Oligodendrocyte wars

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Abstract | Oligodendrocyte precursors first arise in a restricted ventral part of the embryonic spinal cord and migrate laterally and dorsally from there. Later, secondary sources develop in the dorsal cord. Normally, the ventrally-derived precursors compete with and suppress their dorsal counterparts. There are also ventral and dorsal sources in the forebrain, but here the more dorsal precursors prevail and the ventral-most lineage is eliminated during postnatal life. How do the different populations compete and what is the outcome of the competition? Do different embryonic origins signify different functional subgroups of oligodendrocyte?

The developmental origin of oligodendrocytes has been hotly debated for years. Some laboratories, including our own, favoured a unique origin of oligodendrocytes in the ventral neural tube, whereas others went for diversity and multiple origins. The published literature was conflicting and confusing. At last, new *in vivo* approaches are coming to the rescue. As is often the case, the answer is turning out to be more complex than expected.

The established (pre-1990s) view was that oligodendrocytes were probably generated from all parts of the embryonic ventricular zone (VZ) (for an example, see REF. 1). This seemed inherently likely because mature oligodendrocytes are found in all regions of the adult CNS, with no obvious preference for position along dorsal–ventral or anterior–posterior axes. There were also some indications that radial glia, which are widespread throughout the developing CNS, can trans-differentiate into oligodendrocytes at the end of neurogenesis[2–4]. This, too, tended to favour widespread generation of oligodendrocytes.

This view was challenged in the early 1990s by the suggestion, which has been amply confirmed since, that there is a specialized oligodendrogenic domain in the ventral VZ of the embryonic spinal cord[5–12] (for a review, see REF. 13) and possibly also the forebrain[6,14–16]. These ventral germinal zones produce migratory oligodendrocyte precursors that travel laterally and dorsally, sometimes over long distances, to populate all parts of the developing CNS before differentiating into myelin-forming oligodendrocytes. We ourselves favoured the view that ventrally-derived precursors produce most or all oligodendrocytes in the spinal cord and forebrain. This was a tidy idea because it had already been established that different parts of the VZ generate distinct types of neuron under the influence of different cocktails and concentrations of signalling molecules such as sonic hedgehog (SHH) and bone morphogenetic proteins (BMPs)[17]. As there was — and still is — no compelling evidence for functionally distinct classes of oligodendrocytes, this implied that they might have a singular origin. However, this has turned out to be an over-simplification, as several recent articles have now shown conclusively that there are dorsal as well as ventral origins in the spinal cord and brain.

This article aims to provide a historical perspective on the 'origins' debate (BOX 1), which illustrates, in microcosm, the struggle for understanding that runs through all science. A series of recently published articles has revealed that the jostling among rival ideas and laboratories is mirrored by another type of competition among the oligodendrocyte populations themselves[18–21].
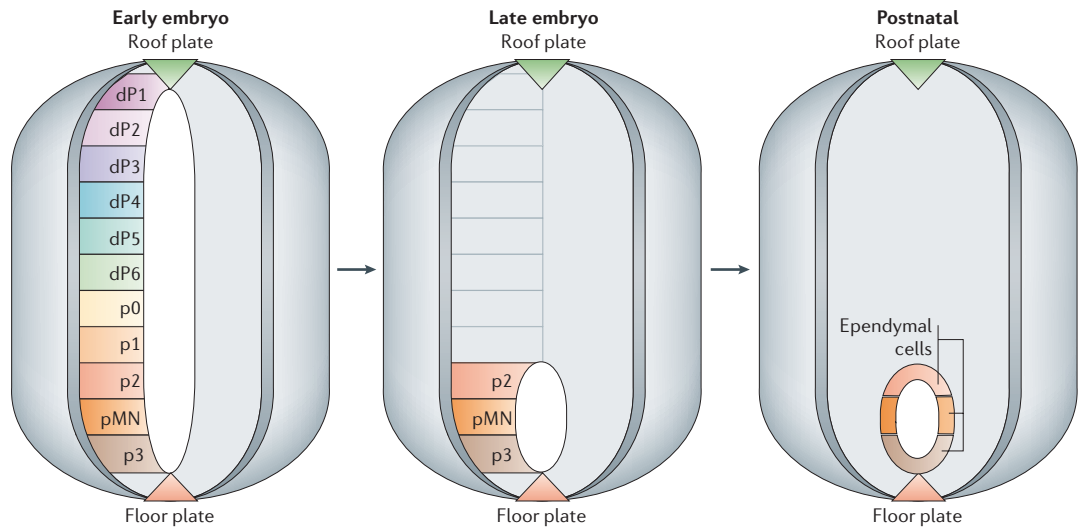
Oligodendrocyte origins — a battle of ideas

