Mini-Review

Oligodendrocyte development in the spinal cord and telencephalon: common themes and new perspectives

Rachel H. Woodruff [a,1], Nicoletta Tekki-Kessaris [a,1], Charles D. Stiles [b],
David H. Rowitch [c], William D. Richardson [a,*]

[a] *Wolfson Institute for Biomedical Research, The Cruciform Building, University College London, Gower Street, London WC1E 6AU, UK*
[b] *Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02115, USA*
[c] *Department of Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA*

Abstract

There are clear parallels between oligodendrocyte development in the spinal cord and forebrain. However, there is new evidence that in both of these regions oligodendrocyte lineage development may be more complex than we earlier thought. This stems from the recent identification of three new transcription factor genes, *Olig1*, *Olig2* and *Sox10*, that are expressed from the early stages of oligodendrocyte lineage development. In this article, we highlight the common themes underlying specification and early development of oligodendrocytes in the spinal cord and telencephalon. Then, we discuss recent studies of *Sox10* and the *Olig* genes and their implications for oligodendrocyte specification. We conclude that although the mechanisms of oligodendrogenesis appear to be fundamentally similar at different rostro-caudal levels of the neuraxis, there are still many unanswered questions about the details of oligodendrocyte specification. © 2001 ISDN. Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

Oligodendrocytes, the myelinating cells of the central nervous system (CNS), develop from oligodendrocyte progenitor cells that arise from a subset of neuroepithelial precursor cells during mid-neurogenesis. As the oligodendrocyte lineage develops further during late embryonic and early postnatal stages, many progenitor cells progress through a series of antigenically and morphologically distinct stages culminating in myelination (Pfeiffer et al., 1993), while others persist in the adult CNS as a population of slowly dividing adult

oligodendrocyte progenitor cells (ffrench-Constant and Raff, 1986; Wolswijk and Noble, 1989; Reynolds and Hardy, 1997) (see Fig. 1).

One of the key questions is how neuroepithelial cells in the developing CNS give rise to the oligodendrocyte progenitor cell population. The molecular marker that we have used most to identify oligodendrocyte progenitors in our studies is the platelet-derived growth factor receptor-alpha (PDGFRα) (Pringle and Richardson, 1993) (see Fig. 1). It is known that PDGFRα⁺ cells are oligodendrocyte progenitors because when they are purified from the late embryonic rat spinal cord and brain by immunoselection, they all differentiate into oligodendrocytes under appropriate culture conditions (Hall et al., 1996; Tekki-Kessaris et al., 2001). Conversely, if cells are selectively removed from spinal cord cultures by antibody-mediated complement lysis, then oligodendrocyte development is strongly inhibited (Hall et al., 1996). Furthermore, the number of oligodendrocytes is reduced by 90% in the spinal cords of mice with a targeted disruption of the platelet-derived growth

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Abbreviations: CNS, central nervous system; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; PDGFRα, platelet-derived growth factor receptor-alpha; PLP, proteolipid protein; Shh, Sonic hedgehog; SVZ, sub-ventricular zone; VZ, ventricular zone.

[1] These authors made equivalent contributions to the work.

* Corresponding author. Tel.: +44-20-76796729; fax: +44-20-72090470.

E-mail address: w.richardson@ucl.ac.uk (W.D. Richardson).

factor-A gene (encoding one of the known ligands for PDGFRα) (Fruttiger et al., 1999). Taken together, this evidence indicates that PDGFRα⁺ cells are the major — maybe the only — source of oligodendrocytes in the spinal cord. Recently, several new markers for the oligodendrocyte lineage have been identified. These are the basic helix-loop-helix proteins *Olig1* and *Olig2* (Lu et al., 2000; Zhou et al., 2000) and the high mobility group protein *Sox10* (Kuhlbrodt et al., 1998). Since they are thought to identify the earliest stages of the oligodendrocyte lineage, these markers might provide new insights into oligodendrocyte specification. In this review, we focus on the origin and early development of oligodendrocyte progenitor cells at two different levels of the neuraxis — the telencephalon and spinal cord — and discuss the impact that the new markers may have on our current understanding of oligodendrocyte development.

