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REVIEW

Axo-glial interdependence in peripheral nerve development

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ABSTRACT

During the development of the peripheral nervous system, axons and myelinating Schwann cells form a unique symbiotic unit, which is realized by a finely tuned network of molecular signals and reciprocal interactions. The importance of this complex interplay becomes evident after injury or in diseases in which aspects of axo-glial interaction are perturbed. This Review focuses on the specific interdependence of axons and Schwann cells in peripheral nerve development that enables axonal outgrowth, Schwann cell lineage progression, radial sorting and, finally, formation and maintenance of the myelin sheath.

KEY WORDS: Schwann cells, Axons, Peripheral nerve

Introduction

During peripheral nerve development, axons and the resident glial cells, the Schwann cells (SCs), undergo fundamental morphological changes that result in the formation of the myelin sheath and a corresponding specialization of axonal domains (Jessen and Mirsky, 1999). Signaling factors derived from the axon, such as the growth factor neuregulin 1 (NRG1), control several developmental processes in SCs and ultimately regulate the formation of the myelin sheath (Birchmeier and Nave, 2008). Recently, substantial progress has been made in identifying additional factors that guide SC development, including the extracellular matrix (ECM) (Feltri et al., 2016). Furthermore, a novel role for mechanotransduction has been discussed in recent reviews (Monk et al., 2015).

In addition to signals that instruct the glial cell, glial support towards axons has proved essential for axonal survival during development, as well as for the formation of axonal structures, such as the nodes of Ranvier, specialized domains of clustered ion channels that give rise to electrical potential generation (Salzer et al., 2008). In adulthood, both cell types depend on each other for long-term survival and integrity; acquired or genetic defects in either of the two cell types can cause a variety of peripheral neuropathies (Dyck and Thomas, 2005). Although the pathological mechanisms of peripheral neuropathies are not the focus of this Review, the analysis of animal models for different monogenetic neuropathies has substantially improved our understanding of SC biology and the essential role of glial cells for axonal function. In this Review, we focus on the specific role of interactions at the axon-glia interface for peripheral nerve development and maintenance, and aim to provide a comprehensive overview of advances and open questions in our understanding of the intimate relationship of those two cell types. For further information on intracellular signaling pathways, the transcriptional control of SC biology, as well as for the crucial role of ECM-associated factors, we refer the reader to seminal recent reviews on these topics (see Castelnovo et al., 2017; Feltri et al., 2016; Monk et al., 2015; Stolt and Wegner, 2016).

Outgrowth of axons and Schwann cells in embryonic development

During early development of the peripheral nervous system (PNS), growing axons are associated with Schwann cell precursors (SCPs), which arise from neural crest cells (NCCs). Whereas the exit of emanating motor fibers from the spinal cord is supported by central nervous system (CNS) glia, the subsequent axonal outgrowth occurs independently of SCPs. However, SCPs remain closely associated with axon bundles and provide trophic support to neurons during the growth of axons. In turn, axons serve as guidance structures for SCP migration, and axonal signaling cues direct lineage progression. Morphologically, early embryonic nerves are characterized by the absence of connective tissue and blood vessels, and proliferating SCPs branch in close apposition to bundles of developing axons, which are uniformly small in size at this stage (Fig. 1A). Eventually, SCs help axons to make contact with their target structures and this timely innervation has proven crucial for long-term neuronal survival.

The role of axons for the specification and function of Schwann cell precursors

The first step in the development of the SC lineage is the specification of SCPs from migratory NCCs at embryonic day (E) 12-13 in mice (E14-15 in rats, Fig. 1A) (Jessen and Mirsky, 2005) (Fig. 2). Although the intrinsic transcriptional network for the generation of SCPs from NCCs is largely known (for reviews, see Jacob, 2015; Jacob et al., 2017; Kastriti and Adameyko, 2017), a possible interplay with extrinsic signaling molecules remains poorly understood. For example, Notch signaling in neural crest (NC) neuronal precursors has been proposed to regulate gliogenesis in neighboring NCCs that give rise to SCs (Morrison et al., 2000; Taylor et al., 2007). However, this function may be restricted to sensory and sympathetic ganglia, because the generation of SCPs in peripheral nerves is unaltered in mice lacking downstream effectors of Notch signaling, e.g. Hes1, Hes5 and RBPJ (Table 1) (Woodhoo et al., 2009). The potential for dual control of SCP specification by intrinsic and extrinsic factors emerged from the observation that SOX10-null mouse mutants lack SCPs in the peripheral nerves (Britsch et al., 2001). However, SOX10 expression is present in all NCCs (which generate different cell types), indicating that additional signaling cues act in conjunction with SOX10 for SCP generation (Britsch et al., 2001; Kastriti and Adameyko, 2017). In addition to SOX10, NCCs express *ErbB3*, which encodes a receptor tyrosine kinase that interacts with neuregulin 1 (NRG1) (Fig. 3), and *ErbB3* expression is maintained solely in the SC lineage (Meyer et al., 1997). *Sox10* mutants have reduced ErbB3 receptor expression in NCCs, which indicates that interplay between ErbB receptor signaling and SOX10 is required for the specification of SCPs (Britsch et al., 2001; Paratore et al., 2001). Indeed, mice deficient for both the ErbB receptor and SOX10 lack SCPs in