The idea of a single, ventral source of oligodendrocytes was controversial when it was first proposed, and not everyone bought into it. In particular, Zalc, Thomas and colleagues took a stand for diversity, arguing for multiple sources both dorsal and ventral[22,23]. Some of their evidence rested on studies with a myelin proteolipid protein (*Plp*)–*lacZ* reporter transgene; these studies could be questioned on the grounds that the transgene might not necessarily reflect the endogenous expression pattern of *Plp* and, even if it did, *Plp* is not necessarily restricted to oligodendrocyte lineage cells at all times and in all parts of the CNS. A major division of opinion developed in the field — single versus multiple origins of oligodendrocytes[23,24]. Fervent debate ensued.

The controversy about oligodendrocyte origins was compounded by the finding that primary cultures of embryonic spinal cord cells contain a population of precursor cells that can generate oligodendrocytes and astrocytes but not neurons in culture[25,26]. These so-called glial restricted precursors (GRPs) can be

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Box 1 | **A tale of two studies**

The two opposing views on oligodendrocyte origins were exemplified in two articles published in the mid-1990s. Both described experiments designed to fate map the spinal cord neuroepithelium using chick–quail chimaeras. The idea of such studies is simple: remove part of the ventral or dorsal spinal cord from a chick embryo *in ovo*, replace it with the equivalent part of a quail spinal cord and wait to see whether the oligodendrocytes that develop in the chimaeric animal are of chick or quail origin. The first such study, by Cameron-Curry and Le Douarin[62], reported that oligodendrocytes are generated more or less equally from all parts of the dorsal and ventral ventricular zones. The other study, from our own laboratory[63], claimed that oligodendrocytes are generated only from the ventral ventricular zone. How could such a stark discrepancy arise from what seem to be replicate sets of experiments?

One reason is that the criteria used to define a 'dorsal' graft differed between the two studies — in an interesting way. As the grafted neuroepithelial cells cannot be observed continuously from the time of surgery to the time of analysis (more than a week), some retrospective way of confirming the initial dorsal or ventral extent of the graft is required. Cameron-Curry and Le Douarin[62] presumed that the presence of graft-derived ependymal cells around the dorsal but not the ventral aspect of the spinal cord lumen at the time of analysis implied that the graft must have been dorsally restricted from the outset. However, this assumes that the dorsal ependymal layer is derived from dorsal neuroepithelial cells, an apparently reasonable assumption that nevertheless turned out to be wrong.

As the spinal cord matures, the central canal shrinks in size and the neuroepithelial cells that surround it are replaced by a layer of ependymal cells. It was recently shown that ependymal cells express the ventral transcription factors Nkx2.2, OLIG2 and Nkx6.1, but not dorsal markers such as paired box 7 (PAX7)[64]. Moreover, our recent fate mapping studies show that progenitor domains more dorsal than p1 (that is, beyond the dorsal expression limit of Nkx6.1) do not contribute to the postnatal ependymal layer[20]. Taken together, the evidence strongly suggests that the ependymal layer is formed exclusively from ventral progenitors in domains p3, pMN and p2, the more dorsal progenitor domains being 'obliterated' during development (see panel)[61].

As Cameron-Curry and Le Douarin's 'dorsal' grafts gave rise to ependymal cells, it follows that, far from being dorsally restricted, the grafts must, in fact, have spread deep into ventral territory. This could have resulted from preferential expansion of the grafted quail tissue in the chicken host, after transplant. The study of Pringle *et al.*[63] specifically excluded grafts that contributed to the ependymal layer.

Ironically, new genetic fate-mapping experiments — not subject to the uncertainties of microsurgery — now demonstrate that there are some dorsally-derived oligodendrocytes in mice[18–20]. Whether the study of Pringle *et al.*[63] simply overlooked this relatively small population, or whether there really is a difference between rodents and birds remains to be seen. dP1–dP6, dorsal progenitor domains.

found in cultures derived from different parts of the spinal cord neuroepithelium, both dorsal and ventral. This, on the face of it, seems to go against the idea of a restricted ventral origin for oligodendrocytes. Moreover, the presence of GRPs emphasizes a developmental relationship between oligodendrocytes and astrocytes, whereas we and others had been emphasizing a relationship between oligodendrocytes and neurons (specifically, motor neurons in the spinal cord). However, this dispute is probably more imaginary than real because it is possible that GRPs could be generated widely throughout the VZ yet constrained by the local environment to generate only (or mainly) oligodendrocytes in some parts (for example, the ventral spinal cord) and mainly astrocytes in others[27]. These spatial constraints would presumably be overruled in culture. In other words, the developmental potential of cells *in vitro* is often different from their actual fates *in vivo*.