2. Common themes in oligodendrocyte development in the spinal cord and telencephalon

2.1. Oligodendrocyte progenitors in both spinal cord and telencephalon have a ventral origin and populate dorsal parts of the neural tube by migration and proliferation

Since oligodendrocytes are evenly distributed throughout the adult CNS, it would be reasonable to suppose that they are produced from all regions of the neuroepithelium. However, there are now several lines of evidence that, in both spinal cord and telencephalon, oligodendrocytes originate from ventral subsets of neuroepithelial precursors.

One line of evidence comes from cell culture experiments. When E14 rat spinal cords are divided into dorsal and ventral halves and the cells from each half are cultured separately, oligodendrocytes develop only in ventral cultures (Warf et al., 1991; Hall et al., 1996). Similarly, cells cultured from the E15 rat ventral telencephalon (striatum) have a much greater oligodendrogenic capacity than those from dorsal telencephalon (cerebral cortex) after short-term culture (Birling and Price, 1998; Tekki-Kessaris et al., 2001) or transplantation into the retina (Kalman and Tuba, 1998). At later stages (E17–18) cells cultured from either the dorsal spinal cord or cerebral cortex readily give rise to numerous oligodendrocytes. Similar experiments have been perfomed with cells from avian spinal cord and forebrain (Orentas and Miller, 1996; Poncet et al., 1996; Pringle et al., 1996, 1998) (N. Tekki-Kessaris, unpublished observations). One interpretation of these results is that, in both forebrain and spinal cord, oligodendrocyte progenitors originate from ventral neuroepithelium and subsequently migrate into dorsal regions. Experiments in vivo with chick-quail chimeras confirm this conclusion (Pringle et al., 1998; Olivier et al., 2000).

Another line of evidence that oligodendrocytes in the spinal cord and forebrain have a ventral origin comes from lineage marker studies in situ. In the spinal cord, PDGFRα⁺ oligodendrocyte progenitor cells first ap-
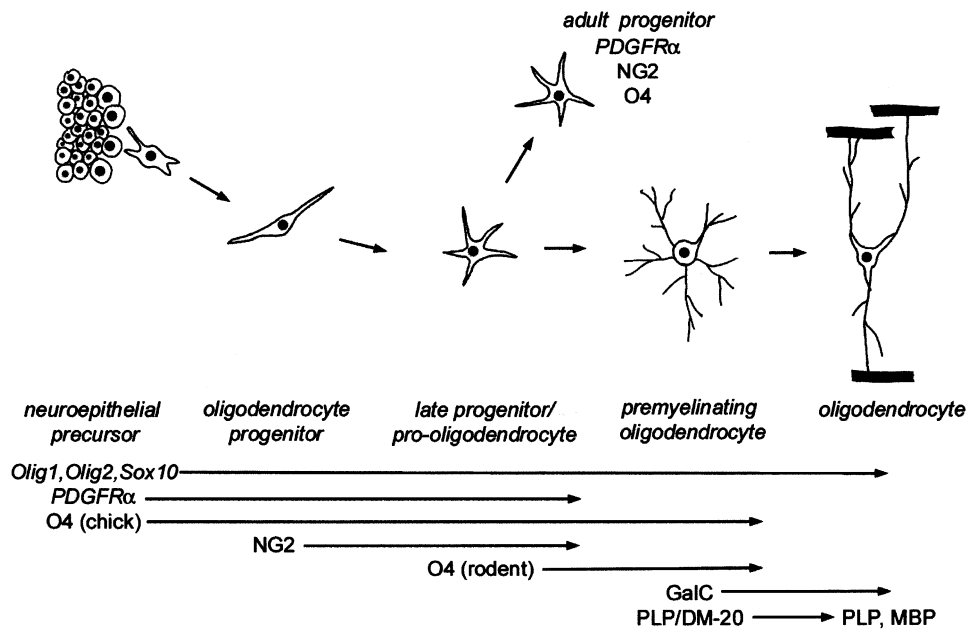

