Control of Schwann cell myelination

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Abstract

Schwann cells ensheath all axons of peripheral nerves. Only around large-diameter axons do they elaborate myelin, forming insulating sheaths that are vital for fast conduction of axon potentials. A series of recent papers has illuminated some of the ways in which the process of myelination is controlled, both by signals from axons and by positive and negative transcriptional mechanisms within the Schwann cells themselves.

Introduction and context

It has long been known that axonal signals control the induction and maintenance of the Schwann cell myelin sheath that surrounds the large-diameter axons in peripheral nerves. However, until very recently, the nature of these signals has remained obscure. In contrast, the identity of the transcription factors in Schwann cells that organise the myelination programme is much better characterised. Well-established transcriptional regulators of this programme include Krox-20 (early growth response gene 2, or Egr-2) and its associated proteins, NAB (nucleic acid-binding protein) 1 and 2, Sox-10, Oct-6 and Brn1 and Brn2. Current knowledge of the mechanisms by which these factors exert their effects on myelination has recently been reviewed [1].

Unlike most other cell types, Schwann cells can readily dedifferentiate. Thus, when myelinating Schwann cells are deprived of axonal contact in injured nerves, they adopt a molecular and morphological phenotype that is similar, though not identical, to the phenotype of immature Schwann cells prior to myelination. Depending on circumstances, therefore, Schwann cells either provide support for mature axons by elaboration of a myelin sheath or provide an environment through which axons can regrow after injury and subsequently remyelinate. We are just beginning to form a more comprehensive picture of how Schwann cells transit between these two phenotypes, with an emerging picture of a

mechanism involving cross-inhibitory interactions between positive and negative transcriptional regulators of myelination [2].

An important advance in our understanding of axonal signalling mechanisms that control myelination has occurred in the past five years. Several papers have shown that the axonal surface protein neuregulin 1 (type IIIβ1), acting via its receptors ErbB2 and ErbB3, controls the thickness of the Schwann cell myelin sheath and is part of the mechanism that controls the expression of myelin genes and the induction of myelination [3-7]. This factor also controls the survival of Schwann cell precursors and is a potent mitogen for Schwann cell precursors and Schwann cells. It remains a challenge to understand the mechanism by which the Schwann cell switches its response to neuregulin from a non-myelinating proliferative phase to a non-proliferative myelination mode. Some evidence suggests that a balance between ERK (extracellular signal-related kinase) 1/2 and JNK (c-Jun N-terminal kinase)/c-Jun (pro-dedifferentiation) and PI3 kinase (phosphatidylinositol-3 kinase)/AKT (pro-myelination) signalling may be involved, but the picture is far from clear [8-12]. To add complications, soluble neuregulin isoforms at high concentrations can also promote demyelination [13]. Although neuregulin is required in peripheral nervous system myelination, it is not required for myelination by oligodendrocytes in the central nervous system [14].

Major recent advances

Recent evidence suggests that neuregulin 1 type III expressed by axons also regulates the formation of mature non-myelinating Schwann cells (Remak bundles). Genetic inactivation of *neuregulin 1 type III* in small-calibre unmyelinated C-fibres, using *Nav1.8-Cre* mice, results in aberrant Remak fibres that contain abnormally large numbers of axons, and the altered morphology is reflected in a reduced response to noxious pressure stimulation [15]. In these mice, *neuregulin 1 type III* was also inactivated in small myelinated A δ fibres. This resulted in an increase in the number of axons in this size category which remained unmyelinated, despite achieving a 1:1 relationship with Schwann cells. This is in line with earlier evidence that neuregulin 1 type III promotes myelination, as discussed above. Despite the altered morphology, the nerves of these mutant mice contain normal numbers of axons and Schwann cells.

One of the ways in which neuregulin signalling is likely to control myelination is by increasing the Ca²⁺ level in Schwann cells. This activates the phosphatase calcineurin, which dephosphorylates nuclear factor of activated T cells (NFAT) c3 and c4, resulting in translocation to the nucleus. Kao and colleagues [16] show that deleting calcineurin B specifically in the Schwann cell lineage results in defects in radial sorting and hypomyelination in newborn mice. Because the mice die shortly after birth, it is not possible to say whether the hypomyelination is transient or permanent. Lack of calcineurin B prevents neuregulin-induced dephosphorylation and activation of NFAT c3 and c4. Furthermore, NFAT c4 complexes with Sox-10, a transcription factor required for myelination [17], to activate the promoter and myelin-specific enhancer of the *Krox-20* gene, which globally regulates peripheral myelination [11,18-20], and also with the promoter of the *myelin protein zero (P₀)* gene, all of which underline the involvement of NFAT proteins in myelination.

