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Oligodendrocyte Wars

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Summary

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 ventral and dorsal sources in the forebrain too 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 outcome of the competition? Do different embryonic origins signify different functional subgroups of oligodendrocytes?

Background

The developmental origin of oligodendrocytes has been hotly debated for years. Some labs including our own favoured a unique origin of oligodendrocytes in the ventral neural tube, while 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 turns out to be more complex than expected.

The established (pre-1990's) view was that oligodendrocytes were probably generated from all parts of the embryonic ventricular zones (VZ) (e.g. reference 1). This seemed inherently likely because mature oligodendrocytes are found in all regions of the adult central nervous system (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 1990's by the suggestion, amply confirmed since, that there is a specialized oligodendrogenic domain in the ventral VZ of the embryonic spinal cord 5–12 (for review see reference 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 neurons under the influence of different cocktails and concentrations of signaling molecules such as Sonic hedgehog (Shh) and Bone Morphogenetic Proteins (BMPs) 17. Since 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, for 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, which illustrates in microcosm the struggle for understanding that runs through all science. A series of recently published articles reveals that the jostling among rival ideas and labs is mirrored by another kind of competition among the oligodendrocyte populations themselves 18–21.

Oligodendrocyte origins – a battle of ideas

The idea of a single, ventral source for oligodendrocytes was controversial at the time 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/DM 20*) – *lacZ* reporter transgene; these studies could be questioned on the grounds that the transgene might not necessarily reflect the endogenous expression pattern of *PLP/DM 20* and, even if it did, *PLP/DM 20* 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 found in cultures derived from different parts of the spinal cord neuroepithelium, both dorsal and ventral. This, on the face of it, appears to go against the idea of a restricted ventral origin for oligodendrocytes. Moreover, GRPs emphasize 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 (e.g. 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 than their actual fates in vivo.

Why should it matter where oligodendrocytes arise during development? Well, if they can be generated from different parts of the VZ under the influence of different signaling pathways, that might imply that completely different regulatory pathways can lead to the same cell type. That would indicate a surprising lack of specificity 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. Thankfully, that resolution now seems to be on the way with a series of recently-published articles, reviewed below.

New approaches to the rescue

Three recent papers – one from the laboratory of Mengsheng Qiu in Louisville, 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 doubly deficient 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 signaling from the notochord and floor plate at the ventral midline. In turn, Nkx6 activates the basic helix-loop-helix (bHLH) 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 31–33. *Nkx6*-null spinal cords therefore lose expression of Olig2 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 PDGFR α and Olig2 continue to be produced in the dorsal spinal cord of *Nkx6* null mice. The dorsal precursors co-express 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, indicating that dorsal production is a normal phenomenon. These precursors were missed previously (e.g. reference 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, suggesting 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 34,35. The ventral precursors start to be generated a couple of days earlier than the dorsal ones (E12.5 compared to ~E15) so they have plenty of time to get pre-established.

Additional evidence for dorsally-derived oligodendrocytes comes from Cre-*lox* fate-mapping experiments in transgenic mice 20. We generated mice that carry a transgene that expresses Cre recombinase under the control of regulatory elements surrounding the *Dbx1* homeobox gene 20. In these mice Cre expression mirrors the normal pattern of *Dbx* expression, which is restricted to neuroepithelial precursors in p1, p0, dP6 and dP5 – i.e. four progenitor domains centred on the dorsal-ventral midline (Fig.1). Crossing the mice with a Cre-dependent reporter line (*Rosa26-GFP* or *Rosa26-lacZ*) permanently labels the *Dbx* precursor cells and all of their differentiated progeny. Unexpectedly, a small number of oligodendrocytes was labeled, as well as the expected radial glia, interneurons and astrocytes. The *Dbx*-derived oligodendrocytes comprised around 3% of all oligodendrocytes in the spinal cord and were spread less widely than the majority – they were mainly located in the lateral white matter radially opposite their site of origin in the VZ (Fig. 2). Some *Dbx*-derived, Olig2-positive cells retained a radial process and transiently co-expressed the radial

glial cell marker RC2, indicating that they are formed by direct inter-conversion from radial glia - as suggested already 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 18. This suggests that the oligodendrocytes labeled 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 appears 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 (Fogarty, M., PhD Thesis, University of London 2005).