Why should it matter where oligodendrocytes arise during development? If they can be generated from different parts of the VZ under the influence of different signalling pathways, this might imply that completely different regulatory pathways can lead to the same cell type. This would indicate a surprising lack of specificity
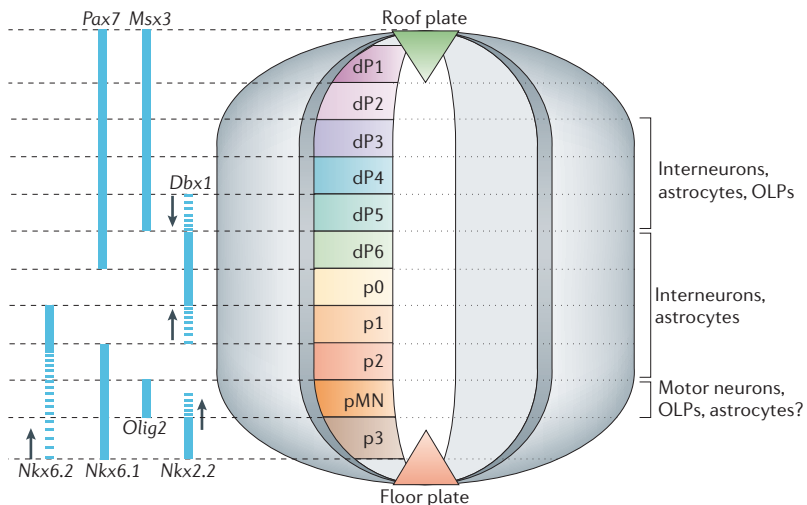
Figure 1 | **Progenitor domains in the embryonic spinal cord and the cell types that they generate.** Neurons are formed before glia (astrocytes and oligodendrocyte precursors (OLPs)). In general, OLPs are formed before astrocytes and ventral cell types before dorsal. The figure shows the expression domains of several transcription factors. Dashed bars indicate that the expression domain boundaries shift during development, in the direction of the small arrows — for example, expression of the transcription factor *Nkx2.2* expands dorsally, and expression of the developing brain homeobox gene *Dbx1* contracts. ~85% of all spinal cord oligodendrocytes are generated from pMN and the remainder from other progenitor domains. It is not known whether astrocytes are also generated from pMN but, if so, they are probably produced in small numbers relative to oligodendrocytes. dP1–dP6, dorsal progenitor domains; *Msx3*, a homeobox gene; *Olig2*, oligodendrocyte lineage gene 2; *Pax7*, paired box gene 7; pMN and p0–p3, ventral progenitor domains.

in the downstream readout of signal transduction pathways. Alternatively, oligodendrocytes with different developmental origins might have distinct functions or properties *in vivo* — an equally intriguing possibility. Either way, it is important to get the story straight.

The field has been in desperate need of a resolution to this question. Thankfully, this now seems to be on the way as a result of a series of recently published articles, reviewed below.

New approaches to the rescue

Three recent papers — one from the laboratory of Mengsheng Qiu in Louiseville, Kentucky, one from Johan Ericson's lab in Stockholm and the other from our own lab — provide persuasive new evidence that oligodendrocytes in the spinal cord are derived from both ventral and dorsal sources[18–20].

The former two articles describe mice that are double mutant for the homeodomain transcription factors Nkx6.1 and Nkx6.2 (*Nkx6* null). The Nkx6 factors are normally expressed in the ventral part of the embryonic spinal cord VZ abutting the floor plate — progenitor domains p3, pMN, p2 and p1 (FIG. 1). *Nkx6* transcription is activated by SHH signalling from the notochord and floor plate at the ventral midline. In turn, Nkx6 activates the basic helix–loop–helix (bHLH) oligodendrocyte transcription factor OLIG2, which is absolutely required for the generation of both motor neurons and oligodendrocyte precursors from progenitors in the ventral progenitor domain pMN[28–30]. *Nkx6*-null spinal cords

therefore lose OLIG2 expression in pMN, so production of both motor neurons and oligodendrocytes from the ventral VZ is completely blocked[18,19].

