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Oligodendrocyte Lineage and the Motor Neuron Connection

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ABSTRACT One of the more surprising recent discoveries in glial biology has been that oligodendrocytes (OLs) originate from very restricted regions of the embryonic neural tube. This was surprising because myelinating OLs are widespread in the mature central nervous system, so there was no reason to suspect that their precursors should be restricted. What we now know about early OL development suggests that they might have as much (or more) in common with ventral neurons—specifically motor neurons (MNs)—as with other types of glia. This has implications for the way we think about glial development, function, and evolution. In this article we review the evidence for a shared MN-OL lineage and debate whether this is the only lineage that generates OLs. We decide in favour of a single embryonic lineage with regional variations along the anterior-posterior neuraxis. *GLIA 29:136–142, 2000.*

OLIGODENDROGENESIS IN THE SPINAL CORD

Throughout the CNS, oligodendrocytes (OLs) develop from migratory, proliferating progenitor cells known as O-2A progenitors or, more simply, OL progenitors (OLPs). The OLPs themselves develop from neuroepithelial precursors in the walls of the embryonic neural tube. In the spinal cord, they come from a subdomain of the ventral neuroepithelium near the floor plate. Several early markers of the OL lineage are expressed in or adjacent to this part of the ventral neuroepithelium in a variety of vertebrate species (Miller, 1996). The marker that we have used most in our studies has been the platelet-derived growth factor alpha-receptor (PDGFRα). PDGFRα transcripts first appear at the ventricular surface of the cervical spinal cord on embryonic day 12.5 (E12.5) in the mouse (E14 in rat, E7 in chick) (Pringle and Richardson, 1993; Pringle et al., 1996). At first, there are only a few cells on each side of the central canal but these soon increase in number and move away from the midline into the parenchyma of the cord. By E17 (in the mouse), the number of PDGFRα-positive OLPs reaches a steady state, and they are distributed more-or-less evenly throughout the cord. They do not start to generate myelinating OLs until just before birth on E19/20, although there is reason to think that nonproductive OL differentiation starts in the cord much earlier than that (Calver et al., 1998).

There are many interesting questions concerning the control of division, migration, and survival of OL lineage cells. However, in this article we concentrate on earlier events—specification of OL precursors in the ventricular zones and their lineage relationships with other cells.

SPECIFICATION OF VENTRAL NEURONS

Most work on cell specification has focussed on neurons—particularly neurons in the ventral spinal cord (Tanabe and Jessell, 1996). Ventral neurons include motor neurons and several types of interneurons. All of these are formed under the influence of signals, including Sonic hedgehog (Shh) protein, from the notochord and/or floor plate at the ventral midline.

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Shh controls the expression of a number of transcription factors in the ventral neural tube, including Pax6. Shh represses expression of *pax6* mRNA so that *pax6* is absent from the ventral-most spinal cord where [Shh] is highest, and distributed in a ventral-to-dorsal (low-high) concentration gradient in the remainder of the ventral cord—i.e., in the inverse direction to the presumed gradient of Shh (Ericson et al., 1997). Pax6 is part of the intracellular machinery that interprets positional information relayed by [Shh] and converts this into appropriate cell fate decisions. It does this by regulating expression of downstream genes in a concentration-dependent way. For example, very low concentrations of Pax6 are sufficient to repress expression of *nkx2.2*, which is therefore confined to the Pax6-negative domain adjacent to the floor plate (Ericson et al., 1997). Other transcription factor genes (e.g., *irx3*, *dbx2*, *nkx6.1*) are expressed in overlapping domains in the ventral neuroepithelium and presumably some or all of these are also under the control of Pax6 (Fig. 1) (Briscoe and Ericson, in press).

The neuroepithelial domains defined by the limits of expression of these transcription factors give rise to different neural cell types (Fig. 1). Neuroepithelial precursors in the *pax6*-negative, *nkx2.2*-positive region adjacent to the floor plate give rise to visceral motor neurons (vMNs) that innervate sympathetic and parasympathetic targets and to an unidentified population of cells that express *sim1*, the vertebrate homologue of the *Drosophila* gene *single minded*. In the brainstem, vMNs include vagal motor neurons, which innervate the heart. In the cervical spinal cord they include phrenic motor neurons, which innervate the diaphragm.