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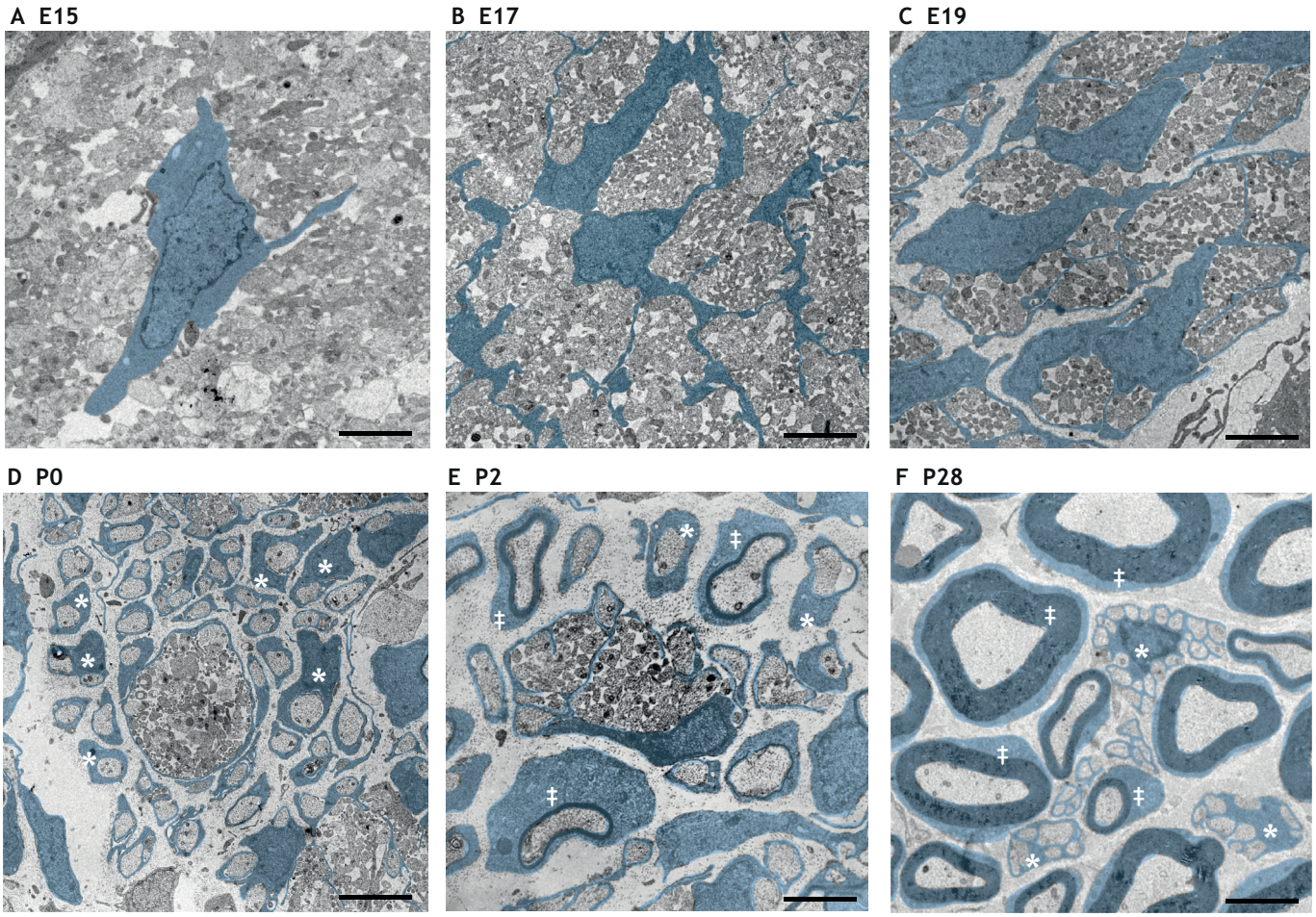

Fig. 1. Electron microscopic pictures of rat sciatic nerve cross-sections during development. (A-F) Shown are embryonic days (E) 15, 17 and 19 (A-C) and postnatal days (P) 0, 2 and 28 (D-F). At E15, Schwann cell precursors (blue in A) form processes in between axon fascicles. From E17 to E19, immature Schwann cells (blue in B and C) form families that engulf bundles of axons. In the perinatal process of radial sorting (P0 and P2), Schwann cells develop into nonmyelinating (Remak) Schwann cells (blue in F with asterisks) or to promyelinating Schwann cells (blue in D and E with asterisks) that have acquired a 1:1 relationship with an axon that they eventually myelinate (blue in E and F with double daggers). Scale bars: 2.5 µm.

peripheral nerves (Britsch et al., 1998; Garratt et al., 2000; Morris et al., 1999; Riethmacher et al., 1997). Moreover, NRG1 promotes SCP generation at the expense of neuronal cell types *in vitro* (Shah et al., 1994). However, a direct interplay between SOX10 and NRG1 signaling remains hypothetical, and the analysis of different ErbB receptor mutant animals may indicate that – in contrast to SOX10 – neuronal NRG1 promotes SCP survival and migration rather than the fate transition of NCCs to SCPs (Garratt et al., 2000; Lyons et al., 2005; Morris et al., 1999; Wolpowitz et al., 2000). Indeed, many studies have clearly demonstrated that NRG1 contributes to SCP survival *in vitro* and in various mouse mutants *in vivo* (Dong et al., 1995., 1999; Grinspan et al., 1996; Riethmacher et al., 1997; Syroid et al., 1996; Sheean et al., 2014). Notably, ablation of the NRG1 downstream molecules ERK and SHP2 (PTPN11) in the NC recapitulates the phenotype of *ErbB3* mutant mice with a virtual absence of SCPs at E11.5-E12.5 (Grossmann et al., 2009; Newbern et al., 2011), which suggests that the ERK pathway may mediate NRG1 signaling at the SCP stage (Fig. 3). Furthermore, SC survival and myelination is completely rescued when downstream MEK/ERK (but not PI3K) signaling is ectopically activated in recombined *ErbB3* mutant SCs *in vivo* (Sheean et al., 2014).

In contrast, zebrafish mutants lacking ErbB receptors have revealed no effect on SCP survival (Lyons et al., 2005), and mice with ablation of ErbB2 receptors or the cysteine-rich domain isoforms of NRG1 show a preservation (although a strong reduction) of SCPs in the nerve roots (Morris et al., 1999; Wolpowitz et al., 2000; Garratt et al., 2000). Together, these results suggest that other factors may contribute to SCP survival *in vivo*. Indeed, other factors have also been shown to promote SCP survival *in vitro*, such as endothelin B, fibroblast growth factor (FGF), insulin growth factor (IGF1) and Notch (Brennan et al., 2000; Gavrilovic et al., 1995; Gu et al., 2014; Mirsky et al., 2008; Syroid et al., 1999). However, *in vivo* studies have revealed that many of these factors are dispensable for the specification and survival of SCPs, and instead play important roles at later stages of SC development (discussed below) (Brennan et al., 2000; Furusho et al., 2009; Woodhoo et al., 2009).

In addition to SCP survival, axonal NRG1 signaling acts as a major factor for the migration of SCPs from the nerve roots to the distal nerve segments along with outgrowing axons *in vivo* (Lyons et al., 2005; Morris et al., 1999; Perlin et al., 2011; Wolpowitz et al., 2000; Yamauchi et al., 2008). Its effect on SCP proliferation is less well understood and remains controversial *in vivo*, although NRG1 has been shown to be an efficient mitogen *in vitro* (Dong et al., 1995, 1999; Lyons et al., 2005; Morris et al., 1999; Morrissey et al., 1995), (see also section on immature SC proliferation). Hence, deciphering the individual functions of NRG1 and other signaling

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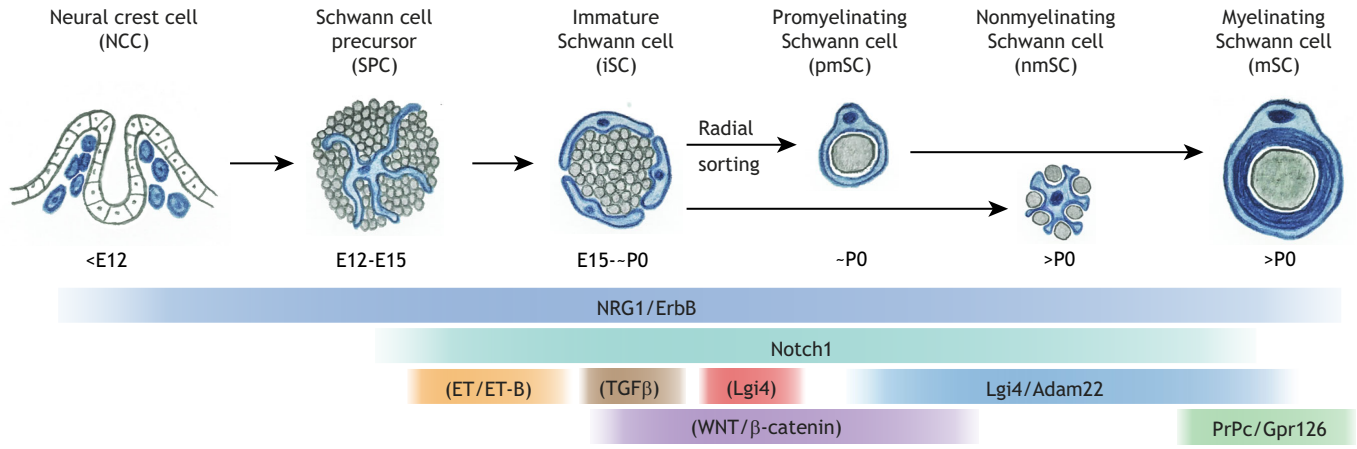