Fig. 1. Illustration of the various stages of oligodendrogenesis. Oligodendrocyte progenitors are specified in the neuroepithelium. Bipolar progenitors subsequently migrate away and proliferate. The majority of progenitors progress through a late progenitor and premyelinating oligodendrocyte stage before maturing into myelinating oligodendrocytes, whereas others persist in the adult CNS as a population of slowly dividing adult progenitor cells. Lineage markers, some of which are stage specific, are shown below.

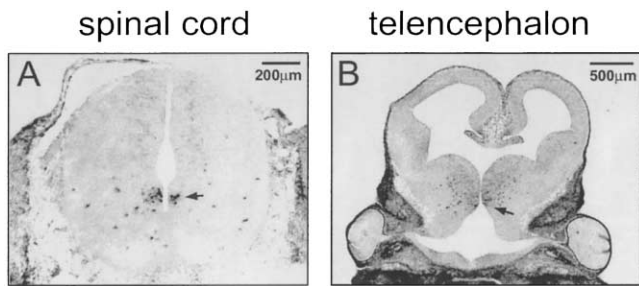## spinal cord   telencephalon

Fig. 2. (A) Transverse section through an E12.5 rat spinal cord; and (B) coronal section through an E12.5 mouse telencephalon showing expression of PDGFRα. In the spinal cord, PDGFRα$^+$ oligodendrocyte progenitors first arise in a ventral region of the neuroepithelium (arrow) and subsequently proliferate and migrate to populate the entire cord. In an analogous manner in the telencephalon PDGFRα$^+$ cells first arise in a ventral region at the boundary between the anterior hypothalamus and the MGE (arrow) and subsequently proliferate and migrate throughout the telencephalon including the cortex.

pear in a highly restricted region of the ventral neuroepithelium around E14 in the rat (E12.5 in mouse, E7 in chick) (Pringle and Richardson, 1993; Pringle et al., 1996) (Fig. 2). This specialised neuroepithelial microdomain also expresses transcripts encoding the myelin protein cyclic nucleotide phosphodiesterase (CNP) (Yu et al., 1994) and antigens recognised by the monoclonal antibody O4 (in the chick) (Ono et al., 1995), both of which are expressed by cells early in the oligodendrocyte lineage. In the forebrain too, there is a discrete ventral focus of PDGFRα$^+$ cells spanning the boundary between the anterior hypothalamus and the medial ganglionic eminence (MGE) that first appears around E13 in the rat (E11 mouse) (Pringle and Richardson, 1993; Spassky et al., 1998; Tekki-Kessaris et al., 2001) (Fig. 2). In the chick forebrain at E5, there is a corresponding focus of PDGFRα$^+$ cells in the entopeduncular area (Perez-Villegas et al., 1999) and also a separate focus at the base of the third ventricle around E7 (R.Woodruff, unpublished observations). The latter focus, which is not found in rodents, presumably corresponds to the ventral source of O4$^+$ oligodendrocyte progenitors described in the chick by Ono et al. (1997).

It has been proposed that there may be a separate lineage of oligodendrocyte progenitors in the forebrain that express mRNA encoding myelin proteolipid protein (PLP) and/or its alternatively-spliced isoform DM-20 (Peyron et al., 1997; Spassky et al., 1998; Perez-Villegas et al., 1999). The arguments for and against separate PDGFRα$^+$ and PLP/DM20$^+$ lineages have been debated elsewhere (Richardson et al., 2000; Spassky et al., 2000; Thomas et al., 2000). However, since the PDGFRα$^+$ and PLP/DM-20$^+$ cells appear to arise from the same ventral territories, this does not alter the basic principle that oligodendrocyte progeni-

tors have a ventral origin in the forebrain, just as they do in the spinal cord.

