

Schwann cell functions in peripheral nerve development and repair



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ABSTRACT

The glial cell of the peripheral nervous system (PNS), the Schwann cell (SC), counts among the most multifaceted cells of the body. During development, SCs secure neuronal survival and participate in axonal path finding. Simultaneously, they orchestrate the architectural set up of the developing nerves, including the blood vessels and the endo-, peri- and epineurial layers. Perinatally, in rodents, SCs radially sort and subsequently myelinate individual axons larger than 1 μm in diameter, while small calibre axons become organised in non-myelinating Remak bundles. SCs have a vital role in maintaining axonal health throughout life and several specialized SC types perform essential functions at specific locations, such as terminal SC at the neuromuscular junction (NMJ) or SC within cutaneous sensory end organs. In addition, neural crest derived satellite glia maintain a tight communication with the soma of sensory, sympathetic, and parasympathetic neurons and neural crest derivatives are furthermore an indispensable part of the enteric nervous system. The remarkable plasticity of SCs becomes evident in the context of a nerve injury, where SC transdifferentiate into intriguing repair cells, which orchestrate a regenerative response that promotes nerve repair. Indeed, the multiple adaptations of SCs are captivating, but remain often ill-resolved on the molecular level. Here, we summarize and discuss the knowns and unknowns of the vast array of functions that this single cell type can cover in peripheral nervous system development, maintenance, and repair.

1. Introduction

The glial cell of the peripheral nervous system (PNS), the Schwann cell (SC), counts among the most multifaceted cells of the body. During development, SCs secure neuronal survival and participate in axonal path finding. Simultaneously, they orchestrate the architectural set up of the developing nerves, including the blood vessels and the endo-, peri- and epineurial layers. Perinatally, in rodents, SCs radially sort and subsequently myelinate individual axons larger than 1 μm in diameter, while small calibre axons become organised in non-myelinating Remak bundles. SCs have a vital role in maintaining axonal health throughout life and several specialized SC types perform essential functions at specific locations, such as terminal SC at the neuromuscular junction

(NMJ) or SC within cutaneous sensory end organs. In addition, neural crest derived satellite glia maintain a tight communication with the soma of sensory, sympathetic, and parasympathetic neurons and neural crest derivatives are furthermore an indispensable part of the enteric nervous system. The remarkable plasticity of SCs becomes evident in the context of a nerve injury, where SC transdifferentiate into intriguing repair cells, which orchestrate a regenerative response that promotes nerve repair. Indeed, the multiple adaptations of SCs are captivating, but remain often ill-resolved on the molecular level. Here, we summarize and discuss the knowns and unknowns of the vast array of functions that this single cell type can cover in peripheral nervous system development, maintenance, and repair.

Abbreviations: c-JUN, c-JUN transcription factor; C3, complement component 3; CCL2, CC motif chemokine ligand 2; CNS, central nervous system; CR3, complement receptor 3; CXCL12, C-X-C motif chemokine 12; CXCR4, C-X-C motif chemokine receptor 4; DCC, deleted in colorectal cancer, Netrin-1 receptor; DHH, desert hedgehog protein; ERBB, Erb-B receptor tyrosine kinase; GDNF, glial cell derived neurotrophic factor; GPCR/GPCRs, G-protein coupled receptor/receptors; HLA, human leucocyte antigen; IH3, Diwanka; LAMA2, laminin subunit alpha 2; MCP1, monocyte chemoattractant protein 1; MHCII, major histocompatibility complex II; NG2, neuron-glial antigen 2; NMJ/NMJs, neuromuscular junction/junctions; NRG1, neuregulin 1; p75^{NTT}, neurotrophin receptor p75; PNS, peripheral nervous system; RNA, Ribonucleic acid; SC/SCs, Schwann cell/cells; scRNAseq, single cell RNA sequencing; SGC/SGCs, satellite glial cell/cells; SOX10, Sry-related HM-Box gene 10; TRAP1, Tumor necrosis factor receptor associated protein 1; USH2A, usherin; VEGFR1, vascular endothelial growth factor receptor 1.