Surprisingly, oligodendrocyte precursors that express the usual markers platelet-derived growth factor receptor-α (PDGFRα) and OLIG2 continue to be produced in the dorsal spinal cord of *Nkx6*-null mice. The dorsal precursors co-express paired box gene 7 (*Pax7*), confirming their dorsal origin. In wild-type mice, some oligodendrocyte precursors in the dorsal part of the cord were also found to express PAX7, which indicates that dorsal production is a normal phenomenon. These precursors were missed in previous studies (for an example, see REF. 6), presumably because they are generated after their ventrally-derived counterparts and mingle with them unnoticed. There are fewer PAX7-expressing oligodendrocyte precursors in wild-type spinal cord than in *Nkx6* mutant cord, which suggests that ventrally-produced oligodendrocyte precursors normally suppress their dorsal counterparts, perhaps because they compete more effectively for essential proliferation and/or survival signals such as PDGF[31,32]. Generation of the ventral precursors starts a couple of days earlier than that of the dorsal ones (embryonic day (E) 12.5 compared with ~E15), so they have plenty of time to get pre-established.

Further evidence for dorsally-derived oligodendrocytes has been provided by Cre-*lox* fate-mapping experiments in transgenic mice[20]. We generated mice that carry a transgene expressing Cre recombinase under the control of regulatory elements surrounding the *Dbx1* (developing brain) homeobox gene[20]. In these mice, *Cre* expression mirrors the normal pattern of *Dbx1* expression, which is restricted to neuroepithelial precursors in p1, p0, dP6 and dP5 – that is, four progenitor domains centred on the dorsal–ventral midline (FIG. 1). Crossing the mice with a Cre-dependent reporter line (*Rosa26*–*GFP* (green fluorescent protein) or *Rosa26*–*lacZ*) permanently labels the *Dbx1* precursor cells and all of their differentiated progeny. Unexpectedly, a small number of oligodendrocytes was labelled as well as the expected radial glia, interneurons and astrocytes. The *Dbx1*-derived oligodendrocytes comprised ~3% of all oligodendrocytes in the spinal cord and were less widely spread than the majority — being mainly located in the lateral white matter radially opposite their site of origin in the VZ (FIG. 2). Some *Dbx1*-derived, OLIG2-positive cells retained a radial process and transiently co-expressed the radial glial cell marker RC2, which indicates that they are formed by direct interconversion from radial glia — as suggested many years ago[2,4].

Not all parts of the dorsal VZ generate oligodendrocytes. The dorsally-derived precursors revealed in *Nkx6*-null mice seem to arise from progenitor domains dP3, dP4 and dP5 (REF. 18). This suggests that the oligodendrocytes labelled in our *Dbx1–Cre* fate mapping experiments might be derived from dP5, the only region of overlap. In more recent fate-mapping studies with *Msx3–Cre* transgenic mice it appeared that 10–15% of all oligodendrocytes in the cervical spinal cord originate in the dorsal half of the cord. Many of these are concentrated in the dorsal funiculus where they contribute up to 50% of the oligodendrocytes[33].
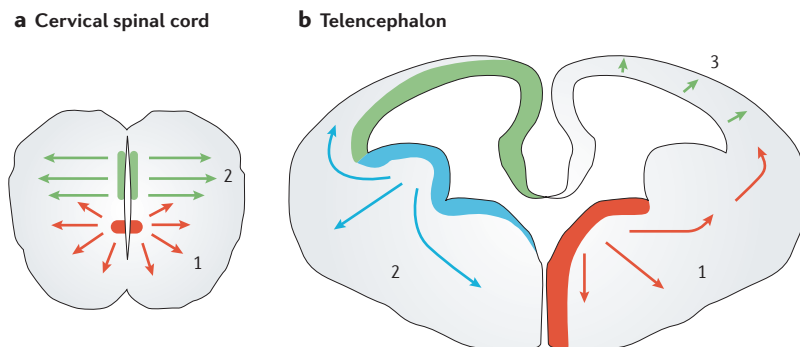
a Cervical spinal cord   **b** Telencephalon

Figure 2 | **Origins and migration of oligodendrocyte precursors in the rodent cervical spinal cord and telencephalon. a** | In the mouse spinal cord, ~85% of oligodendrocyte precursors are generated from pMN in the ventral ventricular zones (1), starting at about embryonic day (E)12.5. At about E15, generation of a secondary wave of precursors starts in more dorsal regions[16–18] by trans-differentiation of radial glia[18] (2). **b** | In the telencephalon, the ventral-most precursors in the medial ganglionic eminence are produced from about E12.5 (1), production of the lateral ganglionic eminence-derived precursors starts a few days later (2), and production of the cortex-derived precursors occurs mainly after birth[19] (3). Diagram not to scale.

