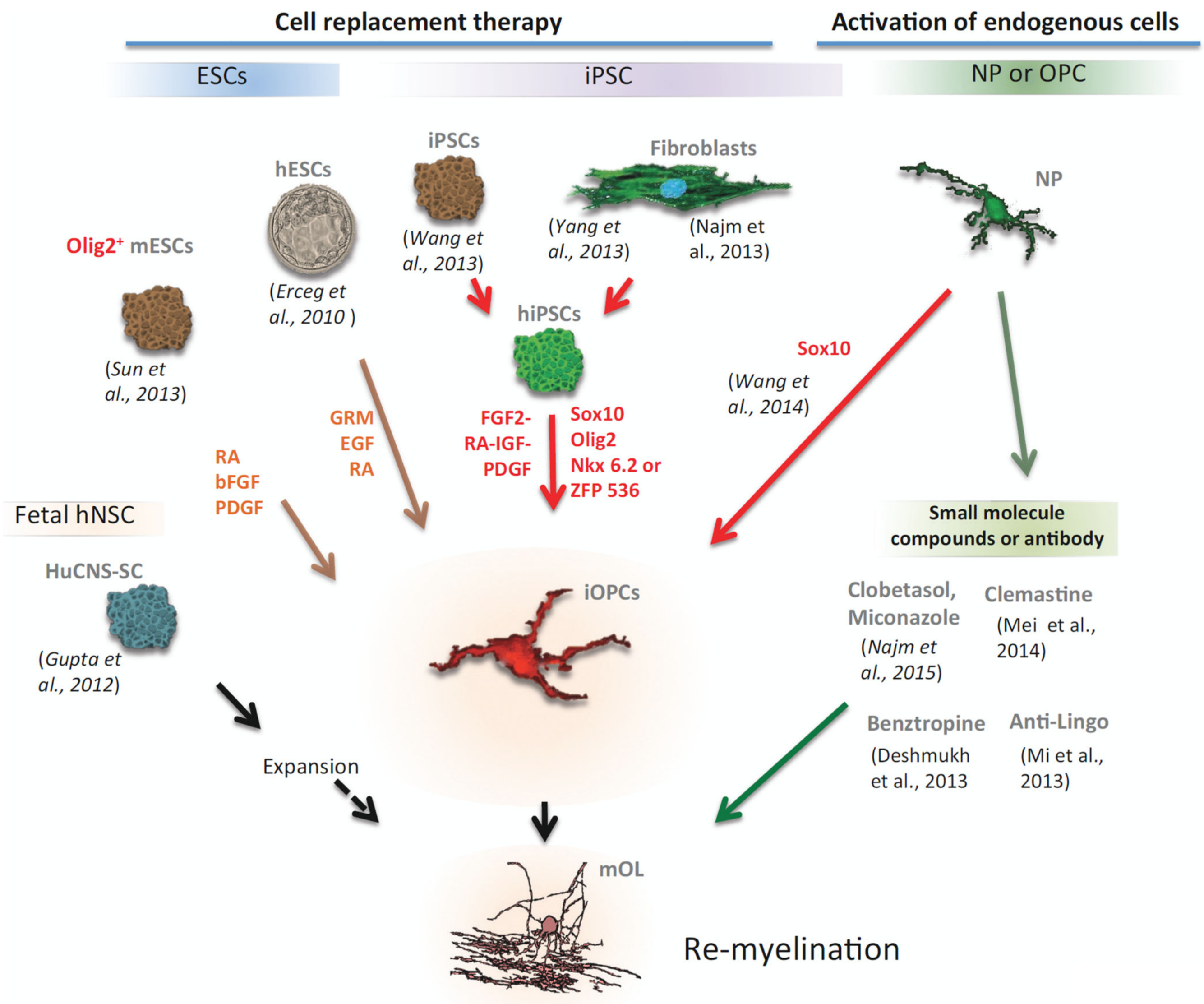

Figure 2. Summary of CNS remyelination strategies

Diverse strategies have been employed to enhance the regeneration of myelinating oligodendrocytes in acquired or demyelinating animal models including hNSCs, ESCs, iPSCs, and specific drugs that act on endogenous neural progenitors. Specific signals or transcription factors that direct the reprograming toward iOPCs are shown. Myelination, remyelination, and behavioral improvement have been reported upon the transplantation of iOPCs into the injured spinal cord or the hypomyelinated brain. Systemic delivery of small molecule drugs enhances remyelination in animal models of MS. Transplantation of expanded hNSCs (left bottom) into the human temporal lobe has been associated with increased myelination (dashed arrows). GRM, glial promoting media; hESC, human ESCs; hNSCs, fetal human neural stem cells; iOPCs; induced oligodendrocyte progenitor cells; iPSCs, induced pluripotent stem cells; Olig2^{+} mESC, Olig2-positive ESCs, HuCNS-SC, human CNS stem cells; NPs, neural precursors.