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2. Schwann cell functions in peripheral nerve development

During early developmental stages, embryonic nerves consist of tightly packed, growing axonal fascicles which are associated with flattened processes from SC precursors that lie among the axons inside the nerve or at the nerve surface (around embryonic day [E] 12 in mice and E14 in rats). No significant extracellular space, matrix or basal lamina is observed at this stage (Fledrich et al., 2019b; Jessen et al., 2015) (Fig. 1). Shortly after, this highly compact architecture is rapidly changed (E15 in mice, E18 in rats). The nerves now contain blood vessels, fibroblasts, and an extracellular space rich in collagen. In parallel, the perineurial sheath starts to be formed at the nerve surface, and SC precursors develop into immature SCs, which start engulfing bundles of axons and forming a basal lamina. At the perinatal stage, immature SCs radially sort axons and, around birth, finally develop into either non-myelinating Remak cells or myelinating SCs (Fledrich et al., 2019b; Mirsky et al., 2002) (Fig. 1). The developing SCs hence perform pivotal functions that contribute to several stages of this stepwise formation of the peripheral nerve which we will define and discuss in the following sections.

2.1. Axonal guidance and target innervation

Neural crest cells that enter the Schwann cell lineage transition into SC precursors, which migrate in close contact with growing axons within the developing PNS, suggesting a potential role of SC precursors in axonal guidance and final target innervation. However, when co-migrating SC precursors in peripheral nerves are experimentally ablated during embryonic development, both sensory and motor neurons are initially formed in sufficient numbers, and their axons group into a nerve, navigate for considerable distances and form initial synapses at their targets (Morris et al., 1999; Riethmacher et al., 1997; Woldeyesus et al., 1999). This was reported in mice and zebrafish with loss of SC at the precursor stage after genetic inactivation of Neuregulin1 (NRG1)-ERBB receptor signalling (Lyons et al., 2005; Morris et al., 1999; Raphael and Talbot, 2011; Riethmacher et al., 1997; Woldeyesus et al., 1999) as well as in the splotch mouse mutant (Grim et al., 1992). Nevertheless, aberrant projections and distal axonal defasciculation, leading to inaccurate location of synaptic sides and impaired target innervation characterizes *Erbb* mutants (Morris et al., 1999). In addition, SC precursors form complex scaffolds around the growth cone, which keep remarkably consistent contacts with axonal membranes (Wanner et al., 2006), and facilitate correct target innervation by regulating nerve fasciculation at the growing nerve endings (Grossmann et al., 2009; Morris et al., 1999;

