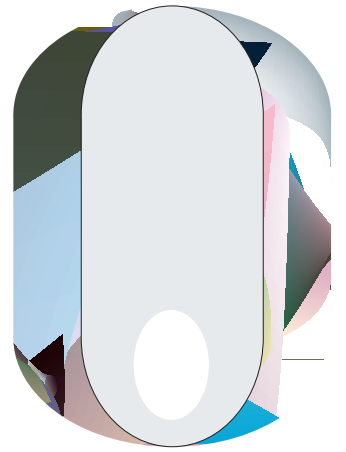
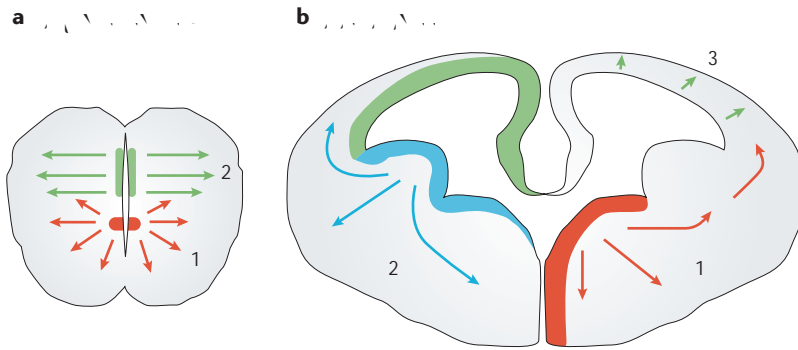


The developmental origin of oligodendrocytes has been hotly debated for years. Some laboratories, including our own, favoured a unique origin of oligodendrocytes in the ventral neural tube, whereas others went for diversity and multiple origins. The published literature was conflicting and confusing. At last, new







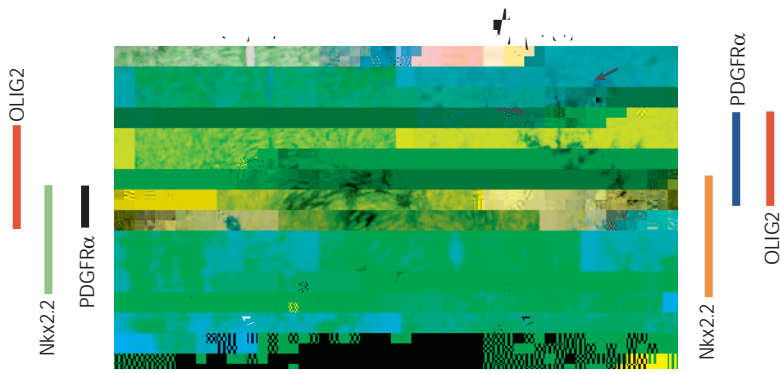
So, there are both ventral and dorsal origins of oligodendrocytes in the spinal cord and brainstem, as predicted by others^{23,34} (FIG. 2). Our own previous position, that ‘most or all’ oligodendrocytes might be generated in the ventral cord²⁴ must now be softened to ‘most but not all’. This is a gratifying 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 (PDGFR α -positive) to the pMN domain, just dorsal to the *Nkx2.2*-positive p3 domain³⁵. 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 PDGFR α -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 matter³⁹. This fits with the idea that *Nkx2.2* is important in maturation, not initial specification of the oligodendrocyte lineage in the mouse spinal cord⁴¹. 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 oligo-



Remarkably, we found that the original population

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 forebrain⁵⁹. In humans, which have undergone an additional, huge cortical expansion compared with rodents, there is also local production of GABA-containing interneurons in the neocortex⁶⁰.

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.

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