Fig. 2. Summary of Schwann cell development and differentiation. Schematic of the stages of the Schwann cell lineage (adapted from Jessen and Mirsky, 2005) with the respective time windows in which they occur (in mice) and including some known examples of axo-glial interaction signaling pathways that are required for the specific steps. When the origin of the ligand is not fully known, the pathway is shown in brackets. ET, endothelin.

factors with regard to fate specification, survival, proliferation and migration in SCPs *in vivo* remains a challenge for future studies in developmental biology.

Schwann cell precursors support axonal survival

The assumption that SCPs provide trophic support to outgrowing axons initially arose from studies in which SCPs were lacking in peripheral nerves, such as in ErbB2 and ErbB3 receptor mutant animals (Table 1) (Morris et al., 1999; Riethmacher et al., 1997). Here, a sequential loss of dorsal root ganglia (DRG) sensory neurons (between E12 and E14) and spinal cord motor neurons (around E18) was observed, suggesting that sensory neurons require SCPs for survival even before target innervation. The survival of motor neurons, in turn, may become SC dependent at the time when axons establish contact with the end organs and glial cells have progressed to immature SCs (Riethmacher et al., 1997). Although the absence of SCPs does not impair the initial growth and pathfinding of axons into the limbs (Grim et al., 1992; Meyer and Birchmeier, 1995; Morris et al., 1999; Woldeyesus et al., 1999), the most distal parts of developing nerves display severe defasciculation (detachment of bundled axons), diffuse terminal branching and fail to innervate the muscle (Grossmann et al., 2009; Morris et al., 1999; Newbern et al., 2011; Wolpowitz et al., 2000). The growth cones of emanating axons are indeed persistently populated by a complex mesh of SCPs (Wanner et al., 2006), pointing to an important function of SCPs in terminal pathfinding and synapse formation. Therefore, in light of the classical concept of target-derived neurotrophic support (Scott-Solomon and Kuruvilla, 2018), impaired target innervation in SCP-deficient mutants may contribute to motor neuron death in addition to loss of trophic support by SCPs themselves.

Immature Schwann cells drive a major morphological conversion of peripheral nerves

The transition from SCPs to immature Schwann cells (iSCs) occurs in two embryonic days in mouse and rats, with essentially all cells being converted into iSCs by E15 in mice and E18 in rats (Fig. 1B,C, Fig. 2) (Jessen and Mirsky, 1999). iSCs cease migration and drive a major morphological conversion of peripheral nerves (discussed below). Their appearance coincides with the generation of the ECM, as well as with the development of endoneurial connective tissue and blood vessels (Jessen and Mirsky, 2005; Webster et al., 1973). Signals derived from iSCs and axons, including desert hedgehog and VEGF, promote the differentiation and organization of arterial and perineurial cells, thereby forming the mature final architecture of peripheral nerves (Mirsky et al., 1999; Mukouyama et al., 2002, 2005; Parmantier et al., 1999; Li et al., 2013). A central role of iSCs is the separation of individual axons from nerve bundles in a process called radial sorting, which starts perinatally and continues until postnatal day (P) 10 in rodent peripheral nerves (Feltri et al., 2016; Jessen and Mirsky, 2005; Webster et al., 1973). Radial sorting requires continuous iSC proliferation and polarization, and the subdivision of axon bundles (Feltri et al., 2016). In the first step of radial sorting, axons become grouped in small bundles by a family of three to eight iSCs, which form a common basal lamina around these axon-glia units (Fig. 1B,C), (Feltri et al., 2016; Jessen and Mirsky, 2005; Webster et al., 1973). Subsequently, iSCs extend lamellipodia-like processes between bundled axons, to segregate the larger caliber axons into a 1:1 relationship with individual promyelinating SCs (Fig. 1D), which surround the axon-glia unit with a basal lamina (defasciculation). In turn, small caliber axons (<1 µm) remain grouped in small families of varying size and are engulfed by SC cytoplasm, together referred to as Remak bundles (Fig. 1E,F). The axon caliber is the crucial variable for the selection by SCs in radial sorting and subsequent myelination, as normally unmyelinated axons become myelinated (*de novo*) when the axon caliber is experimentally increased (Voyvodic, 1989). Remarkably, as demonstrated by elegant partial ligation studies in sympathetic nerves, the axonal caliber (and hence myelination) was shown to depend on the size of the innervated target, suggesting that the initial axon caliber is regulated by signals from the peripheral target tissue (Voyvodic, 1989).

Although the molecular control of iSC generation and radial sorting of axons still involves axonal signaling factors, the mutual dependence of the two cell types becomes more complex. Indeed, with the formation of the basal lamina, iSCs receive essential signaling cues from ECM components, including laminins and collagen, which interact with integrin and dystroglycan receptors and the G protein-coupled receptor Gpr126 (Adgrg6) (reviewed by Feltri et al., 2016; Monk et al., 2015). In addition to axonally derived factors, iSCs acquire – at least *in vitro* – autocrine survival mechanisms that last throughout development until adulthood (Meier et al., 1999).

Here, we focus on the role of bidirectional axo-glial signaling cues for the lineage progression of iSCs, and the radial sorting and segregation of individual axons. For the crucial role of ECM molecules and the basal lamina in the control of immature SCs and

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Table 1. Axo-glial interactions during peripheral nerve development

Schwann cell stage	Glia to axon	Axon to glia
Neural crest cell (NCC)		Notch signaling in the neural crest (NC) subpopulation drives gliogenesis in neighboring NCCs of future sensory and sympathetic tracts
Schwann cell precursor (SCP)	SCPs ensure axonal pathfinding and target innervation and provide trophic support for neuronal survival	Axonal NRG1 mediates SCP specification, survival and migration
Immature Schwann cell (iSC)	iSCs form 'families' around axon bundles and drive radial sorting of individual axons (defasciculation); Lgi4 secretion by iSCs supports axonal sorting	Jagged/Notch signaling mediates generation and proliferation of iSCs from SCPs; Wnt/β-catenin supports radial sorting; NRG1/ErbB signaling important for axonal recognition; axonal caliber dictates sorting by iSCs (if >1 µm)
Nonmyelinating (nmSC)/ promyelinating Schwann cell (pmSC)	Radial sorting establishes a 1:1 ratio of a pmSC and the corresponding axon	Axonal NRG1 type III determines myelin ensheathment fate and myelin sheath thickness
Myelinating Schwann cell (mSC)	Gliomedin (at glial microvilli) and NF186 (axonal) interaction promotes heminodal clustering of sodium channels; paranodal NF155 (glial) and Caspr/contactin (axonal) adhesion supports nodal clustering; mSCs contribute to axonal caliber	Axonal prion protein PrPc is only required for myelin maintenance (at least in part with glial Gpr126); NRG1 type III determines myelin sheath thickness; Notch signaling inhibits myelination; axonal Adam22 promotes myelination

NF, neurofascin.

radial sorting, we refer the reader to recent reviews by Feltri et al. (2016) and Monk et al. (2015).