The next more dorsal region of neuroepithelium—the lower part of the *pax6* gradient—generates somatic motor neurons (sMNs). In the brainstem these project to the jaw and facial muscles (e.g., hypoglossal MNs that innervate the tongue) and in the cervical spinal cord to axial skeletal muscles that lie close to the vertebral column. At limb levels (brachial and lumbar), there are additional motor neuron pools that project to limb muscles.

Further dorsal still, the neuroepithelium generates V2 and V1 interneurons (INs) (Fig. 1). The newly differentiating MN and IN progenitors start to express distinctive new sets of homeodomain proteins as they migrate away from the ventricular surface towards their final resting positions in the ventral spinal cord and brainstem. For example, vMNs express the homeodomain factor *Islet-1 (Isl-1)*, while sMNs express *Isl-1*, *Isl-2*, and *Lim-3* (Ericson et al., 1997). These factors define the ultimate phenotypes of the newly postmitotic neurons.

A LINEAL RELATIONSHIP BETWEEN MOTOR NEURONS AND OLIGODENDROCYTES

How do glia, particularly OLs, fit into the above picture? We mapped the neuroepithelial origin of PDGFRα-positive OLPs in the cervical spinal cord to the same region that generates sMNs; that is, to the lower part of the *pax6* gradient, outside the *nkx2.2*-positive domain that generates vMNs (Fig. 1) (Sun et al., 1998). However, this part of the neuroepithelium does not generate sMNs and OLPs simultaneously. In the rat, MNs (all subtypes) are born between E11 and E13, whereas OLPs do not appear at the ventricular surface until E14 (Yu et al., 1994). In the mouse, the equivalent dates are ~E9–E12 for MNs and E12.5/13 for OLPs (Pringle et al., 1996). sMNs, being more dorsal, form after vMNs—that is, towards the end of MN production and closer to the time of appearance of OLPs. Therefore, OLPs follow close on the heels of sMNs and come from the same part of the neuroepithelium, suggesting that the same set of neuroepithelial precursors first generates sMNs and then switches to production of OLPs (Fig. 2).

There is other evidence suggesting a shared MN-OL lineage in the developing spinal cord. Retroviral lineage analysis in the chick spinal cord has been performed to examine lineal relationships among MNs and other types of cell (Leber et al., 1990; Leber and Sanes, 1995). MN-containing clones frequently contained other types of cells, including glia. Some of the glia were tentatively identified as OLs because of their morphology and location in white matter tracts; astrocytes were also present. However, this evidence for a shared MN-OL lineage is not cast-iron because: 1) unambiguous identification of OLs (especially immature OLs) can be difficult by morphology alone; and 2) we now know that OLPs are highly mobile cells that can migrate relatively long distances along longitudinal fibre tracts, leading to potential difficulties in defining clone boundaries. Moreover, Leber et al. (1990) examined only those clones that contained MNs, so we cannot tell from their data whether OLs are related more closely to MNs than to other types of spinal cord neurons.

In another study, a high proportion of mixed clones containing MNs together with OLs and/or astrocytes was found when neuroepithelial cells from E10.5 rat spinal cord were cultured for 10–15 days at clonal density in vitro (Kalyani et al., 1997). Most of these clones contained all three cell types. These experiments (and all similar in vitro experiments) measure the developmental *potentials* of precursor cells rather than the actual *fates* adopted by the cells in vivo; there is no guarantee that a cell's full developmental potential is actually realised in vivo because there might be constraints imposed by the local environment (i.e., position in the embryo). Nevertheless, the in vivo and in vitro studies together suggest that there might be an in vivo lineage relationship between MNs and OLs that might also include astrocytes (Rao et al., 1998). These in vitro experiments, like the retroviral experiments described above, did not address the question of whether other types of neurons apart from MNs ever appear in clones with OLs.