So there are both ventral and dorsal origins of oligodendrocytes in the spinal cord and brainstem, as predicted by others 23,36 (Fig.2). Our own previous position, that “most or all” oligodendrocytes are 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 over oligodendrocyte origins at a more microscopic level -- whether or not 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 – e.g. *Nkx2.2* in p3, *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 37. 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 chick 38,39, showing 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*) 33,40–42 during later embryogenesis. In mice, oligodendrocyte precursors in the cervical spinal cord are formed within pMN, after motor neuron production is over but starting before the dorsal expansion of *Nkx2.2* 41 (Fig.3). In chicks they are formed after expansion of *Nkx2.2* and then only within the precise region of overlap with *Olig2* 39 (Fig.3) – neither p3 nor pMN but a new, hybrid p3/pMN domain. Here is a subtle species difference between rodents and birds. However, a common feature is that oligodendrocyte precursors develop from *Olig2*-expressing neuroepithelium both in 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 up-regulated in differentiating oligodendrocytes in the white matter 41. This fits with the notion that *Nkx2.2* is important in maturation, not initial specification of the oligodendrocyte lineage in the mouse spinal cord 43. 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 over oligodendrocyte origins 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 *PDGFR α* first appear in the neuroepithelium of the medial ganglionic eminence (MGE) 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(s) in the forebrain?

In the chick, apparently not. 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, *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 44. Other studies provide evidence for either a ventral or a dorsal source 14–16,36,45–48. Again, the lack of consensus is striking.

Recent fate mapping studies from our own laboratory help resolve the confusion 21. We found, using an *Nkx2.1-Cre* transgenic mouse line that marks neural progenitors in the basal forebrain (including MGE, AEP and pre-optic area) that the first oligodendrocyte precursors to arrive in the cortex around E16 are indeed 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) (MGE/CGE) (*Gsh2*-positive territory). At E18, therefore, 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 within the cortex itself (*Emx1*-positive neuroepithelium). So, once again, there are both ventral and dorsal sources – depending on when one looks (Fig.2).

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 remodeling 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 below, Evolution of oligodendrocyte development).

Running parallel to these embryonic studies, there has been a long-running and elegant series of experiments from Jim Goldman and others demonstrating that, in the postnatal forebrain, oligodendrocytes are generated from progenitor cells that reside near the tips of the lateral ventricles 50–54. 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, remaining active and continuing to generate new oligodendrocytes (and other cell types) after birth and into adulthood. The postnatal VZ and its neighbouring subventricular zone (SVZ) is derived mainly from the embryonic LGE and lateral cortex, with no contribution from more ventral regions (references 21, 47 and unpublished). Thus, the most ventral, MGE/AEP-derived progenitors leave no descendants in the postnatal SVZ. This possibly contributes 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 signaling from the notochord and floor plate 10. The dorsally-derived oligodendrocyte precursors also express Olig2 (and other established lineage markers such as PDGFR α and Sox10) even though 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 signaling 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 signaling by binding to its co-receptor Smoothened (Smo) 55,56. In addition, Cai et al.¹⁸ have shown that mouse 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 (i.e. in the presence of cyclopamine) 55,56 so maybe FGF signaling is responsible for specifying oligodendrocytes in the dorsal spinal cord. BMP and Wnt signaling pathways might also be involved 19,57–60

Hedgehog signaling has also been shown to be required (or at least intimately involved) in oligodendrocyte specification in the ventral forebrain 14,15,61. Shh expression is not detected in the embryonic cerebral cortex so the late wave of cortical oligodendrogenesis might also be under different control – again, perhaps FGF. It is known, for example, 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? If they are, it seems that the differences are not critical 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 to birds and this presumably calls for many more cells of all sorts, including oligodendrocytes,

during cortical development. Migration distances would also have increased significantly within 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 GABAergic cortical interneurons are thought to be immigrants from the basal forebrain 49. In humans, which have undergone an additional, huge cortical expansion compared to rodents, there is also local production of GABAergic interneurons within the neocortex 68.