Axonal signaling cues contribute to the generation of immature Schwann cells

Few studies have demonstrated a direct role of axonal signals for the transition of SCPs into iSCs *in vivo*. The main evidence for a role of axonal signaling cues in promoting SC lineage progression is derived from cell culture experiments. *In vivo*, the canonical Notch1 signaling pathway, acting via the downstream transcriptional activator RBPJ, promotes the timely differentiation of iSCs from SCPs (Woodhoo et al., 2009). The Notch1 receptor is expressed by SCs from E14 and the Notch ligands delta 1 and 3 (Dll1, Dll3) and jagged 1 and 2 are expressed on the axonal surface (Woodhoo et al., 2009). In addition, jagged 1 is expressed also by SCs (Woodhoo et al., 2009). The pro-differentiating effect of Notch has been proposed to be mediated by NRG1 and ErbB2 receptors, as Notch activation induced ErbB2 receptor expression in SCPs and increased the sensitivity of SCPs to NRG1 (Woodhoo et al., 2009). Indeed, the exogenous supply of primary SCPs with NRG1 type III promotes differentiation to iSCs independently of cell survival *in vitro* (Dong et al., 1995; Leimeroth et al., 2002). However, the severe phenotype of NRG1 mouse mutants (already at the SCP stage) limits direct conclusions on its particular role of signaling in the transition of SCPs to immature SCs (see above).

In contrast to Notch, endothelins block the differentiation effect of NRG1 on SCPs *in vitro*, and the ablation of the endothelin B receptor in the naturally occurring 'spotting lethal' mutant rat accelerates SC differentiation *in vivo* (Brennan et al., 2000). Hence, the precise timing of the transition from SCPs to iSCs seems to be regulated by axonally derived signaling cues. However, the overall mechanisms that drive the generation of iSCs from their precursors remain largely unknown, and further studies must elucidate the extent to which the transition of SCPs to iSCs is controlled by extrinsic versus intrinsic signals. Notably, at present, only one transcription factor (AP2α; TFAP2A) has been identified to play a role in the transition of SCPs to iSCs (Stewart et al., 2001).

The control of immature Schwann cell proliferation, survival and death

The SCP and iSC stages are characterized by a period of increased cell proliferation, which peaks at the iSC stage (Stewart et al., 1993). Sciatic nerve transection experiments in newborn rats have revealed a strong reduction in SC mitogenesis (Salzer and Bunge, 1980; Salzer et al., 1980), suggesting that SC proliferation is controlled by axonally derived factors. *In vivo*, the canonical Notch pathway drives the proliferation of iSCs, a function that is mediated by the intracellular kinases ERK1/2 and JNK (Woodhoo et al., 2009) and may be controlled by Notch ligands expressed by the axon. Of note, apoptotic cell death is not influenced by Notch activity, indicating that SC proliferation and survival are independently regulated (Woodhoo et al., 2009).

As discussed above for SCPs, NRG1 is mitogenic for SCs *in vitro*, mediated by the tyrosine phosphatase SHP2 (Grossmann et al., 2009; Dong et al., 1995, 1999; Lyons et al., 2005; Morris et al., 1999; Morrissey et al., 1995). However, whether NRG1 plays a direct role in SC division in development *in vivo* remains an open question. *In vivo*, the focal adhesion kinase FAK (PTK2), as well as the Rho GTPase Cdc42, regulate proliferation of iSCs (Benninger et al., 2007; Grove et al., 2007), a function that may be associated with NRG1 signaling. Notably, however, SC proliferation after nerve injury does not depend on NRG1 as revealed by several studies *in vivo* (Atanasoski et al., 2006; Fricker et al., 2011; Stassart et al., 2013).

Transforming growth factor beta (TGFβ), which is expressed by SCs and some DRG neurons, has an important role in controlling SC proliferation *in vitro* and *in vivo* (Einheber et al., 1995; Scherer et al., 1993; Stewart et al., 1995; Unsicker et al., 1991). *In vivo*, ablation of the TGFβ receptor in SCs reduces iSC proliferation (D'Antonio et al., 2006). Likewise, the overexpression of the proto-oncogene Ski, an inhibitor of TGFβ signaling, impairs SC division *in vitro* (Atanasoski et al., 2004). However, whether TGFβ signaling in iSC proliferation represents an autonomous mechanism or not remains to be determined.

In addition to cell division, the balance between SC survival and death is regulated by different axonal and non-axonal signals in iSCs. In general, physiological SC apoptosis characterizes the developing peripheral nerve until about the second postnatal week (Grinspan et al., 1996). Axotomy greatly increases the number of apoptotic SCs during this developmental time window, but not in older animals (Grinspan et al., 1996), suggesting a role for axonally derived survival factors during early postnatal development. In line with this theory, exogenous NRG1 is able to partially compensate

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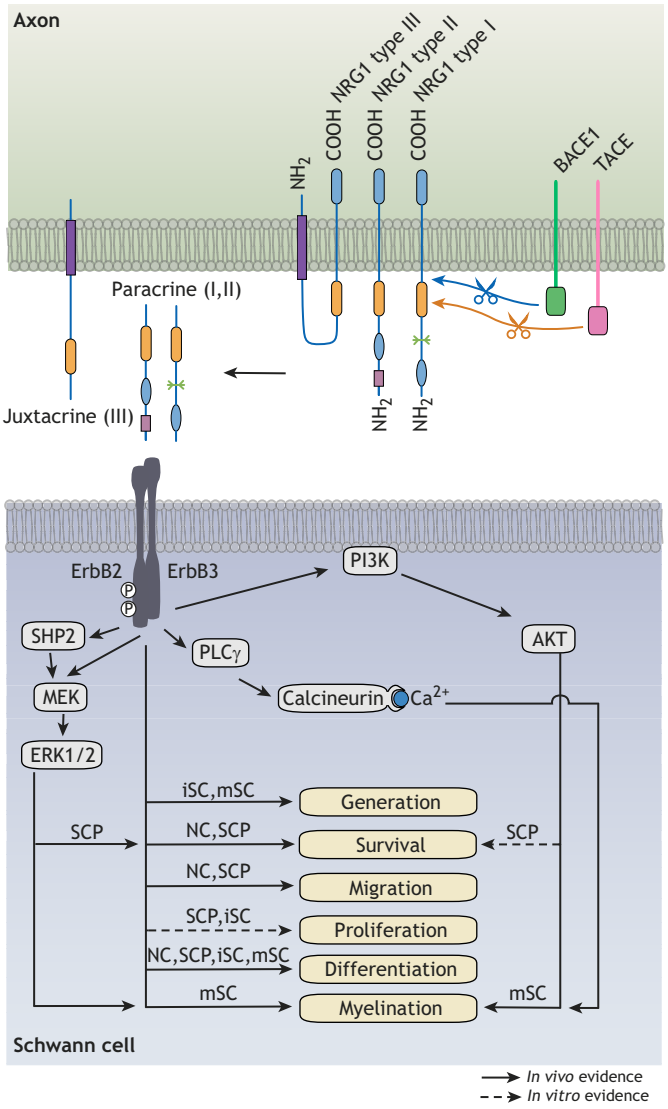