Finally, a link between MN and OL development comes from experiments in which these cell types are

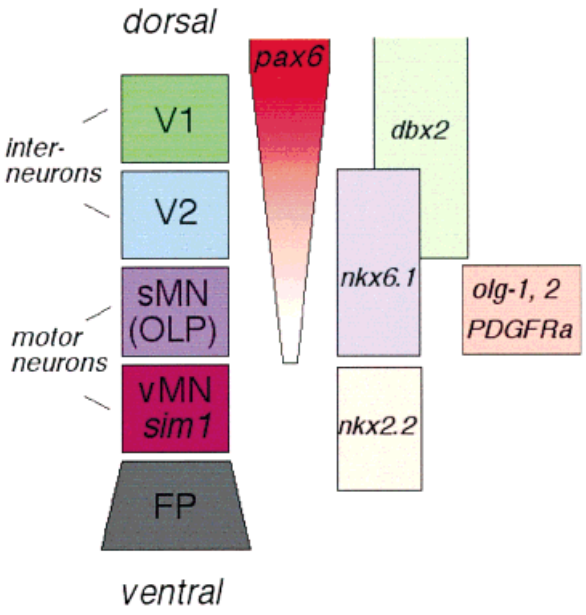

Fig. 1. Diagram of the ventral spinal cord of the mouse from the floor plate to the dorsoventral midline, showing neuroepithelial domains and the cell types that they generate, together with domains of gene expression (to the right). FP, floor plate; vMN, visceral motor neurons; *sim1*, unidentified cells expressing *sim1*; sMN, somatic motor neurons; OLP, oligodendrocyte progenitors; *V2, V1,* different classes of ventral interneurons. vMNs are generated from within the Nkx2.2-expressing domain, sMNs and OLPs from the lower part of the Pax6 domain. For more details, see Briscoe and Ericson, 1999. *olg-1* and *olg-2* are two novel basic helix-loop-helix transcription factors that are expressed in all OL lineage cells including progenitors and myelinating OLs. At E12.5 their expression domain superimposes on that of *PDGDRα*; however, they come on several days earlier than *PDGDRα*, at which time they are expressed throughout the ventral cord. (Lu R, Stiles C, Rowitch D, unpublished observations).

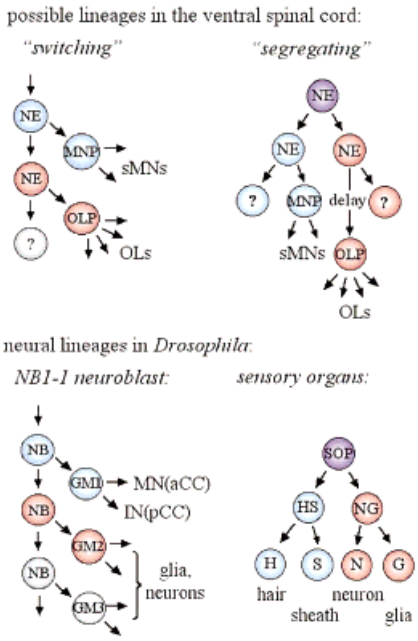

Fig. 2. Hypothetical OL lineage models compared to known *Drosophila* neural lineages. Top left, our proposed cell lineage relating sMNs and OLPs in the ventral spinal cord. A shared pool of neuroepithelial cells (NE) first generates somatic MNs via MN progenitors (MNP) then switches to OL lineage cells. We call this the "switching" model. Lower left, lineage of the ventral NB1–1 neuroblast in abdominal segments of the *Drosophila* embryo for comparison. A stem cell lineage generates sequential ganglion mother (GM) cells that have different fates; GM1 produces a motor neuron (aCC) and an interneuron (pCC) then subsequent GMs produce subperineurial (ensheathing) glia and more neurons. Top right, an alternative sMN/OL lineage (one of several) that would also fit the data. In this model the NE cells that generate MNs or OLPs segregate early but the OL-specific NE cells wait until after MN production is over before generating OLPs. We refer to this as the "segregating" lineage model. Lower right, lineage of peripheral sensory organs in *Drosophila* for comparison. The sensory organ precursor (SOP) divides asymmetrically without self-renewal to generate two bipotential progenitors that divide again to produce the hair cell (H), socket cell (S), neuron (N), and glial cell (G).

