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Review

Oligodendrocyte progenitors: Adult stem cells of the central nervous system?

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ABSTRACT

Oligodendrocyte progenitors (OPs) are a major proliferating cell population within the adult CNS. In response to myelin loss or increasing demand, OPs have the capacity to differentiate into mature, myelinating oligodendrocytes. The name 'oligodendrocyte progenitor' suggests restriction to the oligodendrocyte cell lineage. However, with growing evidence of the lineage plasticity of OPs both *in vitro* and *in vivo*, we discuss whether they have potential beyond that expected of dedicated progenitor cells, and hence may justify categorization as adult stem cells.

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Introduction

Oligodendrocyte progenitors (OPs) have been under the scientific spotlight since their initial isolation from perinatal rat optic nerve more than thirty years ago (Raff et al., 1983). Identified by defined molecular markers, including the proteoglycan nerve-glial antigen 2 (NG2), and platelet derived growth factor receptor alpha (PDGFRα), their natural history has been extensively studied. During embryonic development OPs arise from discrete regions of the ventral and, later, the dorsal neuroepithelium of the spinal cord and brain, before then migrating out into all regions of the central nervous system (CNS). Many of the cells contact nearby axons and differentiate into mature myelinating

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oligodendrocytes, whose functions include the facilitation of efficient action potential propagation and the provision of trophic support to the ensheathed axon (Lee et al., 2012; Nave and Trapp, 2008). However, a proportion of the OP population remains undifferentiated and can be found throughout both the grey and the white matter of the mature CNS (Fig. 1A). Constituting around 5% of the total cell population in the adult CNS (Dawson et al., 2003; Levine et al., 2001; Pringle et al., 1992), OPs represent the major cycling cell population (Dawson et al., 2003). This surprising abundance raises questions over their potential functions; beyond their role as a cell source for lesion repair, OPs are also likely to play key physiological roles in the normal adult CNS. Current research efforts hope to elucidate the nature of those physiological roles.

Following their identification in the adult CNS, a spectrum of contrasting and often confusing names has emerged in an attempt both to describe and to classify this cell population. However, no clear consensus has yet emerged on the most appropriate name. The more commonly used terms include "oligodendrocyte progenitor cell", "oligodendrocyte precursor", "NG2-glia", "glial precursor" and the original "O–2A progenitor" (denoting their ability to differentiate into either oligodendrocytes or type-2A astrocytes *in vitro*) (Raff et al., 1983; Raff, 2003). The terms "precursor cell" and "progenitor cell" are often used interchangeably, but some consider a progenitor cell to have a greater developmental potential than a precursor cell (Raff, 2003). All of these terms reflect the presumption that OPs are lineage-restricted, yet there is a significant body of evidence that OPs have diverse morphologies, behaviours and perhaps functions as well as a relatively broad differentiation potential. Viewing them solely as lineage-restricted progenitor/precursor cells might be misleading and perhaps a more appropriate definition should now be considered. For the purpose of this article we shall use the term "OP" but will discuss whether this nomenclature should be revised. We will review some important characteristics of the OP population using comparisons to adult stem cells in other tissues (summarised in Table 1), and will discuss whether OPs should be regarded as committed progenitor cells or adult stem cells.

Adult stem cells

Adult stem cells are undifferentiated cells capable of a) self-renewal, b) the production of sufficient differentiated progeny to enable tissue maintenance and regeneration and c) the generation of multiple cell types. Based on their ability to generate different cell types, stem cells are classified as pluripotent or multipotent. Pluripotency, defined by the ability to generate all cells of the embryo proper (*i.e.* excluding extra-embryonic tissues such as the placenta), is a feature of embryonic stem cells, whilst the stem cells identified in adult tissues typically show multipotency — the ability to give rise to a subset of cell lineages (Wagers and Weissman, 2004). Various adult stem cell populations have now been identified, such as the haematopoietic stem cells of bone marrow and the satellite cells of skeletal muscle. However, the precise properties that are central to stem cell function are under continuing debate.