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 (escape) – hence their production side-by-side with motor neurons in pMN 24,69. This still seems an attractive speculation. 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 don’t know about yet.

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 end of neurogenesis. Thus, 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 - like 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 essentially been supplanted 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 seem to win out, at least in the short term (see above, *New approaches to the “origins” debate*). 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 (e.g. *Drosophila*) as they metamorphose from embryo to larva to adult.

Another type of explanation for the elimination of MGE-derived oligodendrocytes is suggested by recent fate mapping experiments (reference 21 and unpublished data) that show that the postnatal SVZ 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 SVZ-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 quite 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, for example (reference 21).

Conclusion

The driving force for scientific progress is competition among ideas and individuals. That has certainly been true of our field of glial cell development. At last, the long-running arguments over 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 (“oligodendrocyte wars”).

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 “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 neuroepithelial ancestors? We look forward with anticipation to another decade of cut and thrust ...

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Box 1

A Tale of Two Studies

The two opposing views on oligodendrocyte origins were exemplified in two articles that appeared during the mid-1990's. Both described experiments designed to fate map the spinal cord neuroepithelium using chick-quail chimeras. The basic idea 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 chimeric animal are of chick or quail origin. The first such study, by Cameron-Curry and Le Douarin 28, reported that oligodendrocytes are generated more-or-less equally from all parts of the dorsal and ventral VZ. The other study, from our own laboratory (Pringle et al. 29) claimed that oligodendrocytes are generated only from ventral VZ. How could such a stark discrepancy arise from what appear to be replicate sets of experiments?

One reason was that the criteria used to define a “dorsal” graft differed between the two studies – in an interesting way. Since one cannot observe the grafted neuroepithelial cells continuously from the time of surgery until 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 28 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 turns 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 *Pax7* 30. Moreover, our recent fate mapping studies (see main text) demonstrate that progenitor domains more dorsal than p1 (i.e. beyond the dorsal

expression limit of Nkx6.1) do not contribute to the postnatal ependymal layer (reference 17 and unpublished data). Taken together, the evidence suggests strongly that the ependymal layer is formed exclusively from ventral progenitors in p3, pMN and p2 (see Figure 1, Box 1).

Since 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 Pringle et al.²⁹ study 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 indeed some dorsally-derived oligodendrocytes in mice 18–20. Whether the Pringle et al.²⁹ study simply overlooked this relatively small population or whether there really is a difference between rodents and birds remains to be seen (see main text, Oligodendrocyte wars in the forebrain and Evolution of oligodendrocyte development).

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 Shh in the ventral neural tube to be identical to oligodendrocytes that are specified by different signals (e.g. FGF) in the dorsal neural tube? Different classes of neurons are derived from different parts of the neural tube so perhaps it would not be surprising if the glial products were different too. But what sorts of differences might we expect?

The morphology of oligodendrocytes varies according to the axons that they myelinate 62,63. 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 63,64. Other oligodendrocytes make many internodes – often more than thirty – on small-bore axons 65. There are also molecular differences between oligodendrocytes on large- versus small-bore axons – for example, in their gap junction proteins (connexins) 66. 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 67. This result smacks 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 oligodendrocytes derived from different precursor subtypes (e.g. PDGF-dependent and -independent lineages 15) is an area of active debate 70.

Whether or not there are different subtypes of oligodendrocytes, it seems possible that there might be intrinsically different subtypes of astrocytes. A variety of tasks has been ascribed to astrocytes - inducing endothelial cells to form tight junctions and create the blood-brain barrier, buffering 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 else multiple cell types, perhaps derived from different neurogenic domains.