So, there are both ventral and dorsal origins of oligodendrocytes in the spinal cord and brainstem, as predicted by others[23,34] (FIG. 2). Our own previous position, that 'most or all' oligodendrocytes might be generated in the ventral cord[24] must now be softened to 'most but not all'. This is a gratifying conclusion as everyone can claim credit for being at least partly correct.

The role of Nkx2.2. There has also been controversy about oligodendrocyte origins at a more microscopic level. This concerns whether there is precise correspondence between the ventral oligodendrogenic domain and the ventral precursor domains p3 and/or pMN. This question relates to the transcriptional regulation of gliogenesis itself, because different progenitor domains express and are defined by different sets of transcription factors — for example, Nkx2.2 in p3, and Nkx6.1 and OLIG2 in pMN — and these factors are also involved in cell type specification and later differentiation events. Careful descriptive studies in mice mapped early-forming oligodendrocyte precursors (PDGFRα-positive) to the pMN domain, just dorsal to the Nkx2.2-positive p3 domain[35]. This led us to suggest that oligodendrocytes might have a special lineage relationship with somatic motor neurons. However, this was subsequently challenged by analogous studies in chicks[36,37], which showed that PDGFRα-positive precursors arise entirely within the Nkx2.2-expressing p3 domain in birds.

It turns out that the expression of Nkx2.2 changes with time, spreading dorsally to overlap with the pMN domain (defined by expression of OLIG2)[30,38–40] during later embryogenesis. In mice, oligodendrocyte precursors in the cervical spinal cord are formed within pMN, after motor neuron production is completed but before the dorsal expansion of Nkx2.2 begins (REF. 39; FIG. 3). In chicks, oligodendrocytes are formed after expansion of Nkx2.2, and then only within the precise region of overlap with OLIG2 (REF. 37; FIG. 3) — neither p3 nor

pMN but a new, hybrid p3/pMN domain. This is a subtle species difference between rodents and birds. However, a common feature is that oligodendrocyte precursors develop from OLIG2-expressing neuroepithelium in both rodents and birds, so it seems likely that there is a close lineage connection between motor neurons and oligodendrocytes in both. Another common feature between chicks and mice is that Nkx2.2 is upregulated in differentiating oligodendrocytes in the white matter[39]. This fits with the idea that Nkx2.2 is important in maturation, not initial specification of the oligodendrocyte lineage in the mouse spinal cord[41]. Vallstedt *et al.*[19] have now shown that the 'chick pattern' of Nkx2.2 expression is preserved in the mouse brainstem, so that there is variation even along the mouse neuraxis. Whether this means that there are subtle differences in the properties of oligodendrocytes in the brainstem versus spinal cord is not known.

Oligodendrocyte wars in the forebrain. The controversy about the origins of oligodendrocytes extends to the forebrain. Here, too, there is evidence for a ventral source in the VZ of the basal forebrain. Cells that express oligodendrocyte lineage markers such as OLIG1, OLIG2, SOX10 and PDGFRα first appear in the neuroepithelium of the medial ganglionic eminence (MGE), and appear to migrate laterally and dorsally from there into all parts of the developing forebrain, including the cerebral cortex, before birth[14]. But is there also a dorsal source in the forebrain?

In the chick, it seems there is not. The results of chick–quail grafting experiments indicate that all oligodendrocytes in the avian cortex are derived from precursors originating in the ventral telencephalon (anterior entopeduncular area, AEP)[16]. However, the results of Cre-*lox* fate-mapping experiments using transgenic *Emx1-Cre* mice suggest that a significant fraction of oligodendrocytes in the corpus callosum and other cortical white matter tracts are derived from endogenous cortical precursors[42]. Other studies have provided evidence for either a ventral or a dorsal source[14–16,34,43–46]. Again, the lack of consensus is striking.