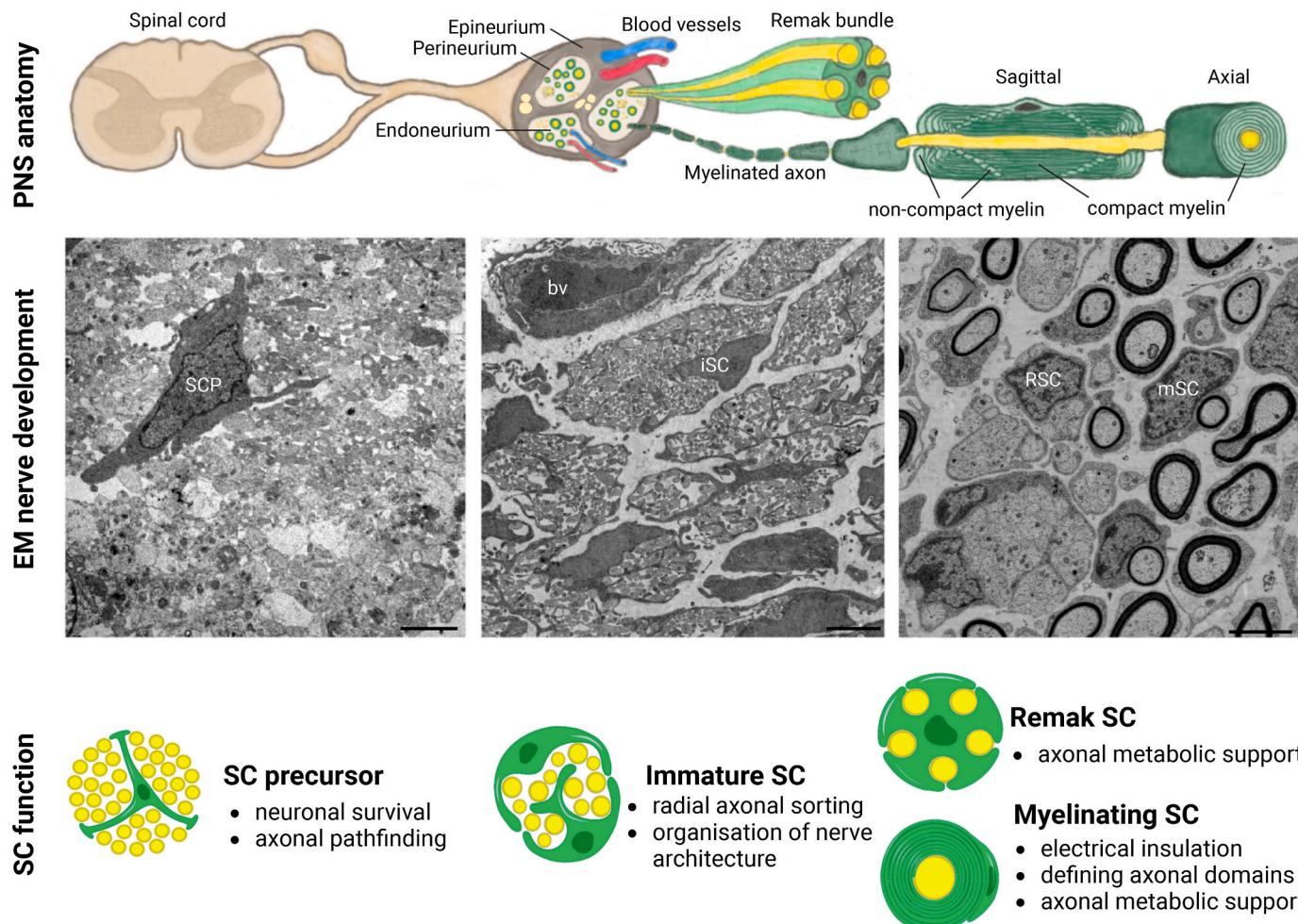


Fig. 1. Developing Schwann cells orchestrate the stepwise formation of the peripheral nerve. In the early stages of nerve development, Schwann cell (SC) precursors promote neuronal survival and contribute to axonal pathfinding. Immature SC organize the nerve architecture, including the blood vessels and the nerve connective layers (endoneurium, perineurium and epineurium). Perinatally, immature SC coordinate axonal sorting and eventually differentiate into either Remak SCs or myelinating SCs. Myelinating SCs define structural and functional axonal domains and ensure the electrical insulation of axons. The nerve architecture is displayed in the “PNS anatomy” section, including both sagittal and axial views of the mature myelin sheath. Electron micrographs exemplify the different developing stages of SCs, including SC precursors (SCP), immature SCs (iSCs), myelinating SCs (mSC) and Remak SCs (RSC) (labelled in white).

Newbern et al., 2011; Wolpowitz et al., 2000). While these data demonstrate in proof of principle that SC precursors contribute to axonal pathfinding and target innervation during peripheral nerve development, how SC precursors facilitate guidance on the molecular level, and whether they may exert distinct functions for specific types of axons, remains to be explored.

Observations in zebrafish indicate that SCs are required for the determination of the correct number of sensory neuromast cells and for the correct positioning of the posterior lateral line, a sensory system in the subepidermal space (López-Schier and Hudspeth, 2005; Raphael et al., 2010). Notably, in mice, the specific ablation of a transient precursor for a subpopulation of SC, the boundary cap cells, causes misplacement of motor neuron cell bodies into the periphery (Radomska and Topilko, 2017; Vermeren et al., 2003). Boundary cap cells reside, early in development, at the junction between the CNS and PNS of the motor exit points and dorsal root entry zones, where motor and sensory axons leave or enter the CNS, respectively (Fontenay and Kucenas, 2018; Kucenas et al., 2008; Vermeren et al., 2003). Hence, these SC precursors might create a “signalling barrier” between the CNS and PNS and thus play a role in determining motor neuronal placement in the spinal cord. In addition, boundary cap-derived glial cells appear to guide fine sensory fibres into the epidermal skin layer (Gresset et al., 2015). Eventually, boundary cap cells also give rise to neurons and satellite glia in sensory ganglia, and most of the SCs of the dorsal and ventral roots (Radomska and Topilko, 2017).