Online summary

- Oligodendrocytes develop from precursor cells that migrate throughout the spinal cord and brain before differentiating and wrapping axons. The oligodendrocyte precursors (OLPs) themselves are generated from neuroepithelial cells that line the central canal of the spinal cord and the ventricles of the brain. Where exactly the OLPs originate in the ventricular zone (VZ) has been a contentious issue, which is now being resolved through the application of mouse genetics.
- The “classic” view was that gliogenesis was the default behaviour of all neuroepithelial cells after they had finished giving rise to neurons. Later, it was a specialized OLP “factory” was discovered in the ventral VZ of the spinal cord; this neuroepithelial domain (pMN) first generates motor neurons before switching to OLPs. Master regulatory genes (*olig1*, *olig2*) that control both motor neuron and OLP production are also expressed in the ventral forebrain, suggesting that ventral production of OLPs is the norm. However, a series of recent articles has debunked that idea by showing that they are generated widely through the VZ of the spinal cord and brain. In the spinal cord, most OLPs are produced in pMN but a minority (~15%) come from more dorsal parts of the VZ. In the forebrain, OLPs are generated from different parts of the embryonic VZ at different times, starting in the ventral forebrain and progressing dorsally into the cerebral cortex. Surprisingly, the earliest-formed OLPs and their progeny are eliminated during postnatal life.
- Specification of ventrally-derived OLPs requires Sonic hedgehog (Shh). However, OLPs from dorsal sources are hedgehog-independent, instead relying on FGF and other local signals. Whether this implies different functional subtypes of oligodendrocytes is not clear.
- In the forebrain, OLPs intermix and compete with one another for territory, because if OLPs from one part of the VZ are ablated in transgenic mice, the remaining OLPs quickly expand into the empty space and the mice survive and behave normally. This implies that there are no major functional differences among OLPs in the forebrain, even though they begin by expressing different region-specific transcription factors such as *nkx2.1*, *gsh2* or *emx1*.
- There is some evidence that OLPs are generated only from ventral territories in birds. Why should they differ from mammals? We propose that ventral production was the “primitive” mode and that recruitment of more dorsal sources was required as the brain, particularly the cerebral cortex, increased in size during vertebrate evolution.

Spinal cord progenitor domains, transcription factors and cell fates

Figure 1.

Progenitor domains in the embryonic spinal cord and the cell types that they generate. Neurons are formed before glia - astrocytes (astros) and oligodendrocyte precursors (OLPs). In general, OLPs are formed before astrocytes and ventral cell types before dorsal. Also shown are the expression domains of transcription factors mentioned in the text. Dotted lines indicate that the expression domain boundaries shift during development, in the direction of the small arrows – e.g. *Nkx2.2* expression expands dorsally and *Dbx1* expression contracts. Approximately 85% of all spinal cord oligodendrocytes are generated from pMN and the remainder from more dorsal 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. FP, floor plate; RP, roof plate; dP1-dP6, dorsal progenitor domains; pMN and p0-p3, ventral progenitor domains.

Figure 2.

Origins and migration of oligodendrocyte precursors in the rodent cervical spinal cord (left) and telencephalon (right). In the mouse spinal cord, approximately 85% of oligodendrocyte precursors are generated from pMN in the ventral VZ, starting around E12.5. Around E15, a secondary wave of precursors starts to be generated in more dorsal regions^{16–18} by trans-differentiation of radial glia¹⁸. In the telencephalon, the ventral-most precursors in the MGE are produced from around E12.5, the LGE-derived precursors start to be produced a few days later and the cortex-derived precursors mainly after birth¹⁹. Diagram not to scale.

Figure 3.

Ventral origin of *Pdgfra*-positive oligodendrocyte precursors. In chick cervical spinal cord, *Pdgfra*⁺ precursors are derived exclusively from the dorsal part of the *Nkx2.2*-expressing domain, within the area of overlap between *Nkx2.2* and *Olig2* – a hybrid p3/pMN domain. In mouse cervical spinal cord, in contrast, they 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 within both the (*Nkx2.2*⁺, *Olig2*⁺) and (*Nkx2.2*⁻, *Olig2*⁺) domains. In both chicks and mice, oligodendrocyte precursors up-regulate *Nkx2.2* as they differentiate into myelinating oligodendrocytes in the white matter 30. Left panel: combined *Nkx2.2* immunolabelling (green fluorescence) and *Pdgfra* in situ hybridization (black). Right panel: double in situ hybridization for *Nkx2.2* (brown reaction product) and *Pdgfra* (blue). In the right panel, we assume that the blue *Pdgfra*⁺ cells in the floor plate region are oligodendrocyte precursors that have migrated ventrally from the ventral VZ, although it is also possible that they arose within the floor plate itself.