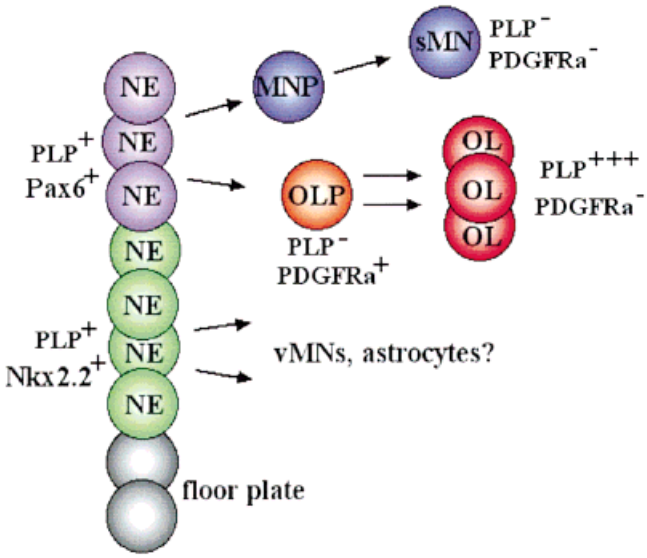

Fig. 3. Putative lineage relationships between *PLP/DM-20*-positive neuroepithelial cells in the ventral VZ of the spinal cord and mature ventral cell types including MNs and glia. We suggest that the *PLP/DM-20*-positive neuroepithelial cells generate a range of cell types including but not restricted to *PDGFRα* OLPs. *PLP/DM-20* is downregulated in cells outside the VZ, but upregulated strongly again in differentiating OLs. This diagram, which is necessarily speculative, is not intended to imply anything about the nature of the lineage connecting sMNs and Ols (see Fig. 2).

specified in vitro with pure Shh. If explants of intermediate or dorsal spinal cord neuroepithelial cells—which do not normally generate any ventral cell types—are cultured in the presence of recombinant Shh, then ventral cell types including floor plate cells, MNs, and OLs can be induced ectopically (Roelink et al., 1994; Pringle et al., 1996; Poncet et al., 1996; Orentas et al., 1999). Higher concentrations of Shh induce floor plate cells in this system, while lower concentrations generate MNs and OLs. The Shh dose-response for MNs overlaps that for OLs (Pringle et al., 1996; Orentas et al., 1999), which is consistent with the idea that Shh induces a common MN-OL precursor cell (i.e., a shared lineage). Other interpretations are possible. For example, signals from previously formed MNs might be required to induce or activate a separate pool of OL precursors—a horizontal rather than a vertical relationship. However, signals from differentiated MNs do not seem to be obligatory for OLs to develop because OLs appear as normal in explants of spinal cord from *Isl-1* null mice, in which MNs fail to develop (Sun et al., 1998). It could be argued that MN *progenitors* are still present in *Isl-1* null cords, and that it is these rather than mature MNs that induce OL production. However, the fact that *PDGFR*α^+ OLPs do not appear in vivo until MN production has ceased—and MN progenitors are no longer around—is hard to square with that idea.

Nevertheless, the case for sMN-OL fate switching is not conclusive. There are other possibilities. For example, separate sMN and OL precursors could exist side-by-side in the same region of the ventral neuroepithelium, the OL precursors sitting dormant during sMN production and becoming active only later when neuronogenesis is complete. This model is still consistent with there being a shared MN-OL lineage, except that the sMN and OL branches would diverge earlier than in the fate-switching model (Fig. 2). It is not yet clear how any of this fits with the tri-potential, glial-restricted progenitor described by Rao et al. (1998) in spinal cord cultures. More direct experiments, such as time-lapse video microscopy of cells developing in vivo or in explant culture, are now required.

MIXED NEURON-GLIAL LINEAGES IN OTHER SYSTEMS

Common neuron-glial precursors occur in invertebrates and in other parts of the vertebrate nervous system. In *Drosophila*, certain CNS neuroblasts generate first neurons, then glia. For example, the neuroblast NB1–1 undergoes several asymmetric (stem cell) divisions to generate a sequence of ganglion mother cells (GM1, GM2, etc.) (Fig. 2). In abdominal segments, GM1 generates a motor neuron (aCC) and an interneuron (pCC) while subsequent GMs generate subperineurial (ensheathing) glia and additional neurons (Bossing et al., 1996). Thus, the fate of the neuroblast can be said to switch from one generation to the next, as we suggest for the putative MN/OL precursors in the ventral spinal cord. However, not all *Drosophila* glia arise from stem cell-like divisions. Longitudinal glia are generated from a dedicated glioblast that never gives rise to neurons. The accessory glia of sensory organs are each produced from the asymmetric division of a bipotential progenitor cell (Fig. 2).