2.2. Neuronal survival

Next to a role in axonal guidance and target innervation, a main function of SC precursors during PNS development is to ensure survival of sensory and motor neurons and their corresponding axons. Indeed, large-scale sensory and motor neuron death (around 70–80%) is observed in the embryos of mouse mutants lacking SC precursors shortly after the initial formation of the nerves (Britsch et al., 2001; Riethmacher et al., 1997; Woldeyesus et al., 1999). There could be two explanations for this phenomenon: (1) SC precursors provide essential survival signals and/or trophic support to growing axons of sensory and motor neurons, and/or (2) defective target innervation prevents access to target-derived growth factors.

Notably, the degeneration of sensory neurons (from E11.5 on in *Sox10* mutants and pronounced at E14.5 in *Erbb3* mutants) starts earlier compared to the loss of motor neurons, suggesting that, for sensory nerves, the direct support provided by SC precursors to neurons whose axons are still growing is highly relevant (Britsch et al., 2001; Riethmacher et al., 1997). In contrast, the loss of motor neurons takes place at more advanced developmental stages, when significant neuron-target interactions have started, i.e. at around E18 in *Erbb3* and *Sox10* mutants (Wolpowitz et al., 2000). Hence, motor neuron loss in these mutants may be attributed to a lack of adequate target-derived support as well as to a simultaneous importance of SC-derived survival signals during the early stages of target innervation (Fledrich et al., 2019b; Riethmacher et al., 1997). Indeed, this suggests that immature SC rather than SC precursors support motor neuron survival during development (Britsch et al., 2001; Jessen and Mirsky, 1999; Riethmacher et al., 1997).

Notably, SC precursors can secrete several survival and growth factors, which promote, to various extents, survival of sensory and motor neurons *in vitro* (reviewed in Davies, 1998 and Newbern, 2015). However, the complete absence of SC precursors caused by ERBB3 mutations leads to much more severe neuronal degeneration than any single neurotrophic factor deletion (Davies, 1998; Lewin and Barde, 1996; Riethmacher et al., 1997; Snider, 1994), suggesting that multiple factors are required for the pro-survival effect of SC precursors on early sensory and motor neurons and/or that other, yet uncharacterized, SC precursor-derived factors might play a major role (Davies, 1998; Lewin and Barde, 1996; Snider, 1994). For instance, recent studies demonstrated that adequate lipid metabolism by SC contributes to sensory neuron

survival at least *in vitro* (Follis et al., 2021). Hence, the general principles and the molecular nature of how SC secure or contribute to axonal and neuronal survival remains unknown so far, and may range from pro-survival signals and classical neurotrophins to a trophic/metabolic support by SC precursors and immature SC. Like for axonal pathfinding, however, elucidating these highly complex mechanisms *in vivo* in the embryonic organism is still technically challenging.

2.3. Organization of the nerve

Peripheral nerves present a fascinating flexibility while being extremely sturdy. This biomechanical protection is provided by the connective tissue layers surrounding the nerve, which contribute to the stiffness and elasticity of the peripheral nerve microenvironment (Belin et al., 2017; Rosso et al., 2017a; Rosso et al., 2017b). In detail, the flexible collagen-rich extracellular matrix of the endoneurium surrounds each axon-glia unit, followed by the perineurium which forms nerve fascicles and finally the outermost epineurial layer, which defines individual nerves (Belin et al., 2017; Jessen and Mirsky, 1999b; Shanthaveerappa and Bourne, 1966). Notably, developing SCs coordinate the formation and growth of these three layers particularly during the transition from SC precursors to immature SC (Jessen and Mirsky, 1999b) (Fig. 1).

At this stage, a proportion of SC precursors also transitions to fibroblasts, which remain within the nerve and start secreting extracellular matrix molecules (mainly collagen) that subsequently fill up the space among different axonal fibres (Jessen and Mirsky, 1999b). Indeed, recent studies have discovered new functions for SC precursors as a class of multipotent progenitors, which can generate several different cell types (Kastriti et al., 2022a, 2022b; for a comprehensive review, see Furlan and Adameyko, 2018).