After the initial appearance of PDGFRα$^+$ cells in the ventral spinal cord and telencephalon, these cells soon increase in number and begin to disperse, first through the ventral and then the dorsal spinal cord and telencephalon (Pringle and Richardson, 1993; Tekki-Kessaris et al., 2001) (see Fig. 3). These findings are mirrored in studies using other markers for oligodendrocyte progenitors, such as antibodies against NG2 proteoglycan (Levine and Stallcup, 1987; Stallcup and Beasely, 1987; Nishiyama et al., 1996; Dawson et al., 2000). It is clear from studies in which oligodendrocyte progenitors were labelled at source with DiI in vivo, that they are able to migrate distances of the order of several millimetres during development (Ono et al., 1997). The timing of appearance of PDGFRα$^+$ cells in the dorsal spinal cord and cerebral cortex corresponds to the marked increase in oligodendrogenic capacity of cells from the dorsal spinal cord and cerebral cortex (Warf et al., 1991; Birling and Price, 1998; Kalman and Tuba, 1998; Tekki-Kessaris et al., 2001) (see above). The implication of these findings is that oligodendrocyte progenitors populate the dorsal spinal cord and cerebral cortex by migration from their origins in the ventral spinal cord and anterior hypothalamus, respectively.

The experiments described above do not by themselves exclude the possibility that some oligodendrocytes might develop from dorsal parts of the neural tube. This has been addressed directly by the use of chick-quail chimeras, in which quail tissue is grafted into the equivalent position of a chick host at the same stage of development (homotypic, homochronic grafts). Using this paradigm, Pringle et al. (1998) found that donor-derived oligodendrocytes develop from ventral, but not dorsal, grafts of spinal cord neuroepithelium. Furthermore, Olivier et al. (2000) found that oligodendrocytes fail to develop from grafted cortical tissue. Taken together, the evidence suggests strongly that most or all oligodendrocytes in the spinal cord and cerebral cortex develop from progenitor cells that originate in the ventral neuroepithelium.
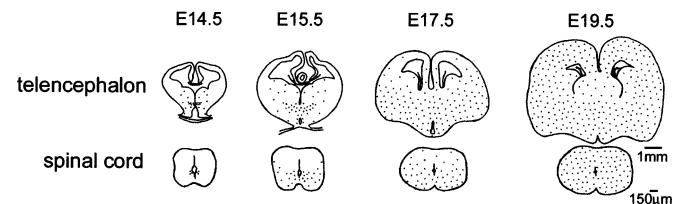

Fig. 3. Comparison of the development of PDGFRα$^+$ oligodendrocyte progenitors in the spinal cord and telencephalon. Grey dots indicate PDGFRα$^+$ cells. In both telencephalon and spinal cord, PDGFRα$^+$ oligodendrocyte progenitors have a ventral origin and spread into the surrounding mantle zones via proliferation and migration.

2.2. Specification of oligodendrocyte progenitors is dependent on Sonic hedgehog

The mechanisms involved in specifying oligodendrocyte precursors in the ventral neuroepithelium appear to be fundamentally similar in the spinal cord and forebrain. Specification is dependent on signals from the ventral midline, a major component of which is the secreted protein Sonic hedgehog (Shh), which is thought to act as a graded morphogen through its receptors patched and smoothened.

