The evolution of Olig genes and their roles in myelination

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INTRODUCTION

Which came first – central or peripheral myelin?

Myelinin the CNS and Schwann cells in the PNS. Since development of these cells and their myelinating programmes are controlled by gene regulatory networks, exploring the molecular evolution of myelin-specific transcription factors and their binding sites

2008). These observations

e idea that hinged jaws and myelinated nerves olved in parallel, permitting the evolution of a style. Jawbones and the Schwann cells that myelinate cranial nerves both develop from the cranial neural crest, providing a rationale for their co-evolution (Colman ., 1996; Zalc and Colman, 2000; Donoghue ., 2008; Zalc ., 2008).

An alternative or parallel idea is that myelin evolved for rapid locomotion and the ability to from predators. In favour of this is the observation that most OLs in the spinal cord develop from the same precursors as motor neurons (MNs; Sun ., 1998; Richardson ., 2000; Lu ., 2002; Park ., 2002; Zhou and Anderson, 2002; Takebayashi ., 2002a), suggesting that CNS myelin might first have evolved to ensheath motor circuits and accelerate escape reactions (Richardson , 1997; 2000). Moreover, myelin-like glial sheaths that are found in some invertebrates (annelids and crustaceans) are specifically associated with axons that drive escape and/or startle responses (Roots, 1993; Davis ., 1999; Hartline and Colman, 2007). On the other hand, hagfish (which lack myelin) swim slowly and cannot accelerate to escape capture (see supplementary movie online). Fish swim using axial muscles that lie adjacent to the spinal cord, so motor axons extend only a short distance outside the CNS. Perhaps motor axons were initially ensheathed along their entire length by OLs, if there was no barrier to their leaving the neural tube via the ventral roots.

The question of whether PNS (Schwann cell) or CNS (OL) myelin is ancestral therefore boils down to what came first – vertebrate predation, or escape from predators? That sounds like a 'chicken and egg' situation but it is worth bearing in mind that formidable predators existed already before the advent of the vertebrate jaw – the top predators in Ordovician waters (~450 Mya) were arthropods (including Erypterids or 'sea scorpions', some of which came to exceed 2 metres in length; Braddy ., 2008). These probably preyed on bottom-dwelling ostracoderms – extinct armoured fish that are regarded as the (jawless) precursors of all present

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day fish (Forey and Janvier, 1994; Janvier, 1996). Thus, there could have been evolutionary pressure for primitive vertebrates to ‘get moving’ in order to escape predation long before the advent of the vertebrate jaw.

Regardless of where the primary selection came from, once the myelinating programme started to evolve in one cell type, all or part of the programme could have been activated in other cells, given appropriate cues. Therefore, evolution of CNS and PNS myelin would have gone largely hand in hand. In the CNS, OL precursors (OLPs) acquired the ability to migrate and myelinate widely and thereby myelin became ubiquitous throughout the CNS, with major advantages for all kinds of neural processes and tasks. Co(d)-484.artteia .s0(t)16.5(igoc2eO)1t460.lal aln6621.4(ro)16..2(l7)-44g0.8(c)0(6)16.6.2(l6721.(tt)16

with other OL transcription factors including SOX10 (Li ., 2007). OLIG1 changes its cellular localization from nucleus in

), three teleosts (zebrafish, puffer fish and fugu fish), three cartilaginous fish (little skate, dogfish and elephant shark), one cephalochordate (lancelet) and a hemichordate (acorn worm). Consistent with previous reports, mammals, amphibians and teleosts all have Olig1/2/3, whereas Olig4

Olig2/3/4 are all first detected at gastrulation. Later on, at the neurulation stage, Olig2 expression is restricted to the precursors of MNs and OLPs in the ventral neural tube, Olig3 expression can be seen in the dorsal part of the neural tube and Olig4 is also expressed in dorsal neuroepithelium, which gives rise to several kinds of interneurons as well as astrocytes (Zhou ., 2000; Lu ., 2000; Park ., 2002; Takebayashi ., 2002b; Bronchain ., 2007).

Piecing together the evidence, we can construct a plausible (but highly speculative!) version of events in the lead-up to CNS myelination. As a result of two rounds of genome duplication during early vertebrate evolution, a single ancestral Olig gene gave rise to Olig2, Olig3 and Olig4. These subsequently evolved independently and ultimately specified distinct neuronal identities, one of which (under Olig2 control) was MN identity. The ancestral Olig gene might have already been involved in neural specification – possibly even MN specification – prior to genome duplication. As OLIG2 function diverged further, MNs underwent reprogramming of their gene expression profiles by acquiring or losing OLIG2-binding -regulatory elements to enable other pre-existing or newly evolved genes to be expressed under OLIG2 control, leading to primitive glial cells (‘motor glia’) that resembled today’s OLPs. Initially these motor glia were not highly migratory but interacted with and perhaps ensheathed neurons, including MNs, that lay close to their site of origin in pMN. Later, a myelination programme evolved, under the control of myelin determinants like SOX10 (Wegner and Stolt, 2005). After OLIG1 arrived on the scene in teleost fish, it gained the ability to bind directly to SOX10 (Li ., 2007), enhancing the myelination programme and adapting it to the needs of the CNS.

The lack of an Olig1 homolog in birds, which have CNS- and PNS-specific myelin like other vertebrates, is seemingly at variance with the above interpretation. Perhaps it is premature to conclude on the basis of one example (chicken) that all avian species lack Olig1. Nevertheless, if birds as a group do turn out to have lost Olig1 then this would imply that birds grammelos6-237occurr

a firm footing, but so far no evolutionarily conserved OLIG or SOX10 binding sites have been mapped in genes other than Mbp.

CONCLUSION

It is likely that parallel evolution of Olig genes and their -regulatory elements in target genes were important for the emergence of myelination programmes in early vertebrates. Many questions are waiting to be answered. Which Olig genes are present in Agnathans, where are they expressed and what are their functions in these animals? Do they, for example, have ensheathing glia in their CNS that resemble OLPs? What are the direct gene targets of OLIG transcriptional regulation and how did their target set expand during