Fig. 3. Neuregulin 1 signaling in peripheral nerve development. The neuregulin 1 isoforms type I, II and III are expressed on the axonal surface. All isoforms share an EGF-like domain (orange), type I and II harbor Ig domains (blue ovals), type I is glycosylated (green cross), type II has a kringle domain (pink) and type III is characterized by a transmembrane cysteine-rich domain (purple). Neuregulin 1 isoforms are processed through proteolytic cleavage by the secretases TACE or BACE1. Whereas NRG1 type I and type II are released as soluble factors after a single cleavage step, NRG1 type III remains membrane anchored by its N-terminal second transmembrane domain. During development, axonal NRG1 type III activates ErbB2/3 receptors on the Schwann cell surface and regulates many important steps in the Schwann cell lineage progression. Depicted are signaling pathways MEK/ERK, PLC/calcineurin and PI3K/AKT from which strong *in vivo* (solid lines) or *in vitro* (dashed lines) evidence is available from the literature to regulate generation, survival, migration, proliferation or differentiation of the lineage stages: neural crest cell (NCC), Schwann cell precursor (SCP), immature Schwann cell (iSC) or myelinating Schwann cell (mSC).

for the increased SC apoptosis after axotomy *in vivo* (Grinspan et al., 1996), consistent with its essential role for the survival of SCPs (see above). However, in addition to an axonal control of SC survival, iSCs have been shown to acquire autocrine survival circuits *in vitro* from E18 on, which include autostimulation with IGF2, NT-3 (NTF3), PDGFB, leukemia inhibitory factor and lysophosphatitic acid (Meier et al., 1999). Indeed, the dependence of SCs on axonal factors for survival gradually decreases with age (Grinspan et al., 1996) and mature SCs in the adult nerve survive for a long time period upon the loss of axonal contact before undergoing cell death (Vuorinen et al., 1995; Weinberg and Spencer, 1978). Furthermore, the conditional ablation of ErbB2 in immature SCs, rather than ErbB3 ablation in SCPs, does not reduce SC numbers (Garratt et al., 2000; Sheean et al., 2014). Hence, the presence of auto/paracrine survival loops *in vivo* are highly likely, although not yet formally proven.

In addition to positive regulators of SC survival, negative 'death signals' regulate SC numbers and apoptosis in late embryonic and early postnatal nerves. One of those signals is TGFβ, which, in addition to its role in promoting iSC division, also drives iSC apoptosis in perinatal nerves (D'Antonio et al., 2006; Parkinson et al., 2001). Indeed, TGFβ receptor mutant mice show decreased SC proliferation and death, ultimately resulting in unchanged SC numbers within peripheral nerves (D'Antonio et al., 2006). Although the exact cellular source of TGFβ is not yet known, its effect on iSCs (proliferation or apoptosis) has been suggested to rely on the presence of axonal contact, but this is not yet formally proven (D'Antonio et al., 2006).

Axonal signals in Schwann cell polarization and sorting

Polarization of SCs starts at the iSC stage and requires the organization of the cytoskeleton, the formation of lamellipodia and the domain-specific expression, localization and signaling of several proteins and lipids (for reviews, see Feltri et al., 2016; Pereira et al., 2012). Indeed, axonal contact has recently been shown to induce prominent changes with regard to the local control of protein expression, translation, sumoylation and metabolism in cytoplasmic SC processes, called pseudopods (Poitelon et al., 2015). Although much progress has been made in unraveling the molecular mechanisms that govern and facilitate SC polarity and iSC differentiation, the molecular control of fiber sorting – and segregation itself – remains less well understood (Table 1).

SCs polarize in two dimensions: longitudinally along the axon between two nodes of Ranvier, and radially from the axonal membrane (apical domain) to the basal lamina (basolateral domain). Signals from the basal lamina are crucial for the basolateral polarization of SCs and activate different receptors, including integrin, dystroglycan and Gpr126, which interact with downstream signaling cascades involved in the remodeling of the cytoskeleton (for reviews, see Feltri et al., 2016; Monk et al., 2015). Recently, another G protein-coupled receptor (GPR56; ADGRG1) has been shown to promote the timely radial sorting of axons via RhoA and modulation of the actin cytoskeleton (Ackerman et al., 2018). In addition, the transcriptional co-activators Yap and Taz control radial sorting and the transcription of basal lamina receptor genes in addition to SC proliferation (Poitelon et al., 2016). Yap/Taz are activated in differentiating SCs by mechanical stimuli and by laminin, revealing an essential role for mechanotransduction in SC development (Poitelon et al., 2016). It is most likely that components of the basal lamina and the cytoskeleton converge with axonally derived signaling molecules at the apical signaling membrane for SC polarization. Indeed, many second messenger cascades, such as cAMP, the Rho family of GTPases, ILK, PKA, PI3K/AKT signaling and others, are regulated by both ECM and axonally derived factors (for reviews on this topic, see Ackerman and Monk, 2016; Castelnovo et al., 2017; Feltri et al., 2016; Pereira et al., 2012).

Proteins of the Par complex, including Par-3 (Pard3), Par-4 (LKB1/Stk11) and Pals1 (Mpp5), mediate SC apical polarity *in vivo*. Moreover, embryonic ablation of Pals1 in iSCs in mice results in a radial sorting phenotype, along with a reduced ability of