The signals that determine the lineage transition of SC precursors into fibroblasts or immature SC are not known, but may include local environmental (including axonal) factors as well as the co-activation and/or repression of transcriptional programs (Kastriti et al., 2022a; Kastriti et al., 2022b). Immature SCs further enhance the formation of the extracellular matrix and deposit a basal lamina around each SC family, engulfing bundles of still uniformly small sized axons at this developmental stage (Obremski et al., 1993) (Fig. 1).

Moreover, immature SCs secrete desert hedgehog (DHH), which interacts with patched receptors on cells of the surrounding tissue and is required for the formation of the peri- and epineurial sheaths that surround mature nerves (Parmantier et al., 1999). Indeed, a bidirectional interaction between SC precursors and perineurial cells is essential for successful peripheral nerve development (reviewed in Kucenas, 2015; Reed et al., 2021). Interestingly, mice with an ablation of DHH do not only show a disorganized perineurium, but also a compromised blood nerve barrier (Mirsky et al., 1999; Parmantier et al., 1999; Sharghi-Namini et al., 2006), although the underlying mechanisms remain unresolved so far. In addition, an impaired arterial differentiation and blood vessel-nerve alignment in the developing skin was observed in *Erbb3* knockout mice that lack peripheral nerve SCs (Mukouyama et al., 2002). At the time when SCP transition to immature SC (around E16 in mice), the first blood vessels inside the endoneurial nerve compartment also start to appear. Whereas the initiation of the endoneurial vascularization does not depend on SCs, its maturation as well as its limitation are modulated by SCs and myelin (Taib et al., 2022). Ablation of SCs at the immature stage or arrest of SC lineage progression at the pro-myelin stage leads to increased angiogenesis and a disorganized and disrupted endoneurial vasculature (Taib et al., 2022). SCs therefore not only participate in the formation of the endo- and perineurial nerve compartments, but also modulate its vascularization. The precise glial factors, however, that would limit angiogenesis inside the nerve remain to be identified.

2.4. Radial sorting

The organization of the nerve structure, together with the transition from SC precursors to immature SC and the formation of the basal lamina is followed by a process referred to as radial sorting (Feltri et al., 2016). During radial sorting, immature SC segregate large calibre axons from small calibre axons to achieve a 1:1 relationship between one proto-myelinating SC and one axonal segment. This process starts perinatally and continues until around day 10 in rodents, and was first characterized in 1973 by Webster and colleagues by performing serial reconstructions of electron micrographs (Webster et al., 1973). They observed that first, immature SCs subdivide axons into bundles surrounded by a group of 2–8 immature SCs and a common basal lamina (SC families). Then, immature SCs extend lamellipodia-like processes into the axon bundle, specifically detect and surround large calibre axons, segregate them to the periphery of the bundle and finally form a separate basal lamina around these axons, a process referred to as defasciculation. At this point, immature SCs proliferate to meet the cell numbers required for the establishment of a 1:1 relation with axons that finally will be myelinated. Timely cell division is critical for radial sorting, and premature exit from the cell cycle results in myelination of entire bundles of nonsorted axons (Porrello et al., 2014). Once all large calibre axons have been sorted (until around P15 in rodents), the remaining small calibre axons will be embraced by an immature SC that differentiates into a Remak SC (Feltri et al., 2016; Reed et al., 2021). To accomplish these morphological adjustments, immature SCs rely on the orchestration of several processes: (1) deposition of extracellular matrix components and the organization of the basal lamina, (2) establishment of SC polarity between the basal lamina and the axons, (3) cytoskeleton remodelling, and (4) recognition and interaction with axons, in addition to the above mentioned (5) proliferation, cell cycle exit and differentiation (Feltri et al., 2016; Monk et al., 2015).

Hence, a precise molecular regulation of immature SC function is required to successfully sort axons by their calibre and, next to SC expressed proteins, extracellular matrix molecules and signals from the basal lamina play a crucial role for the different, underlying cellular steps (for seminal reviews on this topic see Feltri et al., 2016; Monk et al., 2015; Previtali and Zambon, 2020). Of note, also mechanical stimuli have been identified to contribute to this process and revealed an essential role of mechanotransduction in SC development (Belin et al., 2017; Poitelon et al., 2016). Most likely, components of the extracellular matrix and basal lamina converge with axonal signalling molecules to control SC polarization and sorting, and many second messenger proteins are regulated by both extracellular matrix and axonally derived factors (Feltri et al., 2016; Fledrich et al., 2019a; Previtali, 2021). Notably, the maturation of SCs is not fully synchronized during the perinatal period and the steps described above occur simultaneously in a developing nerve, which hampers our understanding of the role of individual signalling molecules on each morphogenetic modification (Feltri et al., 2016). In line, in comparison to our knowledge of the molecular mechanisms that facilitate SC polarity and immature SC differentiation, the molecular control of fibre sorting and segregation itself remains less well understood.