In the spinal cord, high concentrations of Shh produced by the notochord induce formation of the floor plate in the adjacent neural tube, which itself becomes a secondary source of Shh (Echelard et al., 1993; Placzek et al., 1993; Roelink et al., 1994). It is thought that Shh protein diffuses dorsally and induces different classes of ventral cell types at different distances from the ventral midline (Orentas and Miller, 1996; Poncet et al., 1996; Pringle et al., 1996; Ericson et al., 1997; Orentas et al., 1999). Likewise in the forebrain, Shh produced by the prechordal plate (which in this respect, is analogous to the notochord) induces the expression of Shh by neuroepithelial cells at the ventral midline of the anterior diencephalon (Echelard et al., 1993; Roelink et al., 1994; Dale et al., 1997), and is involved in the specification of different classes of neurons in the ventral forebrain (Ericson et al., 1995; Ye et al., 1998). However, the role of Shh in forebrain oligodendrogenesis has not been investigated until recently. By the time oligodendrocyte progenitors appear in this region, the Shh expression domain has expanded into the sub-ventricular zone (SVZ) of the MGE (Kohtz et al., 1998; Tekki-Kessaris et al., 2001). Thus, in both the spinal cord and forebrain, oligodendrocyte precursors arise in close proximity to localised sources of Shh signalling. Shh signalling is required for oligodendrocyte production in vivo in both spinal cord and telencephalon because when explants from chick and rat prosencephalon (forebrain vesicle) or chick spinal cord are cultured in the presence of neutralising anti-Shh antibody, oligodendrocyte production is strongly inhibited (Orentas et al., 1999; Tekki-Kessaris et al., 2001). In the Danforth's short tail mutant mouse, in which the notochord is discontinuous in caudal parts of the spinal cord in heterozygous mutants, PDGFRα^+ oligodendrocyte progenitors fail to appear at the ventricular surface wherever the notochord is missing (Pringle et al., 1996), presumably due to the absence of Shh signalling in these regions. Moreover, in mice with a targeted deletion of the *Nkx2.1* gene (Kimura et al., 1996), which lack only the most anterior domain of Shh expression in the ventral hypothalamus/MGE (Sussel et al., 1999), PDGFRα^+ oligodendrocyte precursors fail to appear in the anterior hypothalamic neuroepithelium at the appropriate stage (E12). By E16.5, PDGFRα^+ oligodendrocyte progenitors do appear in the telencephalon of *Nkx2.1* null mice, but these progenitors probably migrate into the telencephalon from more posterior regions of the CNS (Tekki-Kessaris et al., 2001).

In conclusion, there are strong parallels between the early stages of oligodendrocyte development in the spinal cord and forebrain, suggesting that similar mechanisms of oligodendrogenesis operate at anterior and posterior levels of the neuraxis.

3. New perspectives

3.1. Early specification of oligodendrocytes in the spinal cord and telencephalon

Two recent studies have reported that the basic helix-loop-helix proteins *Olig1* and *Olig2* and the high mobility group protein *Sox10* might be involved in the early specification of the oligodendrocyte lineage (Lu et al., 2000; Zhou et al., 2000). During development, *Olig1* and *Olig2* are expressed predominantly in the CNS and in the adult their expression is most abundant in oligodendrocyte-rich areas (white matter predominantly). *Sox10* is expressed in both the central and peripheral nervous systems and appears to be restricted to myelin-producing cells (Kuhlbrodt et al., 1998). Ectopic expression of *Olig1* in cortical precursor cells in vitro promotes the generation of NG2$^+$ oligodendrocyte precursors (Lu et al., 2000) and ectopic expression of *Olig2* in vivo leads to an upregulation of *Sox10* (Zhou et al., 2000). The pattern of expression of *Olig1*, *Olig2* and *Sox10* in the neuroepithelium of the developing spinal cord and telencephalon overlaps that of PDGFRα (Lu et al., 2000; Tekki-Kessaris et al., 2001; Zhou et al., 2000) (Fig. 4) and double labelling has shown coexpression of *Olig1* and PDGFRα within the same cells (Lu et al., 2000; Zhou et al., 2000). Collectively the data suggest that all four genes — *Olig1*, *Olig2*, *Sox10* and PDGFRα — are involved in the development of oligodendrocytes.