Recent fate-mapping studies from our own laboratory have helped resolve the confusion[21]. Using an *Nkx2.1-Cre* transgenic mouse line that marks neural progenitors in the basal forebrain (including the MGE, AEP and pre-optic area), we found that the first oligodendrocyte precursors to arrive in the cortex about E16 are immigrants from ventral territories. These invaders populate the entire cortex by E18, but are then joined by a second wave of oligodendrocyte precursors from the lateral and/or caudal ganglionic eminence(s) (LGE/CGE) (genomic screened homeobox 2 (*Gsh2*)-positive territory). Therefore, at E18, all oligodendrocyte lineage cells in the cortex are ventral in origin. After E18, however, the contribution of ventral cells starts to decrease as they are joined by yet another wave of oligodendrocyte precursors that originates in the cortex itself (*Emx1*-positive neuro-epithelium). So, once again, there are both ventral and dorsal sources — depending on the stage of development studied (FIG. 2).
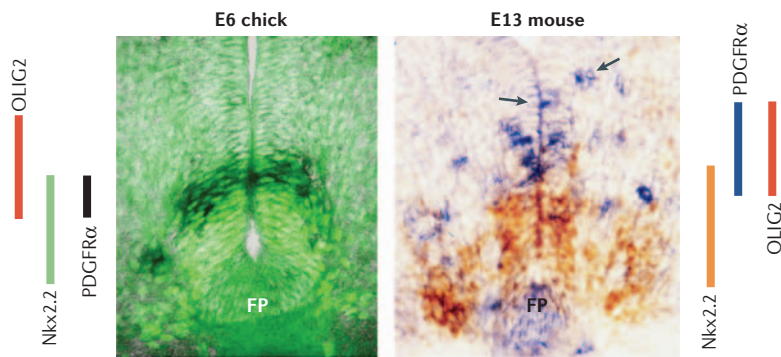
Figure 3 | Ventral origin of PDGFRα-positive oligodendrocyte precursors. In the chick cervical spinal cord, platelet-derived growth factor receptor-α-positive (PDGFRα⁺) precursors are derived exclusively from the dorsal part of the Nkx2.2-expressing domain, within the area of expression overlap between the transcription factors Nkx2.2 and OLIG2 — a hybrid p3/pMN domain (p3 and pMN are the ventral-most progenitor domains). By contrast, in the mouse cervical spinal cord PDGFRα⁺ precursors initially arise within the OLIG2⁺ pMN domain, outside the dorsal limit of Nkx2.2⁺ expression (arrows). Later, after dorsal expansion of Nkx2.2 expression, they appear to arise in both the (Nkx2.2⁺, OLIG2⁺) and (Nkx2.2⁻, OLIG2⁺) domains. In both chicks and mice, oligodendrocyte precursors upregulate Nkx2.2 as they differentiate into myelinating oligodendrocytes in the white matter[30]. Left panel: combined Nkx2.2 immunolabelling (green fluorescence) and PDGFRα *in situ* hybridization (black). Right panel: double *in situ* hybridization for Nkx2.2 (brown reaction product) and PDGFRα (blue). In the right panel, we assume that the blue PDGFRα⁺ cells in the floor plate region are oligodendrocyte precursors that have migrated ventrally from the ventral ventricular zone, although it is also possible that they arose within the floor plate (FP) itself. E, embryonic day.

Remarkably, we found that the original population of MGE/AEP-derived precursors disappears after birth, being rapidly eliminated from the cortex and more gradually from all other parts of the brain. Almost no trace can be found of the initial Nkx2.1-derived oligodendrocyte population anywhere in the adult[21]. This is reminiscent of the nervous system remodelling that occurs during the embryo–larva transition in *Drosophila*. Do the early-forming oligodendrocyte precursors in the mouse have some special function that is not required in the adult? Or is the MGE/AEP-derived population an evolutionary relic that lost its importance as new sources developed in the expanding brain? We revisit these questions later (see section on evolution of oligodendrocyte development, below*).*

Running parallel to these embryonic studies has been a long-running and elegant series of experiments from Jim Goldman and others showing that, in the postnatal forebrain, oligodendrocytes are generated from progenitor cells that reside near the tips of the lateral ventricles[47–51]. What is the relationship between the embryonic and postnatal germinal zones? As neurogenesis comes to an end during late embryogenesis, the forebrain VZ regresses until only a remnant remains at the cortico-striatal boundary, which remains active and continues to generate new oligodendrocytes (and other cell types) after birth and into adulthood. The postnatal VZ and its neighbouring subventricular zone is derived mainly from the embryonic LGE and lateral cortex, with no contribution from more ventral regions[21,47]. Therefore, the most ventral, MGE/AEP-derived

progenitors leave no descendants in the postnatal subventricular zone. This might contribute to the gradual loss of MGE/AEP-derived oligodendrocytes during postnatal life.

Different sources, different cells?