Self-renewal and production of differentiated progeny

In practice, stem cells can be defined using two simple criteria: the ability to self-renew and the ability to maintain a population of at least one differentiated cell type throughout the life span of an organism (Collins et al., 2005). OPs meet both these criteria; they are capable of self-renewal and are responsible for maintenance of the oligodendrocyte lineage. The OP population persists at a stable density in the adult CNS (Rivers et al., 2008) and continues to proliferate throughout the organism's life span (Young et al., 2013). Differentiation into mature oligodendrocytes ensures that myelin integrity is maintained, that new myelin demands are met and that areas of myelin loss are efficiently remyelinated (Kang et al., 2010; Psachoulia et al., 2009; Rivers et al., 2008; Zawadzka et al., 2010; Zhu et al., 2011b). Repeated episodes of demyelination do not result in OP depletion, indicating successful self-replenishment in the face of increasing demands (Penderis et al., 2003).

Multipotency

The haematopoietic archetype introduces multipotency as a common, though not essential feature of the stem cell (Collins et al., 2005; Raff, 2003; Wagers and Weissman, 2004). Whilst the term "oligodendrocyte progenitor" suggests lineage restriction, this restriction is not absolute. Whilst all mature oligodendrocytes in the developing and adult CNS arise from OPs, the genesis of other cell types from OPs has been reported, although this remains somewhat controversial, being attributed by some to discrepancies between OP multipotency *in vitro*

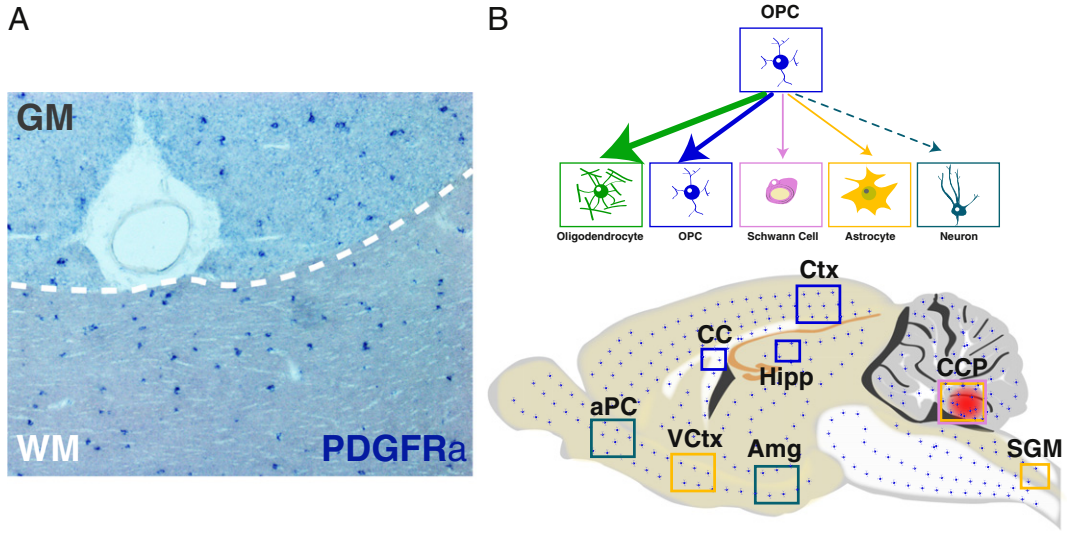

Fig. 1. (A) Representative *in situ* hybridization for *Pdgfra* mRNA, a marker of OPs in the adult rat corpus callosum white matter (WM) and adjacent grey matter (GM) cingulate cortex. Note the broad distribution of OPs in GM and WM. (B) Schematic representation of OP distribution throughout the rodent CNS. OPs generate all oligodendrocytes in the CNS but also self renew, and generate Schwann cells, astrocytes and possibly neurons. Colour coded boxes represent approximate areas where OP multipotency and self-renewal have been demonstrated in normal and damaged (red field) CNS. Key: Arrow weights indicate commitment potential, anterior piriform cortex (aPC), ventral cortex (VCtx), amygdala (Amg), hippocampus (Hipp), corpus callosum (CC), cortex (Ctx), spinal cord grey matter (SGM) and remyelinating lesions of the rat caudal cerebellar peduncle (CCP).