In the vertebrate retina, all retinal neurons, as well as Müller glia, are formed from the same precursors—although the shape of the lineage tree is not known, so we do not know whether specialised glial and neuronal progenitors segregate early or whether there is a stem cell-like lineage as for *Drosophila* NB1–1 neuroblast. Different cell types are generated at different times—retinal ganglion neurons early, rod photoreceptors late, for example—so there might be some form of fate switching involving stem cell-like divisions.

In the cerebral cortex, dedicated progenitor cells that generate clones of a single cell type (pyramidal neurons or astrocytes, say) have been identified (Parnavelas et al., 1991; Grove et al., 1993), but so have multipotent precursors that generate both neurons and glia (Williams et al., 1991; Davis and Temple, 1994). Presumably, the emphasis on pluripotent or dedicated precursors depends on how far back in the lineage one looks (how early one infects with a retroviral lineage marker, for example). Again, it is not known whether there is early segregation of neuronal and glial progenitors or whether there is a stem cell-like lineage that switches fates with successive divisions. However, recent time-lapse studies of single cortical cells dividing in culture has provided evidence for both asymmetric divisions (Qian et al., 1998) and common neuron-glial lineages (S. Temple, personal communication).

A SINGLE OLIGODENDROCYTE LINEAGE IN THE SPINAL CORD AND BRAINSTEM

There has been controversy recently over whether there is just one, or several, OL lineages (see Spassky et al., 1999).

The main evidence for more than one OL lineage comes from comparative studies with two OL lineage markers: *PDGFR*α and the myelin proteolipid protein *PLP*/*DM-20*. In the mouse spinal cord, *PLP*/*DM-20* is expressed in a very few cells just outside the ventral VZ after E14.5 (Timsit et al., 1995). This is very close to where *PDGFR*α cells first appear 2 days earlier on E12.5. This proximity, together with the fact that E14.5 is long before differentiated OLs were originally thought to appear (usually taken to be around birth on E19/20), led to the reasonable suggestion that the *PLP*/*DM-20* cells must be OL progenitors (Timsit et al., 1995). However, we now know that the number of *PLP*/*DM-20* cells does not increase between E14.5 and E17, they do not move during this time, and they do not incorporate BrdU—indicating that they are nondividing cells and therefore unlikely to be progenitors in the usual sense (Hardy and Friedrich, 1996). During the same period

the *PDGFR*α cells increase in number, incorporate BrdU, and migrate throughout the cord (Calver et al., 1998), which is how we would expect OL progenitor cells to behave. Indeed, we know they are OL progenitors because they can be immuno-purified with an antibody against the extracellular domain of *PDGFR*α and placed in culture, when they all generate OLs (Hall et al., 1996). Complement killing of *PDGFR*α cells in mixed cultures of rat spinal cord cells dramatically reduces the number of OLs that develop in vitro (Hall et al., 1996). Moreover, only around 10% of the normal number of OLs (and very little myelin) develops in the spinal cords of mice with a targeted disruption of the *PDGF-A* gene (encoding one of the known ligands for *PDGFR*α) (Fruttiger et al., 1999). This evidence supports the view that ventrally derived *PDGFR*α cells are the major, probably the only source of OLs in the spinal cord.

What of the *PLP*/*DM-20* cells? Since they appear to be post-mitotic, strongly express other markers of mature OLs (e.g., CNP, MBP) (Peyron et al., 1997), and are complex, process-bearing cells, we suppose they are differentiated, nonmyelinating OLs that develop for some reason before the main wave of oligodendrogenesis that begins around birth. It is possible that they lie dormant in the embryo "waiting" for axons to myelinate; if so, they could perhaps be described as postmitotic OL progenitors. Alternatively, they might have some specialised function that we do not know about. In any case, they are only present in mice, not rats, so they cannot have an essential function in all species (unpublished observations from WDR's lab).

All of the above arguments also apply to the somewhat more numerous *PLP*/*DM-20* cells that appear along the VZ of the brainstem after E12.5 (Fruttiger et al., 1999). We conclude that the early forming *PLP*/*DM-20* cells in the spinal cord and brainstem are not progenitor cells in the usual sense, but are more likely to be early forming, differentiated but nonmyelinating OLs. It seems very likely to us that OLs in the spinal cord and brainstem all develop from a single class of *PDGFR*α-positive progenitors—the single MN-OL lineage described above. This is now becoming accepted (Spassky et al., 1999).