In the spinal cord, expression of OLIG2 in the ventral VZ depends on SHH signalling from the notochord and floor plate[10]. The dorsally-derived oligodendrocyte precursors also express OLIG2 (and other established lineage markers such as PDGFRα and SOX10), although it seems unlikely that SHH can act at that distance from the floor plate. This suggests that oligodendrocyte lineage specification might be controlled by a different signalling system in the dorsal cord. A hedgehog-independent pathway clearly does exist, because oligodendrocytes can be generated from dorsal spinal cord or telencephalic precursors cultured in the presence of cyclopamine, a drug that blocks all hedgehog signalling by binding to its co-receptor smoothened (SMO)[52,53]. In addition, Cai *et al.*[18] have shown that mouse embryonic stem (ES) cells derived from *Smo*-null blastocysts can generate oligodendrocyte lineage cells in culture. It has been shown that fibroblast growth factor (FGF) can induce oligodendrocyte precursors in culture independently of SHH (that is, in the presence of cyclopamine)[52,53], so maybe FGF signalling is responsible for specifying oligodendrocytes in the dorsal spinal cord. BMP and WNT signalling pathways might also be involved[19,54–57].

Hedgehog signalling has also been shown to be required (or at least intimately involved) in oligodendrocyte specification in the ventral forebrain[14,15,58]. SHH expression has not been detected in the embryonic cerebral cortex, so the late wave of cortical oligodendrogenesis might also be under different control — perhaps, again, by FGF. It is known that FGF can induce oligodendrocyte production in cultures of embryonic cortical cells[10,14].

If the ventral and dorsal telencephalic lineages are specified differently, does this mean that they are intrinsically different cells — specialized oligodendrocyte subtypes with distinct molecular and/or functional properties (BOX 2)? If they are, it seems that the differences are not crucial because, when we killed either the ventral- or dorsal (cortex)-derived populations at source by targeted expression of a diphtheria toxin transgene, neighbouring populations moved in to fill the space, a normal number and distribution of oligodendrocytes developed and the animals survived and behaved normally[21].

Evolution of oligodendrocyte development

If, as discussed above, there is a dorsal source of oligodendrocytes in the mouse telencephalon but not in the chick, what might the significance of this species difference be? Mice (and mammals in general) have a greatly increased cortical volume compared with birds and this presumably calls for many more cells of all types, including oligodendrocytes, during cortical development. Migration distances would also have increased

Box 2 | Do all roads lead to Rome?

Can cells that are born of progenitors in different parts of the embryo — under the influence of different positional signals and expressing different sets of patterning genes — ever converge on precisely the same phenotypic endpoint? Would we expect oligodendrocytes that are specified by sonic hedgehog (SHH) in the ventral neural tube to be identical to oligodendrocytes that are specified by different signals (for example, fibroblast growth factor (FGF)) in the dorsal neural tube? Different classes of neuron are derived from different parts of the neural tube, so perhaps it would not be surprising if the glial products also differed. But what types of difference might we expect?

The morphology of oligodendrocytes varies according to the axons that they myelinate[65,66]. Those that ensheath large-diameter axons have a large cell body that lies close to the axon and they synthesize only a single internode's worth of myelin[66,67]. Other oligodendrocytes make many internodes — often more than 30 — on small-bore axons[68]. There are also molecular differences between oligodendrocytes on large- versus small-bore axons — for example, in their gap junction proteins (connexins)[69]. It is not known whether these are intrinsic differences or phenotypic variations of a single, plastic cell type. When oligodendrocyte precursors are purified from rodent optic nerve (which contains uniformly small-diameter axons) and transplanted into the ventral spinal cord (mixed large- and small-diameter axons), the grafted cells myelinate both large and small axons in the host[70]. This result is indicative of phenotypic plasticity; however, it is also possible that the optic nerve contains a mixture of oligodendrocyte precursor subtypes but that the large-bore variety normally fail to find suitable axonal partners and lie dormant in the nerve. The general idea that there might be different subclasses of oligodendrocyte derived from different precursor subtypes (for example, platelet-derived growth factor (PDGF)-dependent and -independent lineages[15]) is an area of active debate[71].

Regardless of whether there are different subtypes of oligodendrocyte, it seems possible that there might be intrinsically different subtypes of astrocyte. Various functions have been ascribed to astrocytes, such as the induction of endothelial cells to form tight junctions, thereby creating the blood–brain barrier, and the buffering of extracellular neurotransmitter concentrations, providing trophic support for neurons or oligodendrocytes. It remains to be seen whether these diverse functions are fulfilled by a single multi-tasking cell or multiple cell types, perhaps derived from different neurogenic domains.

significantly in the larger cortex. These changes might have provided selective pressure for the evolution of an additional, local source of oligodendrocytes in the cortex, to supplement those that migrate in from the basal forebrain. There is a nice precedent for this. In rodents, all GABA (γ-aminobutric acid)-containing cortical interneurons are thought to be immigrants from the basal forebrain[59]. In humans, which have undergone an additional, huge cortical expansion compared with rodents, there is also local production of GABA-containing interneurons in the neocortex[60].

