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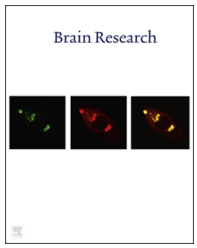

Review

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.

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1. 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.

2. 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 and Leblond, 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) (Fig. 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 (Fig. 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).