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nonmyelinating SCs to segregate and ensheath axons (Zollinger et al., 2015a). Furthermore, Par-4-specific deletion in the SCs also results in a mild axonal sorting phenotype together with impaired developmental myelination in respective mouse mutants (Shen et al., 2014). However, the exact interaction with extrinsic (i.e. axonal) cues remains to be established, and may include various adhesion molecules and growth factor receptors, such as N-cadherin (cadherin 2), Necl4, integrin, neurotrophin receptors, L1 (L1cam), LRP/Frizzled, Lgi4 and ErbB2/3 receptors. However, there is currently little evidence for a role of these molecules in SC polarization and axonal sorting itself. Of these examples, the interaction between axonally expressed NRG1 and SC-expressed ErbB2/3 receptors is likely to be important for axonal recognition and sorting. The precise effect of NRG1 and ErbB receptors is difficult to test *in vivo*, because most null mutants exhibit a severe overall SC phenotype. Nonetheless, conditional ablation of ErbB2 in SCs at the SCP stage in mice revealed a mild axonal sorting defect with occasional small groups of large caliber fibers lacking myelin that were still surrounded by a basal lamina (Garratt et al., 2000). Furthermore, analyses of NRG1 type III heterozygous mice has shown that Remak bundles are incompletely segregated into SC 'pockets', and in NRG1-deficient co-cultures, many large caliber axons remain unsorted (Taveggia et al., 2005). Notably, the application of small molecule inhibitors for ErbB signaling directly prior to myelination in zebrafish impaired axonal sorting and the process of extension of SCs into axon bundles (Raphael et al., 2011), and the inactivation of Gab1 (a downstream signaling molecule of NRG1) results in abnormal Remak bundles with the presence of unsorted, large caliber fibers in mice (Shin et al., 2014). Aberrantly ensheathed Remak bundles are also seen in mice with ablation of the protein Erbin, which binds and stabilizes the ErbB2 receptor (Tao et al., 2009). Moreover, calcineurin-NFAT signaling in SCs, presumably downstream of NRG1/ErbB, has been linked to radial sorting and myelination (Kao et al., 2009). More recently, mice with an SC-specific deletion of the endosomal PI3-kinase Vps34 (Pik3c3) have delayed radial sorting, potentially mediated via altered endosomal trafficking of ErbB2/3 receptors (Logan et al., 2017).

Further to NRG1 signaling, Wnt/β-catenin signaling has been implicated in radial sorting. Wnt and its co-activator R-spondin are expressed by neurons and may be released by axons where they bind to receptors of the Frizzled, LPR and Lgr families on SCs (for an extensive review and details, see Grigoryan and Birchmeier, 2015). Ablation of β-catenin in SCs results in a mild sorting defect, whereas the overactivation of β-catenin accelerated axonal sorting *in vivo* (Grigoryan et al., 2013; Lewallen et al., 2011). Concordantly, Wnt/β-catenin signaling affects cell spreading and lamellipodia formation in cultured SCs (Grigoryan et al., 2013).

In addition, Lgi4 secreted by SCs contributes to radial sorting *in vivo* (Bermingham et al., 2006; Darbas et al., 2004; Ozkaynak et al., 2010). However, the ablation of its axonal binding partner Adam22 only causes a defect in later SC development and hence, how Lgi4 and Adam22 interact with other SC signaling molecules, such as components of the ECM, remains an interesting open question (Ozkaynak et al., 2010; Sagane et al., 2005). Moreover, the deletion of prohibitin 2 in SCs impairs radial sorting *in vivo* (Poitelon et al., 2015). Prohibitin 2 interacts with proteins of the plasma membrane and is induced upon contact with neuronal membranes, suggesting that axonal signals may mediate prohibitin 2 function, possibly via immunoglobulin adhesion molecules (Poitelon et al., 2015).

Finally, in addition to classical axonal signaling molecules, neurotransmitters represent promising candidates for the regulation of axonal sorting with regard to axonal recognition and subsequent segregation (see Feltri et al., 2016). Indeed, radial sorting and the appearance of electrical activity in peripheral neurons occur in the same time window (Fitzgerald, 1987). Interestingly, the ablation of the neurotransmitter receptors P2X7 in mice and GABA-B in SCPs leads to abnormalities of Remak bundles (Faroni et al., 2014a,b, 2019; Magnaghi et al., 2008). However, a further role of electrical activity and neurotransmitter signaling from axons for iSC development needs to be elucidated in future.

Conversely, whether immature SCs provide unique support towards axons or specifically modulate axonal properties during radial sorting has not been shown so far. Notably, studies of mouse mutants with axonal sorting defects such as laminin-deficient mice or SC-specific Gpr126 knockouts have revealed no signs of axonal damage and axons remain permissive for myelination (Feltri et al., 2016; Mogha et al., 2013; Yang et al., 2005).

From promyelinating Schwann cells to myelin formation

Radial sorting establishes a 1:1 unit of a promyelinating SC and the corresponding axon with a surrounding basal lamina; a prerequisite for subsequent myelin formation. In the PNS, only axons with a diameter greater than 1 µm become myelinated and myelin sheath thickness is proportional to the axonal diameter, also quantified as the 'g-ratio'. The concept that neuronal signals control myelination has initially been demonstrated in cross-anastomosis and graft experiments, in which previously nonmyelinating SCs have been shown to acquire a myelinating phenotype upon contact with axons destined for myelination (Aguayo et al., 1976; Weinberg and Spencer, 1975, 1976). As discussed above, SC processes and their membranes become polarized, which is required for the initial ensheathment and determines the site of membrane growth (Pereira et al., 2012; Simons and Trotter, 2007; Simons et al., 2012). The assembly of large quantities of myelin components occurs in the secretory path and is regulated within distinct subcellular compartments. It requires high-level lipid biosynthesis and translation, as well as proper trafficking of myelin proteins. Generally, tight coordination of gene expression and membrane growth is necessary in order to maintain the unique stoichiometry of lipids and proteins; SCs are sensitive to an imbalance or impairment of this process, which is reflected by several forms of inherited neuropathy (Fledrich et al., 2012, 2018). Myelin membrane growth occurs in two dimensions, radially and longitudinally. Whereas myelin sheath thickness is essentially controlled by the axonally expressed growth factor NRG1 type III (Michailov et al., 2004), internodal length has been recently linked to mechanotransduction downstream of postnatal body growth (Fernando et al., 2016; Tricaud, 2018). Next, we focus on the role of axon-glia signaling factors for the active phase of myelination and discuss, in turn, how promyelinating SCs contribute to the specialization of axonal domains and the regulation of axonal size during the process of myelin formation (Table 1) (Fig. 2).

The promyelinating Schwann cell state and the active phase of myelination

Myelination is associated with a continuous cellular polarization that enables the SC to elongate both radially and longitudinally during myelin formation. Indeed, proteins that localize asymmetrically to the site of the SC-axon interface have been implicated in the process of myelin formation in addition to their role in axonal sorting. For example, the SC-specific ablation of Par-4 results in impaired initiation of myelination, but interestingly also in reduced myelin sheath thickness in adult mice (Shen et al., 2014). Par-4 colocalizes with Par-3 to the SC-axon interface and Par-3 has

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been proposed to interact with p75NTR (NGFR) and axonally derived BDNF at the onset of myelination (Chan et al., 2006; Tep et al., 2012). Par-3 knockdown in zebrafish, and mice at P0, attenuates myelination with thinner myelin sheaths and reduces the number of myelinated axons, although this could be a transient effect (Tep et al., 2012). Interestingly, Par-3 also interacts with the adhesion proteins Necl4 (Cadm4) and Necl1 (Cadm3) at the glial and axonal sites, respectively, and both promote myelination *in vitro* (Meng et al., 2019). However, deletion of Necl proteins *in vivo* does not cause a major defect in myelin formation (Golan et al., 2013; Maurel et al., 2007; Park et al., 2008; Spiegel et al., 2007).