Radial sorting is an absolute prerequisite for myelination and the formation of Remak bundles. Hence, SC dysfunction at this stage unequivocally results in alterations of nerve development and function. A common example of pathologies caused by defects in radial sorting are the so-called LAMA2-related neuropathies, which are caused by recessive mutations in the *LAMA2* gene, which encodes the $\alpha 2$ chain of laminin 211, an essential signalling protein present in the extracellular matrix during radial sorting. These mutations result in muscular dystrophy, dysmyelinating neuropathy, and brain abnormalities in human patients, emphasizing the crucial function of the extracellular matrix for nervous system development (Previtali, 2021; Previtali and Zambon, 2020).

2.5. Myelination

The acquisition of myelin constitutes a major evolutionary hallmark in vertebrates as it laid the anatomical basis for rapid nerve conduction. Before myelin evolved, axonal wrapping by ensheathing glia, as seen today, for example, in insects, already physically separated neighbouring axons to prevent electrical (ephaptic) coupling (Kottmeier et al., 2020; Nave and Werner, 2021). The development of actual myelin around axons increased the resistance and reduced the capacitance at the individual internode, thereby minimizing the current flow through internodal surfaces and allowing impulses to occur only at the exposed nodes of Ranvier. Restricted depolarization at a node increases the membrane charge and, upon reaching the depolarization threshold level, elicits depolarization at the neighbouring node, thereby allowing action potentials to jump from node to node, giving rise to fast saltatory impulse propagation (Cohen et al., 2020; Hartline and Colman, 2007; Tasaki, 1939). The electrophysiological properties of the axon are further determined by myelin quality parameters, such as thickness and length, and in healthy nerves the thickness of the myelin sheath is proportional to the axon calibre (Donaldson and Hoke, 1905; Fraher and Dockery, 1998). Indeed, computational analyses suggest that myelin sheath thickness within a specific g-ratio range (the ratio between inner axonal diameter and total outer myelin diameter) results in a maximized conduction velocity (R. S. Smith and Koles, 1970; Waxman, 1980). Likewise, internodal length is critical for optimal conduction velocity and nerve conduction speed is supposed to increase with internodal elongation until a “flat maximum” is reached, beyond which no further gains in conduction velocity will occur (M. H. Brill et al., 1977; Court et al., 2004; Huxley and Stämpfli, 1949; Michailov et al., 2004; Sherman and Brophy, 2005; Simons and Lyons, 2013; Waxman, 1980; Wu et al., 2012). Notably, the internodal capacitance per surface area decreases with increasing fibre diameter, and, consequently, myelin proportionally accelerates conduction velocities with increasing axon calibres. In contrast, in nonmyelinated axons, conduction velocity and axon calibre only maintain a square root relation (Moore et al., 1978).

In rodents, myelination takes several weeks to complete and starts in promyelinating SCs (but not Remak SC) after radial sorting, not earlier than at E19/20 in mouse (E21 in rat), and lasts until at least four weeks after birth (reviewed in Fledrich et al., 2019b; Jessen et al., 2015; Mirsky et al., 2002). Myelination is a complex process that requires the interplay of several inducers, signalling pathways, epigenetic and transcriptional factors to regulate the expression of the myelin-specific genes necessary to produce vast quantities of myelin proteins and lipids. Indeed, myelinating SCs increase their membrane surface area by several thousand fold (Birchmeier and Nave, 2008). Numerous studies have investigated the respective molecular actors that induce and regulate myelination on the DNA, RNA and protein level in SCs and we refer the reader to seminal review articles for detailed information on this topic (Arthur-Farraj and Moyon, 2020; Bolino, 2021; Duman et al., 2020; Monk et al., 2015; Salzer, 2015; Sock and Wegner, 2019; Svaren, 2014).