Although *Olig1*, *Olig2*, *Sox10* and PDGFRα all appear in the same region of the developing spinal cord, the timing of their appearance is different (Lu et al., 2000; Zhou et al., 2000). In the mouse spinal cord *Olig1*, *Olig2* and *Sox10* have an early expression pattern throughout the entire ventral third of the neuroepithelium (excluding the floor plate) at E9.5. By E12–E13, their neuroepithelial expression domains narrow down to a small stripe overlapping with that of PDGFRα, immediately dorsal to the expression domain of the homeodomain transcription factor *Nkx2.2*. Shortly after this *Olig$^+$/Sox10$^+$/PDGFR$^+$* cells begin to emerge from the ventricular zone (VZ). The narrow expression domain of *Olig1/Olig2/Sox10* appears about 1 day before PDGFRα. In the telencephalon, all four
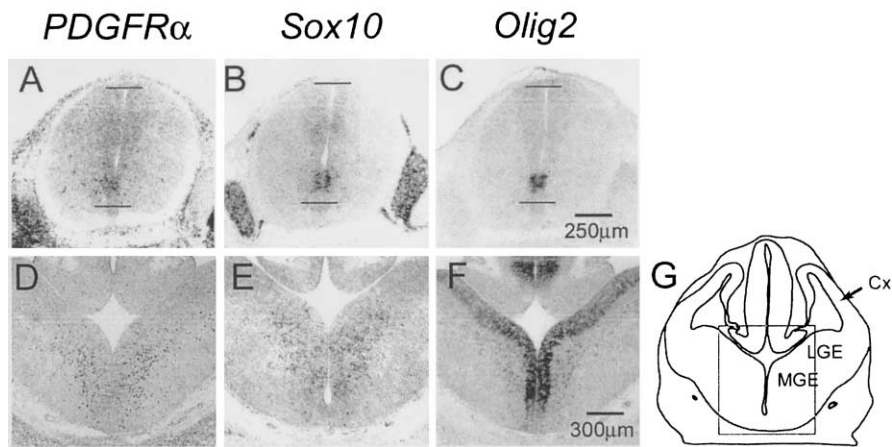
Fig. 4. Overlapping expression of PDGFRα, *Sox10*, and *Olig2* in the developing spinal cord and telencephalon. (A–C) Serial transverse sections through the mouse spinal cord at E13.5. (D–F) serial coronal sections through the mouse telencephalon at E12.5. PDGFRα (A and D), *Sox10* (B and E) and Olig2 (C and F) show overlapping patterns of expression both in the ventral spinal cord and ventral telencephalon. Expression of *Olig2* in the telencephalic neuroepithelium extends further than the others throughout the MGE and LGE. (G) Diagram of the E12.5 telencephalon showing the position of sections D–F.

genes are expressed in the neuroepithelium at the boundary between the anterior ventral hypothalamus and the MGE at the time when PDGFRα[+] oligodendrocyte precursors are being produced (Tekki-Kessaris et al., 2001). *Olig2*, however, has an earlier and wider expression pattern, spanning the entire neuroepithelium of the MGE and lateral ganglionic eminence (LGE) (Tekki-Kessaris et al., 2001) (Fig. 4). The early appearance of these three putative transcriptional regulators in the germinal zones both in the spinal cord and telencephalon suggests that the oligodendrocyte specification program may be initiated at least 1 day before the emergence of PDGFRα^{+} cells and that the *Olig* genes and/or *Sox10* may lie upstream of and possibly regulate PDGFRα expression. PDGFRα may thus be one of the last markers of oligodendrocyte precursors during the specification phase, turning on just before the dedicated progenitor cells emerge from the VZ.

3.2. Oligodendrogenesis may continue until late during gestation

As well as appearing earlier than PDGFRα in the VZ, the two *Olig* genes also persist longer than PDGFRα both in the spinal cord and telencephalon. At E18.5 in the rat spinal cord *Olig1* and *Olig2* can still be detected in the neuroepithelium and *Olig1*^{+}/*Olig2*^{+} cells still appear to be emerging from the germinal zones (Fig. 5). The region from which these cells emerge at this later stage abuts the floor plate and falls within the *Nkx2.2* expression domain. Thus, the *Olig1/Olig2* domain starts dorsal to the *Nkx2.2* domain but 'sinks' into the *Nkx2.2* domain between E14 and E18. Cells apparently migrating out of the ventricular zone at E18.5 express *Olig1/Olig2*, (N. Tekki-Kessaris, unpub-