It has long been known that elevation of intracellular cyclic AMP levels induces cultured Schwann cells to express myelin proteins and adopt many other aspects of the myelinating Schwann cell phenotype, suggesting that cAMP is part of the signalling system that promotes myelination [21]. A recent paper now provides important *in vivo* evidence for this proposition [22]. In experiments using mutant zebrafish, the authors found that the G protein-coupled receptor GPR126 is essential for myelination in the peripheral nervous system and that the defect is confined to signalling within Schwann cells rather than axons. Significantly, treatment of the developing mutant fish with forskolin, which elevates intracellular cAMP levels, restores myelination, suggesting that this orphan receptor acts by controlling Schwann cell cAMP levels. Because levels of neuregulin and ErbB3 receptors

remain normal in the mutant fish, it is likely that GPR126 functions independently of neuregulin to regulate myelination. Additional evidence for the involvement of cAMP and cAMP-dependent protein kinase A (PKA) in myelination comes from studies of the transcription factor nuclear factor-kappa-B (NF- κ B) [23]. In Schwann cell-dorsal root ganglion (DRG) co-cultures, inhibition of NF- κ B activation inhibits proper association of Schwann cells with axons and myelination, and co-cultures using cells from mice lacking the p65 active subunit of NF- κ B show marked inhibition of myelination [24]. Significantly, phosphorylation of the p65 subunit by PKA increases transcriptional activity but not DNA binding and is required for upregulation of Oct-6 by cAMP. Although the experiments remain to be confirmed *in vivo*, the results suggest that this factor transduces cAMP signals within Schwann cells and promotes myelination at early stages of myelin induction. Linking these findings to those from zebrafish, it may also be significant that there are two binding sites for NF- κ B within the GPR126 promoter.

Cell-cell interactions between axons and Schwann cells are vital to the process of myelination. Two recent papers reveal new roles for nectin-like cell adhesion molecules (Necns), members of the immunoglobulin superfamily of cell adhesion molecules, at the onset of myelination [25,26]. *Necn2* and *Necn4* are expressed in Schwann cell membranes, principally in the internodal region and in Schmidt-Lanterman incisures while *Necn1* and *Necn2* are expressed by axons. *Necn4* interacts heterophilically with *Necn1*, expressed on axons, to facilitate myelination. Knockdown of *Necn4* by shRNA (short hairpin RNA) severely inhibits myelination in DRG-Schwann cell co-cultures. Although Schwann cells can line up along the axons and even enclose them, they fail to make even 1.5 turns around the axons, pointing to a requirement for these proteins at the early stages of myelination to ensure proper wrapping and spiralling of the Schwann cell membrane. In addition, levels of the transcription factors Oct-6 and *Krox-20* remain low in these co-cultures. It remains to be determined, however, whether this phenotype will be reproduced by knockout of *Necn4* *in vivo*.

In addition to transcription factors that promote myelination, such as NFAT, NF- κ B, Sox-10, *Krox-20* and Oct-6 (discussed above), there is increasing evidence that myelin differentiation is subject to negative transcriptional regulation. *In vivo*, selective inactivation of Notch 1 in Schwann cells accelerates myelination while overexpression of the active intracellular domain of Notch (NICD) delays it, indicating that myelination is negatively controlled by Notch signalling [27]. The major role of negative regulation is likely to be that of driving Schwann cell demyelination/dedifferentiation. NICD levels rise

rapidly in injured nerves, and the resulting demyelination is slower if the NICD elevation is prevented. Conversely, demyelination is accelerated in injured nerves engineered to overexpress NICD. Even in uninjured nerves, activation of Notch is sufficient to induce rapid demyelination [27]. Another transcription regulator, c-Jun, is similarly elevated in the Schwann cells of injured nerves, and as with Notch 1, demyelination is delayed when this elevation is prevented [12]. c-Jun is also required for the generation of the characteristic molecular and morphological phenotype of the dedifferentiated cell [28]. Other transcription factors that negatively regulate myelin differentiation in cell culture include Sox2 and Id2 and Id4 [2,29].

Future directions

Lipids form major components of the myelin sheath and we are just beginning to explore how myelin lipid synthesis is synchronised with that of the myelin proteins [30-32]. The pathways activated by established Schwann cell signals, such as cAMP and neuregulin, are actively being clarified as exemplified by the work on GPR126 and NF- κ B mentioned above and by the recent identification of BACE1 (β -site APP cleaving enzyme), the PDZ (post-synaptic density 95-discs large-zonula occludens 1) domain protein erbin and the tyrosine phosphatase Shp2 (src homology 2 domain-containing protein tyrosine phosphatase 2) as participants in neuregulin signalling and myelination [33-36]. The downstream targets of novel Schwann cell signalling molecules (for example, the Necl proteins) will also have to be determined. We can expect to learn more about the role of epigenetic mechanisms in myelination and to understand more about how positive and negative transcriptional regulators of myelination are integrated at the molecular level and how they exert control over the promoter regions, intronic elements and downstream elements of myelin genes [1].

The mechanisms that control radial sorting and the generation of the pro-myelin cell, a prerequisite for myelination, are the focus of extremely active investigation outside the scope of this commentary. Rapid progress can be expected in this field in the near future.

Surprisingly, recent work shows that normal prion protein is involved in the control of myelin maintenance. Ablation of this prion protein in mice results in a chronic demyelinating neuropathy, although myelin is initially formed normally. The authors show that depletion of prion protein in neurons but not Schwann cells triggers the neuropathy, and that cleavage of the protein at the amino terminal end is required. It remains to be determined whether axonal prion protein interacts directly with Schwann cells or whether this protein affects myelin maintenance indirectly [37].

Abbreviations

DRG, dorsal root ganglion; GPR126, G protein-coupled receptor 126; Necl, nectin-like cell adhesion molecule; NF- κ B, nuclear factor-kappa-B; NFAT, nuclear factor of activated T cells; NICD, Notch intracellular domain; PKA, protein kinase A.

Competing interests

The authors declare that they have no competing interests.

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