A threshold level of NRG1 type III on the axonal surface serves as an instructive signal for myelination, and determines the myelination fate of axons larger than 1 μ m in calibre in rodents (Taveggia et al., 2005). Serving as a surrogate marker for the axon diameter, the amount of axonal NRG1 type III also controls the extent of radial myelin growth and thus determines the resulting myelin thickness (Michailov et al., 2004). However, the correlation between internodal length and axonal diameter is less clear compared to myelin thickness. Also, internodal length is regulated independently of NRG1 type III (Michailov et al., 2004). Instead, mechanical stretching of nerves during body growth is thought to be conveyed as a signal to promote internodal growth, a process that is regulated at least in part by YAP/TAZ signalling and the Hippo pathway (Feltri et al., 2021; Fernando et al., 2016; Tricaud, 2018). In addition, disruption of the bands of Cajal, non-compact myelin domains that define the outer cytosolic network in myelinating SC,

results in shorter internodal length (Court et al., 2004), indicating that Cajal bands may also play a role in regulating internodal length.

In this context, it is important to note that myelin is not a simple insulating sheath but a highly organized structure. The compact myelin is flanked and interspaced by specialized non-compact myelin regions termed paranodal loops and Schmidt-Lanterman incisures, respectively (Fig. 1). These non-compact transverse domains connect the inner axonally oriented cytoplasmic SC lip with the above mentioned outer non-compact myelin domains (Cajal bands) that build an interface to the extracellular endoneurial environment. The function of the non-compact myelin domains is not yet entirely resolved but growing evidence suggest they may serve as transport routes for metabolites that would support axon function (Boucanova and Chrest, 2020; Nave, 2010; Shackleford et al., 2022; Stassart et al., 2018); a SC function that is discussed in more detail below.

2.6. Myelinating Schwann cells define several axonal compartments

Myelinated nerve fibres are compartmentalized structures comprising different domains which are defined during myelination by the interaction between the myelinating SC and the axon. Each SC wrapping around the axon defines the first domain; a segment of compact myelin referred to as the internode. The lateral edges of each SC membrane loop form finger-like structures called paranodal loops, which are bound together via tight, adherens and gap junctions and are attaching the underlying axonal membrane (*i.e.*, axolemma) via septate-like junctions. Furthermore, the lateral edges of the SC membrane also form microvilli, which face the node. The paranodal loops define three more axoglial domains: (1) the juxtaparanode, which is the portion of compact myelin immediately adjacent to the septate-like junctions, (2) the paranode, where the SC lateral edges attach to the axon, and (3) the node of Ranvier which is the space between two opposing paranodes from two consecutive SCs on the same axon. Each of these domains is characterized by the specific accumulation of structural proteins that consolidate the axoglial unit and organize voltage-gated ion channels in their correct position. 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 is most likely 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 the expression of the protein gliomedin in the microvilli of SCs, which interacts with axonal-membrane tethered proteins and the extracellular matrix to organize the nodal clustering of the voltage-gated sodium channels (Amor et al., 2014; Eshed et al., 2005, 2007; Feinberg et al., 2010; Labasque et al., 2011; Maertens et al., 2007). In addition, various anchoring molecules as well as the paranodal-axonal transverse bands (forming septate like junctions) restrict electrical activity to the nodal compartment and hinder the lateral diffusion of axonal membrane proteins (Rosenbluth, 2009; for more details on the molecular players see Duménieu et al., 2017; Poliak and Peles, 2003; Rasband and Peles, 2021; Salzer, 2003; Salzer et al., 2008).

Myelination also induces a substantial remodelling of the axonal cytoskeleton, which comprises small actin filaments, large microtubules with microtubule-associated proteins, and intermediate-sized neurofilaments (Stassart et al., 2018). Accordingly, in the internode there are less microtubules and less densely packed but more phosphorylated neurofilaments than in the node, leading to a narrowing of the axon's diameter at the node (Reles and Friede, 1991).