In addition to Par-3, the viral silencing of Pals1 in postnatal myelinating SCs *in vivo* results in thinner and shortened myelin sheaths (Ozcelik et al., 2010). However, the conditional ablation of Pals1 in mice resulted in no major alteration of myelin thickness and length (Zollinger et al., 2015a) and further studies are needed in order to better understand these different observations. Generally, the interacting partners of the apical polarity proteins mentioned above, and their potential cooperation with axonal signals remain poorly understood. Recently, the apical polarity protein Crb3, which is active in SC microvilli, has been shown to mediate longitudinal myelin growth downstream of nerve stretching and mechanotransduction, as demonstrated by viral silencing *in vivo* (Fernando et al., 2016). However, it remains to be determined whether mechanical stimulation during body growth is mediated via adhesion molecules at the axon-glia interface, via the ECM or via both components (Belin et al., 2017; Tricaud, 2018).

Radial myelin growth in peripheral nerves is controlled by axonally derived NRG1 type III expression, which has no influence on internodal length. The first evidence that NRG1/ErbB signaling regulates myelination came from hypomyelinated mouse mutants that lacked ErbB2 selectively in EGR2-expressing SCs (Garratt et al., 2000). Indeed, animals heterozygous for NRG1 in peripheral nerve axons are only thinly myelinated (Michailov et al., 2004). In contrast, neuronal overexpression of NRG1 type III in transgenic mice induces a hypermyelination phenotype (Michailov et al., 2004; Taveggia et al., 2005). This increase in myelin sheath thickness is specific for the type III isoform of NRG1, as the equivalent overexpression of the soluble type I isoform in neurons does not result in hypermyelinated axons (Michailov et al., 2004). Notably, hemizygous ErbB2 receptor knockout mice are fully myelinated, demonstrating that only the ligand, not the receptor, is rate limiting for myelination (Michailov et al., 2004). Importantly, NRG1 additionally serves as an instructive signal for myelination and provides SCs with information about axons that have reached the radial size of ∼1 µm for myelination (Taveggia et al., 2005). Indeed, overexpression of NRG1 type III in normally unmyelinated fibers results in their *de novo* myelination *in vitro* (Taveggia et al., 2005).

NRG1 is post-translationally controlled by secretases, and NRG1 cleavage by the β-secretase BACE1, which is strongly expressed in neurons but also weakly in SCs, activates NRG1 signaling (Fig. 3) (Hu et al., 2006; Velanac et al., 2012; Willem et al., 2006). In contrast, the α-secretase ADAM17 (also known as TACE) negatively regulates peripheral myelination, most likely by cutting within the EGF-like domain, thereby reducing the functional levels of NRG1 type III (Bolino et al., 2016; La Marca et al., 2011). Alongside extracellular cleavage, the γ-secretase complex is responsible for an intramembrane proteolysis of NRG1 type III in axons (Bao et al., 2003). This induces a feedback signal towards the neuronal cell body and stimulates the expression of the prostaglandin D2 synthase PTGDS (Bao et al., 2003; Trimarco et al., 2014). PTGDS, in turn, leads to expression of the G protein-coupled receptor GPR44 (PTGDR2), which promotes myelination, most likely by activating the transcription factor Nfatc4 in SCs (Trimarco et al., 2014).

Upon binding to ErbB2/3 receptors on the SC surface, NRG1 type III activates different second messenger cascades for myelination, most importantly PI3K/AKT and MAPK/ERK signaling (reviewed by Castelnovo et al., 2017; Figlia et al., 2017; Taveggia, 2016). Of these, overactivation of the MAPK/ERK pathway is able to compensate for a loss of NRG1/ErbB signaling in SC development and myelination (Sheean et al., 2014). Indeed, the SC-specific ablation of ERK prevents myelination, and mice lacking the downstream molecules SHP2 or Gab1 show a hypomyelinating phenotype (Grossmann et al., 2009; Newbern et al., 2011; Shin et al., 2014). The role of PI3K/AKT signaling downstream of axonal NRG1 type III is more complex, as the activation of AKT signaling by a constitutively active AKT in myelinating glia or the ablation of PTEN leads to not only hypermyelination, but also a progressive myelin pathology with aberrant myelin growth resulting in myelin outfoldings and so-called tomacula (Domenech-Estevez et al., 2016; Goebbels et al., 2012). More recently, progress has been made in identifying the important role of mTOR signaling in SC development and myelination. Specifically, mTORC1 ablation in SCs causes a persistent hypomyelination of peripheral nerves (Norrmén et al., 2014; Sherman et al., 2012; reviewed by Figlia et al., 2017). Notably, the scaffold protein discs large homolog 1 (DLG1) and DNA-damage-inducible transcript 4 (DDIT4) have been identified as inhibitors of myelination that counteract AKT/mTOR activity in SCs, most likely thereby preventing overmyelination during myelin sheath assembly (Cotter et al., 2010; Noseda et al., 2013).

Importantly, laminin 211 limits neuregulin 1 type III signaling by inhibiting PKA activation in small caliber fibers, thereby providing insight into the integration of ECM and axonal signals for myelination (Ghidinelli et al., 2017).

In addition to NRG1/ErbB, Lgi4/Adam22 interaction promotes myelin formation *in vivo* (Bermingham et al., 2006; Ozkaynak et al., 2010; Sagane et al., 2005). Lgi4 is secreted by SCs and binds to Adam22 on the axonal surface (Kegel et al., 2013). However, the mechanism by which Lgi4/Adam22 regulates myelination remains poorly understood. It may include the conversion of Adam22 into a promyelinating factor upon Lgi4 binding as well as additional factors.

Although Wnt/β-catenin signaling has primarily been implicated in axonal sorting (Grigoryan and Birchmeier, 2015; Grigoryan et al., 2013), inhibition of Wnt/β-catenin in zebrafish results in hypomyelination, and Wnt/β-catenin signaling promotes myelin gene expression *in vitro*, which suggests an additional role of this pathway for myelin formation (Tawk et al., 2011). Finally, Notch signaling serves an inhibitory signal at the onset of myelination; mice overexpressing the Notch intracellular domain (NICD) *in vivo* show a hypomyelination and delayed onset of myelination (Woodhoo et al., 2009).

Myelinating Schwann cells induce local changes in axons

Myelination induces a substantial remodeling of the corresponding axon, which comprises specialization of axonal domains as well as organization of the axonal cytoskeleton. Indeed, it has been known for some time – even before the first molecular players were identified – that the formation of the nodal region of axons coincides with myelination, and hence most likely is instructed by SCs (Tao-Cheng and Rosenbluth, 1983). At a molecular level, one of the first steps in the formation of the node of Ranvier is expression of the protein gliomedin in the microvilli of SCs, which associates with the axonal adhesion molecule neurofascin 186 (NF186; neuronal isoform of NFASC) in a process known as heminodal clustering

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(Eshed et al., 2005, 2007; Feinberg et al., 2010). NF186 then recruits the cytoskeletal scaffolding protein ankyrin-G (Ank3), thereby inducing the primary clustering of voltage-gated sodium (Na_v) channels in the nodal region (Dzhashiashvili et al., 2007; Gasser et al., 2012; Ho et al., 2014; Zollinger et al., 2015a). In addition, paranodal junctions, consisting of NF155 (glial isoform of NFASC) and contactin on the glial side and Caspr (Cntnap1) on the axonal side, contribute to ion channel clustering (Charles et al., 2002; Zollinger et al., 2015b).