However, the story has a twist. Apart from the strongly *PLP*/*DM-20*-positive cells discussed above, the ventral neuroepithelium close to the floor plate of the spinal cord seems to express *PLP*/*DM-20* (weakly) as early as E12 in the rat (Yu et al., 1994)—well before the appearance of *PDGFR*α on E14. A similar thing is observed in mouse. These *PLP*/*DM-20* cells presumably are precursors that give rise to ventral neurons, glia, or both. It is possible that they are lineally related to (even precursors of) the later-forming *PDGFR*α progenitors in the VZ. If so, then *PLP*/*DM-20* cells and *PDGFR*α cells could both be OL precursors, but at successive stages of a single lineage (Fig. 3). This idea would require that the other progeny of the lineage (e.g., MNs) would later downregulate *PLP*/*DM-20*, whereas OLs would upregulate it. A similar model has been suggested before by Perez Villegas et al. (1999).

OLIGODENDROGENESIS IN THE FOREBRAIN: ONE OR MORE LINEAGES?

There are also *PDGFR*α -positive cells in the ventral part of the diencephalon (Spassky et al., 1998). These first appear in the VZ beneath the medial ganglionic eminence (pre-optic area) around E12 in the rat (E10.5 in mouse) (Pringle and Richardson, 1993; Spassky et al., 1998). They then increase in number and spread through the developing hypothalamus and thalamus, apparently invading the developing cortex after E16 (rat) (Pringle and Richardson, 1993). Similar *PDGFR*α cells are present in the chick, and presumably correspond to the O4-positive cells in the pre-optic area that have been described in chick by Ono et al. (1997). The behaviour of these *PDGFR*α cells in the forebrain is strikingly reminiscent of *PDGFR*α OLPs in the spinal cord and it would be surprising indeed if they were not similar in nature. In fact, we have immunoselected these cells from the rat forebrain and shown that they are OLPs like those in other parts of the CNS. They also originate near a site of Shh expression in the ventral diencephalon, and blocking Shh activity with an antibody in explant cultures of chick prosencephalon obliterates OL development in vitro (our unpublished results). Therefore, there do appear to be strong analogies between OL development in the forebrain and in the spinal cord.

If we accept that MNs and OLs are lineally related in the spinal cord then OLs in the forebrain must belong to a different lineage since there are no MNs in the forebrain. However, it is possible that OLs in the forebrain are lineally related to some other class of neuron that is analogous (perhaps phylogenetically related) to spinal MNs; in that sense it could be said that they were regional variations on a single lineage. There are neurons in the pre-optic area of the ventral forebrain that are known to be involved in motor control, for example.

There are also individual *PLP*/*DM-20*-positive cells in the ventral diencephalon at least in the chick (Perez Villegas et al., 1999), and it has been proposed that these represent precursors of a novel OL lineage in the forebrain (Spassky et al., 1999). This is certainly possible, though the fact that they arise in the same ventral territory as the *PDGFR*α cells, around the same time (Spassky et al., 1999), means that one would want to look very carefully at the alternative possibility—that they represent successive stages of the same lineage. The fact that few if any of the *PLP*/*DM-20* cells co-express *PDGFR*α (Spassky et al., 1999) is not a strong argument for separate lineages because we know that *PDGFR*α is downregulated rapidly in differentiating OLs (Hall et al., 1996; Butt et al., 1997); if the *PLP*/*DM-20* cells in the forebrain were early differentiating OLs like their counterparts in the spinal cord and brainstem, we would not expect there to be significant overlap.

Spassky et al. (1999) also argue that, since some *PLP*/*DM-20* cells are present in *PDGF-A* knockout

mice (Fruttiger et al., 1999), this shows that they do not depend on *PDGFR*α and therefore develop independently of *PDGFR*α -positive progenitors. This does not follow. We have shown that some *PDGFR*α progenitors persist in some areas in the *PDGF-A* knockout, demonstrating that *PDGFR*α cells themselves do not depend absolutely on *PDGF-A* (Fruttiger et al., 1999). They might also be stimulated by *PDGF-BB* in some areas but not others (depending on the availability of the ligand), or by a yet-undiscovered third isoform of PDGF,[1] or by some other mitogen/receptor combination unrelated to PDGF. In any event, the fact that there are *PDGFR*α cells present in the *PDGF-A* knockout leaves open the possibility that these *PDGFR*α cells are responsible for the appearance of the *PLP*/*DM-20* cells in the knockout. In fact, we found that those parts of the CNS that had the greatest number of *PDGFR*α cells in the knockout (e.g., medulla) were also those regions with the greatest number of *PLP*/*DM-20* cells and myelin sheaths, consistent with the idea that the *PLP*/*DM-20* cells and myelin are derived from *PDGFR*α progenitors (Fruttiger et al., 1999).

