32 Lee, F.S. *et al.* (2001) The uniqueness of being a

An 'oligarchy' rules neural development

David H. Rowitch, Q. Richard Lu, Nicoletta Kessaris and William D. Richardson

Recent reports show that *Olig* genes, which encode the basic helix–loop–helix Olig transcription factors, are essential for development of oligodendrocytes. Surprisingly, Olig function is also required for formation of somatic motor neurons. These findings alter our views of how the oligodendrocyte lineage is generated and raise further questions about the underlying developmental relationships between neurons and glia.

d Leber, S.M. and Sanes, J.R. (1995) Migratory paths of neurons and glia in the embryonic chick spinal cord. *J. Neurosci.* 15, 1236–1248
e Kalyani, A. *J. Neurosci.*

References

a Richardson, W.D. *et al.* (1997) Origins of spinal cord oligodendrocytes: possible developmental and evolutionary relationships with motor neurons. *Dev. Neurosci.* 19, 54–64

b Richardson, W.D. *et al.* (2000) Oligodendrocyte lineage and the motor neuron connection. *Glia* 12, 136–142

c Leber, S.M. *et al.* (1990) Lineage, arrangement, and death of clonally related motoneurons in chick spinal cord. *J. Neurosci.* 10, 2451–2462

floor-plate-derived Sonic hedgehog (Shh) [2]. Regulation of *Olig* genes by Shh [7] is possibly indirect, via homeodomain proteins Nkx6.1 and Nkx6.2 [13].

An initial clue to Olig function was the finding that virus-mediated expression of *Olig1* in rat neuroepithelial cells was sufficient to promote development of OLPs but not differentiated oligodendrocytes *in vitro* [7]. Subsequently, retroviral infection *in vivo* confirmed that *Olig1* can drive the production of differentiated oligodendrocytes in the mouse neocortex [14]. In the spinal cord, however, forced expression of either *Olig1* or *Olig2* failed to generate OLPs [9,15,16]. When *Olig2* was coexpressed with *Nkx2.2*, it was possible to form *Sox10+* OLPs and differentiated oligodendrocytes [15,16]. Thus, Olig proteins evidently require context-dependent protein interactions to specify oligodendrocytes [17,18]. These experiments indicate roles for class B bHLH–homeodomain interactions in neural tube development but leave open the question of whether such interactions are direct or indirect. Furthermore, because the overlap between Olig and Nkx2.2 is only partial in the mouse spinal cord at embryonic day (E) 12.5 [15], it is likely that factors other than Nkx2.2 collaborate with Olig proteins to generate OLPs outside the region of overlap.

Recent studies from several laboratories provide compelling evidence that Olig proteins are essential for development of all oligodendrocytes in the CNS. Lu *et al.* [19] performed individual knockouts of *Olig1* and *Olig2*, while Zhou and Anderson [20] targeted *Olig1* and *Olig2* simultaneously. (The single gene mutations cannot be recombined by breeding because the *Olig* genes lie close together on the same chromosome.) Comparison of the three knockout phenotypes indicates a spectrum of severity. *Olig1*-null animals are viable, but show a delay in oligodendrocyte maturation. *Olig2*-null animals entirely lack OLPs in the spinal cord. They do, however, generate small pockets of OLPs in the forebrain and near-normal numbers in the midbrain

and hindbrain. All surviving OLPs in *Olig2*-null animals appear to express *Olig1*, suggesting functional redundancy between the two genes in certain region of the CNS. Strikingly, no OLPs were observed anywhere in the CNS of compound *Olig1;Olig2* mutants [20]. Combined, these results indicate overlapping functions for Olig proteins in oligodendrocyte specification, although the activities of *Olig1* and *Olig2* appear to be highly context dependent. Finally, loss-of-function studies in zebrafish indicate that the fish homologue *Olig2* has a conserved role in formation of both oligodendrocytes and motor neurons [12].

Olig function: required for the development of all somatic motor neurons

Olig proteins are expressed in motor neuron precursors in pMN–OL but are downregulated in differentiated motor neurons – a pattern associated classically with proneural genes [4]. Gain-of-function studies show that *Olig* genes can in fact promote motor neuron development [11]. Ectopic expression of *Olig2* along the entire dorso–ventral axis of the chick spinal cord resulted in a dorsal expansion of the pMN–OL domain and led to increased numbers of motor neurons. The expansion was only modest, however, being limited to the neuroepithelium immediately dorsal to pMN–OL. These experiments indicate intrinsic functional limitations of the *Olig* genes. By themselves (i.e. at ectopic locations) they are evidently insufficient to promote motor neuron specification and presumably must work in concert with other factors. In keeping with this, Mizuguchi *et al.* reported that coexpression of the gene encoding Neurogenin 2 (*Ngn2*) with *Olig2* resulted in ectopic production of motor neurons in dorsal regions of the neural tube [10]. Thus, it appears that Olig proteins act in concert with other transcription factors to promote a motor neuron fate. The details of the transcriptional complexes with which Olig proteins normally interact remain to be identified, as do their downstream targets during motor neuron development. Data indicating that Olig proteins act as transcriptional repressors raise the possibility that the transcriptional targets of Olig proteins are themselves antagonists of motor neuron development – so that Olig proteins effectively promote the motor neuron fate by repressing the repressors of that fate [10,11].

The *Olig1* knockout mouse is viable, whereas *Olig2* null mice die at birth from failure of spontaneous breathing. Further analysis of *Olig2*–/– animals revealed a total absence of somatic motor neurons in the hindbrain and both somatic and visceral motor neurons in the thoraco–lumbar spinal cord. As previously mentioned, *Olig1* is able to compensate partially for *Olig2* function, at least in the development of OLPs in the rostral CNS. Conversely, even though *Olig1* is expressed within precursors of motor neurons and *Olig1* expression is upregulated in the pMN–OL domain of *Olig2* mutant animals, *Olig1* appears to be insufficient for production of motor neurons anywhere along the neuraxis. Might these results reflect differences in early patterning functions of *Olig1* and *Olig2* proteins? In the absence of *Olig2* function, neural pattern is relatively unaffected, showing unaltered expression of some pMN markers, including *Olig1*, *Nkx6.1*, *Ngn2* and others (Fig. 1). However, *Irx3* expression expands ventrally into the pMN from p2 [19]. Dramatically, in *Olig1;Olig2* compound mutants, all known markers of the pMN are obliterated and the pMN undergoes a homeotic transformation into p2 (Fig. 1). Thus, the failure of motor neuron development in *Olig2* mutant mice could result from the limited patterning capability of *Olig1*, especially the inability of the latter to repress *Irx3* within the pMN [21]. Alternatively, *Olig2* could have unique functional properties that are necessary for motor neuron production.

Down syndrome, a role for *Olig* genes in the neurological aspects of this common genetic disorder cannot be ruled out. In sum, investigation of *Olig*