Myelinating SCs also contribute to the increase in axonal size and the organization of the axonal cytoskeleton. The first evidence that axonal caliber is locally modulated by myelinating SCs was derived from graft experiments in the dysmyelinating 'Trembler' mouse, which showed that changes in axonal diameter, neurofilament phosphorylation and density, as well as axonal transport rates, were confined to regions with abnormal myelination (de Waegh et al., 1992). Indeed, radial axonal growth is linked to neurofilament accumulation and spacing in the axonal cytoplasm, which has been supposed to be mediated by a slowing of axonal transport as well as by increased neurofilament phosphorylation downstream of myelination (Hsieh et al., 1994a,b; Monsma et al., 2014). Although the exact mechanisms remain to be elucidated, a role for the myelin protein MAG has been previously suggested (Yin et al., 1998). In summary, the appearance of the myelin sheath exerts profound changes of the corresponding axons and gaining a further understanding of the glial signals that contribute to this process is an exciting task for the future.

Myelin maintenance and nerve integrity in adulthood

Axo-glial signaling in myelin maintenance and Schwann cell integrity

Although SCs depend on axonal signaling cues during peripheral nerve development, the dependence of glia on axonal factors reduces in the adult nerve. For example, induced conditional ablation of NRG1 in adulthood in a subset of neurons does not cause myelin or neuromuscular junction alteration until 22 weeks after recombination (Fricker et al., 2011). Supporting this, conditional ErbB2 ablation reveals no morphological changes in peripheral nerve myelin in the short term (Atanasoski et al., 2006), suggesting that NRG1 is dispensable for the maintenance of the myelin sheath in the healthy adult nerve. However, dominant-negative ErbB2 expression results in a late sensory phenotype (Chen et al., 2003). Whether axo-glial NRG1/ErbB signaling becomes important again in the ageing nerve remains to be determined.

Notably, the axon-derived prion protein PrPc (Prnp) is only required for myelin maintenance, and its ablation or perturbed proteolytic procession results in late-onset demyelinating neuropathy (Bremer et al., 2010). Axonal PrPc operates, at least in part, via Gpr126 in myelinating SCs, which may suggest that continuous cAMP signaling is necessary to maintain myelin (Küffer et al., 2016). Hence, the nature of axonal signals that contribute to myelin and SC integrity in adulthood and ageing appears to differ from the developing nerve. Indeed, more research is necessary to understand this relationship. Interestingly, PNS myelin appears to respond plastically to changes in axonal electric activity: experimental immobilization of the hind limbs, with a consecutive increased movement of the fore limbs, results in myelin thinning or thickening in nerve fibers of the hind and fore limbs, respectively (Canu et al., 2009).

The role of Schwann cells in maintaining the integrity of the axon-glia unit in adulthood

In addition to their essential role in the development of peripheral nerves, SCs are thought to provide indispensable support for nerve integrity throughout life (Nave, 2010; Stassart et al., 2018). In the CNS, oligodendrocytes provide metabolic support to the axon, most likely by exporting energy-rich metabolites via monocarboxylate transporters (Fünfschilling et al., 2012; Lee et al., 2012). However, whether and how SCs fulfill a similar role in the PNS remains unclear. *Ex vivo*, myelinated axons of aglycemic sciatic nerves develop a functional impairment that is dependent on the level of glycogen storage in the nerve, most likely in SCs, whereas unmyelinated axons show no such relation (Brown et al., 2012). The same authors suggest that fructose can be directly utilized by unmyelinated fibers, whereas myelinated axons of the same nerve are supported by fructose-derived lactate, again in *ex vivo* experiments (Rich and Brown, 2018).

Moreover, different studies have analyzed the effect of mitochondrial function and metabolic regulators in the PNS *in vivo*. Interference with glial mitochondrial function in mouse mutants results in a peripheral neuropathy with myelin abnormalities and axonal degeneration, but myelinating SCs remain viable (Fünfschilling et al., 2012; Viader et al., 2013). However, mitochondrial dysfunction has also been associated with the generation of toxic lipid products, which complicates the interpretation of these results (Viader et al., 2013).

Furthermore, the SC-specific ablation of the tumor suppressor Par-4, which exerts a central role in cellular metabolism, causes nerve defects (Beirowski et al., 2014; Pooya et al., 2014). Of note, although Par-4 deletion during development results in hypomyelination, selective ablation in adult nerves leads to primary degeneration of small unmyelinated Remak axons, but, again, myelinating SCs remain alive (Beirowski et al., 2014; Pooya et al., 2014). Moreover, interference with NAD+ metabolism in SCs causes peripheral neuropathy and SC dedifferentiation in adult nerves (Sasaki et al., 2018). However, the overall interference with SC metabolism and function in all of these mutants limits direct conclusions on the specific role of SC as an energy supplier for nerve fibers.

Finally, in the CNS, monocarboxylate transporter 1 (MCT1; SLC16A1) heterozygosity causes axonal degeneration (Lee et al., 2012). However, analyses of the sensory sural nerve in the PNS of animals heterozygous for monocarboxylate transporters indicates that they appear to be normal (Lee et al., 2012; Morrison et al., 2015; Stassart and Nave, 2015). Together, these data demonstrate that peripheral nerve metabolism most likely does not reflect a simple recapitulation of the CNS. Although these studies reveal important new insights into the role of SC metabolism, many questions remain unanswered in this newly emerging field. These include the potential differences between the metabolic demands in development and adulthood, and differences between myelinated and unmyelinated axon-glia units.

Conclusions and future perspectives

The development of peripheral nerves includes outgrowth and target innervation of axonal nerve fibers and maturation of the adjacent SC lineage. SCs and axons tightly interact with and depend on each other. Together, they drive drastic morphological remodeling of developing peripheral nerves. Ultimately, this results in small bundles of mature slow-conducting sensory fibers that are not myelinated, and in larger caliber fibers that are capable of fast impulse propagation due to myelination by SCs (Fig. 1). The close interdependence of glial cells and their corresponding nerve fibers first becomes apparent during early embryonic development, and is illustrated by the neuregulin 1 signaling cascade, through which both cell types communicate (Fig. 3). Interference with NRG1 signaling on either side, in glial or neuronal cells, proves fatal in early development and obstructs nerve maturation when perturbed later. Although a number of essential factors for nerve maturation at the axo-glial interface have now been

identified, the precise nature of signal regulation, including initiation, integration and termination, remains poorly understood. Ongoing research that focusses on the sensitive cellular interactions involved will not only improve our current understanding of peripheral nerve development, but will also provide the basis for the development of therapeutic strategies for rare and frequent peripheral nerve disorders.

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Competing interests
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