Note that *PLP*/*DM-20* neuroepithelial cells are also found in the germinal zones of the brain at very early times—as early as E9 in the basal plate of the mouse diencephalon, for example (Timsit et al., 1992). These are quite different and easily distinguishable from the individual, scattered *PLP*/*DM-20* cells that appear later outside the VZ. This crucial distinction is not always emphasised. As in the ventral spinal cord, the *PLP*/*DM-20*-positive neuroepithelial cells must be neural precursors of some sort. Judging by their early appearance, they are probably multipotential; and by the large size of their territories, they are likely to generate a large proportion of the cells in their respective brain regions. It is possible that they give rise to OLs among other cells, including neurons. In that sense the *PLP*/*DM-20*-positive neuroepithelial cells in the brain could be regarded as OL precursors, but they are most unlikely to generate only OLs. We suggest that some of the *PLP*/*DM-20*-positive neuroepithelial cells in the forebrain give rise to *PDGFR*α -positive OLPs, as suggested earlier for the spinal cord (Fig. 3). Perhaps oligodendrogenesis in the spinal cord and forebrain is more similar than initially meets the eye.

POSTNATAL OLIGODENDROGENESIS IN THE FOREBRAIN

We have only considered OL development in the embryonic CNS. Goldman and his colleagues have identified pluripotent precursor cells that can generate neurons, OLs, and astrocytes, in the subventricular zones of the postnatal rodent forebrain (Levison and Goldman, 1993, 1997). It is not clear how, or if, these precursors are related to those in the embryo. Perhaps the pluripotent precursors in the postnatal brain recapitulate the developmental lineage of embryonic neuroepithelial cells. They might also be related to (or identical to) the neural stem cells that persist in the CNS throughout adulthood. How embryonic precursors, postnatal precursors, and adult stem cells are connected poses an interesting question for the future.

EVOLUTIONARY IMPLICATIONS OF THE MN-OL CONNECTION

It is curious that OLs develop in close relation to MNs, since OLs do not show a preference for myelinating ventral neurons in mammals. We have suggested before that the developmental connection between MNs and OLs might reflect a phylogenetic relationship (Richardson et al., 1997); perhaps OLs as we know them evolved from a modified form of MN that somehow acquired the ability to enwrap and insulate its neighbours. This could have conferred a selective advantage if it had a beneficial effect on motor responses—escape from predators, for example. This could make sense of why OLs in the spinal cord seem to be related specifically to somatic (skeletal), not visceral (sympathetic/parasympathetic), MNs. In keeping with this idea, pseudomyelin in other phyla (annelids and crustacea) is preferentially associated with axons required for rapid escape responses (Roots, 1993; Davis et al., 1999). Moreover, hagfish (*Myxinus*), which have no myelin (or fins, or jaws), swim at a constant, stately rate and seem unable to accelerate to avoid capture (WDR, unpublished observations).

CONCLUSION

There is persuasive evidence that OLs in the spinal cord and brainstem all develop from *PDGFR*α progenitors that in turn arise in the ventral neuroepithelium as close relatives of somatic motor neurons. Further anterior, the situation is less clear, but there are some obvious analogies between oligodendrogenesis in the forebrain and spinal cord. In our view the available evidence can be interpreted in terms of either a single lineage or multiple lineages but, in the absence of compelling evidence to the contrary, we prefer to err on the side of simplicity—a single embryonic OL lineage (with regional variations) at all anterior-posterior levels of the neuraxis.

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[1]The prospect of an undiscovered "PDGF-C" is not fanciful. The phenotype of the *PDGFR*α null mutant mouse is more severe than either the *PDGF-A* knockout or the *PDGF-A*/*PDGF-B* double-knockout (C. Betsholtz, personal communication): for example, there are profound craniofacial and skeletal defects in the receptor knockout that do not appear in the double ligand knockout. This indicates the likely existence of another ligand acting through *PDGFR*α.

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