According to the above scheme, the ventral source of oligodendrocytes is 'primitive' and the more dorsal sources were later evolutionary additions that were necessary to allow cortical expansion. By analogy, the primary source of oligodendrocytes in the spinal cord should be ventral (pMN) and the dorsal sources a later evolutionary addition. We have suggested before that the original selection for oligodendrocytes in the caudal neural tube might have been specifically to myelinate motor axons in order to facilitate rapid locomotion (for example, to allow rapid escape from predators) — hence their production side-by-side with motor neurons in pMN[24,69]. This still seems an attractive idea. But what was the

evolutionary selection for an additional source in the dorsal spinal cord? Perhaps it is simply an inconsequential by-product of the 'space race' going on in the brain. Or the dorsally-derived oligodendrocytes could have some specialized role that we are not yet aware of.

An alternative scenario is that all neuroepithelial cells throughout the CNS, regardless of position, are programmed to generate relatively small numbers of oligodendrocytes and astrocytes after the completion of neurogenesis. Therefore, their default behaviour is to generate neurons followed by glial cells — this is the classical view of gliogenesis. The oligodendrocyte 'factory' in pMN might, then, have been a later evolutionary response to pressure for more oligodendrocyte lineage cells, available earlier in development. According to this model we would expect to find small numbers of both astrocytes and oligodendrocytes being generated from all spinal cord neuroepithelial domains, with some domains — such as pMN — specializing in production of extra oligodendrocytes or astrocytes.

The mechanism by which the embryonic, MGE-derived oligodendrocytes are eliminated from the brain after birth — and the reason for their removal — is a mystery. If the need for them has been replaced by more local sources, then they might have no special function in the cortex and might simply be out-competed for proliferation and survival signals by the local precursors. Competition between ventral and dorsal progenitors has already been noted in the spinal cord, except in that case the ventral progenitors seemed to win out, at least in the short term (see section on new approaches to the 'origins' debate, above). A more interesting (but less likely) idea is that the early-forming lineage has a specific function in the embryonic cortex that is no longer required postnatally — akin to the nervous system re-modelling that occurs in invertebrates (for example, *D. melanogaster*) as they metamorphose from embryo to larva to adult.

Another type of explanation for the elimination of MGE-derived oligodendrocytes has been suggested by recent fate-mapping experiments[21] that show that the postnatal subventricular zone is descended from cells in the embryonic LGE and cortex, with no contribution from the MGE. Therefore, if there were significant turnover of oligodendrocytes throughout the life of the animal, new subventricular zone-derived cells would be expected to gradually replace previous generations of oligodendrocytes and would lead to the gradual loss of MGE-derived cells over time. It should be stressed that we do not yet know whether there is any turnover of oligodendrocyte lineage cells *in vivo*; it is possible that oligodendrocytes survive for the lifetime of the axons that they ensheath. However, it is known that new oligodendrocytes continue to be generated throughout life[50–54], so it will be interesting to discover whether these are to replace lost oligodendrocytes or to supplement the existing population — to myelinate new axons, for example. Note that not all ventrally-derived cells are eliminated in the adult — MGE-derived cortical interneurons and basal forebrain neurons persist long-term[21].

Conclusion

The driving force for scientific progress is competition among individuals and ideas. That has certainly been true of our field of glial cell development. At last, the long-running arguments about the site(s) of origin of oligodendrocytes are being settled — the answer is that there are both dorsal and ventral sources that become active at different times during development and that compete with each other for territory.

The old arguments will soon be forgotten as the field moves on, but they were important in passing, because controversy focuses the mind, attracts attention and brings newcomers into the field. Scientific progress is ultimately a group effort in which controversy and dispute play an essential part.

Perhaps we can draw a line under the oligodendrocyte origins debate and move on to new questions. How diverse are glia, especially astrocytes? Does developmental origin predict cell function? What are the molecular mechanisms of cell fate selection and neuron–glial fate switching? Do glial precursors in the adult CNS have a physiological or structural role in addition to generating new glia? Can they also generate neurons? Do adult precursor/stem cells 'remember' their origins in the embryonic VZ and, if so, do they retain the lineage restrictions of their neuro-epithelial ancestors? We look forward, with anticipation, to another decade of cut and thrust.

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