lished observations) as well as *Nkx2.2* (Xu et al., 2000) (Fig. 5). This raises the question of how long new migratory oligodendrocyte progenitors continue to be generated in the ventral VZ. The current data suggest that oligodendrocyte progenitors are still being born at E18.5 and the region from which they emerge is displaced more ventrally at these later stages. However, the identity of these late emerging cells remains to be
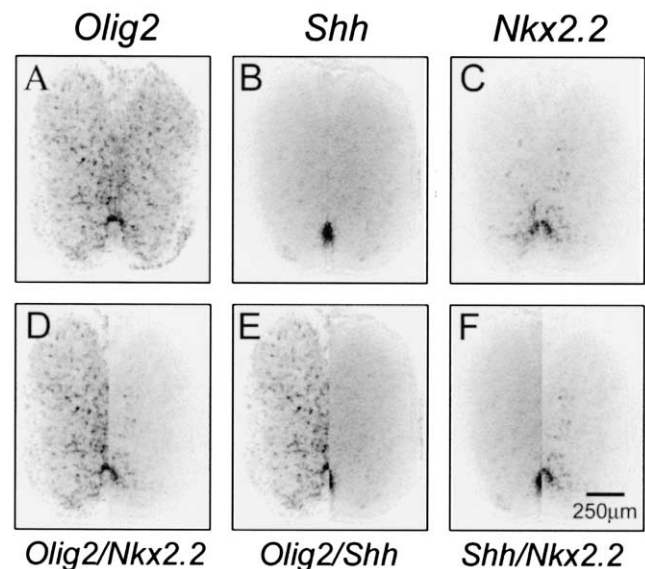

Fig. 5. Comparative expression of *Olig2*, Shh and *Nkx2.2* in the rat spinal cord at E18.5. (A–C) Serial transverse sections through the rat spinal cord at E18.5 showing expression of *Olig2* (A), Shh (B) and *Nkx2.2* (C). (D–F) Alignment of adjacent sections showing expression of *Olig2/Nkx2.2* (E), *Olig2*/Shh (F) and Shh/*Nkx2.2* (G). Neuroepithelial expression of *Olig2* at this stage is shifted ventrally to a small region abutting the Shh-expressing floor plate and overlapping the *Nkx2.2* expression domain. Cells migrating away from the midline appear to express *Nkx2.2*.

determined and it remains possible that they are not oligodendrocyte progenitors but some other type of late-developing cell, for example astrocytes. In the telencephalon too, expression of *Olig2* persists in the ventral VZ after PDGFRα⁺ neuroepithelial cells disappear and *Olig2*⁺ cells can be seen to emerge from the VZ of the LGE (Tekki-Kessaris et al., 2001). Again, the identity of these late-appearing cells remains to be clarified but it is possible that oligodendrocytes might emerge from the entire ventral telencephalon and oligodendrogenesis might occur over an extended period of time. There is evidence from retroviral labelling studies that oligodendrocytes are generated postnatally in the cerebral cortex from progenitor cells originating in the SVZ of the lateral ventricles (Levison and Goldman, 1993; Levison et al., 1999). Taken together, these data raise the possibility that, unlike neurogenesis, oligodendrogenesis does not cease abruptly but might occur continually from mid-embryonic stages until after birth.

4. Conclusions

Three common themes appear to underlie the development of oligodendrocytes in the telencephalon and spinal cord: (1) they originate from localised regions of the ventral neuroepithelium; (2) Shh signalling is required for their specification; and (3) specified oligodendrocyte progenitors migrate out of the germinal zones to populate the surrounding mantle zones throughout the dorso-ventral axis. Although these basic principles of oligodendrogenesis have been known for some time, especially in the spinal cord, the fine details of how these processes are regulated remain unclear. The availability of new presumptive early lineage markers should enable us to build on the current simple model and further dissect the mechanisms of oligodendrocyte lineage specification.

Acknowledgements

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