The most critical physical determinant of the calibre of a mature axon is the expression and phosphorylation status of its medium neurofilaments (reviewed by Garcia et al., 2003; Kirkcaldie and Dwyer, 2017; Rao et al., 2003) and mouse models with neurofilament-deficient axons are characterized by reduced mature axon calibres and decreased conduction velocities (Cleveland et al., 1991; Sakaguchi et al., 1993). First evidence that axonal calibre is locally defined by the myelinating SC arose from graft experimental studies in the dysmyelinating

"Trembler" mouse, which showed that regions with abnormal myelination were associated with changes in axonal calibre (de Waegh et al., 1992). To regulate axonal calibre, the myelinating SC promotes neurofilament accumulation and spacing in the axonal cytoplasm, which has been supposed to be mediated via a slowing of axonal transport as well as by increased neurofilament phosphorylation (Hsieh et al., 1994a, 1994b; Monsma et al., 2014; de Waegh et al., 1992; reviewed in Martini, 2001). In line, the non-myelinated stem process of DRG neurons contains less phosphorylated and more densely packed neurofilaments compared to the more distal, myelinated large calibre axons (Hsieh et al., 1994b; Martini, 2001). The same characteristics also hold true for the node of Ranvier, which is also characterized by a reduced axonal diameter (Mata et al., 1992). Interestingly, mice deficient for the myelin protein MAG display fully myelinated axons but show decreased axon calibres along with changes in neurofilament phosphorylation and spacing (Dashiell et al., 2002; Hsieh et al., 1994a; Kumar et al., 2002; Pan et al., 2005; Yin et al., 1998). Hence, SC-driven cytoskeletal changes are likely not dependent on the myelin sheath itself, but mediated by still poorly understood signalling mechanisms, which may partially involve MAG as well as other, unknown molecular players. Notably, the Trembler mouse mutant was also shown to be characterized by an altered stability, composition and phosphorylation of axonal microtubules (de Waegh et al., 1992; Kirkpatrick and Brady, 1994; Sahenk and Brady, 1987), however, the role of Schwann cells for axonal microtubule characteristics also remains poorly defined.

A glial protein that limits axonal radial growth has recently been identified, CMTM6, which localizes to the adaxonal membrane. Accordingly, conditional ablation of the SC expressed CMTM6 resulted in increased axonal calibres (Eichel et al., 2020). Interestingly, CMTM6 appears to function independently of both neurofilament phosphorylation and MAG, and considering the periodic distribution of CMTM6 in the adaxonal SC membrane, the authors speculate that SC may restrict secondary axonal growth via axonal actin/spectrin rings (Eichel et al., 2020). Finally, myelinating SC also contribute to axonal transport, as again first shown by graft experiments in the Trembler mouse mutant (de Waegh et al., 1992; Kirkpatrick and Brady, 1994). Subsequent studies in the CNS suggest that this may likewise be a glial function independent of myelin itself (Stassart et al., 2018), and may be linked to glial metabolic support.

2.7. Metabolic support to the axon

The continuous firing of axons requires vast amounts of energy. Given that peripheral nerve axons can reach meters in length in larger mammals, the distance from their cell bodies keeps axons critically dependent on local energy supply. Metabolite provision from the extracellular milieu, however, is hampered by myelin ensheathment which limits exchange to exposed axonal areas such as the nodes of Ranvier (Nave, 2010). Therefore, metabolic supply by myelinating SC is highly likely and a growing body of data suggest that this is indeed the case. In the CNS, myelinating oligodendrocytes can cope with their own and axonal energy needs solely by glycolysis when mitochondrial respiration is inhibited (Fünfschilling et al., 2012). Together with the finding that disruption of monocarboxylate transporter 1 (MCT1), expressed by oligodendrocytes, led to progressive axonal deterioration (Y. Lee et al., 2012), these data suggest that lactate produced in oligodendroglial glycolysis is transported towards axons to maintain axonal energy homeostasis. In the PNS, however, axo-glial metabolism is less well understood. Several studies have shown that interfering with mitochondrial homeostasis in SC during development is not tolerated and results in developmental sorting problems and dysmyelination, but also in malformation of Remak SC (Beirowski et al., 2014; Fünfschilling et al., 2012; Pooya et al., 2014; Viader et al., 2011, 2013). It is therefore difficult to untangle the primary glial pathology from potential specific defects in axonal support. Studies that would allow a comparison with the CNS findings would need to target mitochondrial respiration only

after the completion of glial differentiation. In contrast to oligodendrocytes, SC are rich in glycogen granules, and *ex vivo* electrophysiological studies have shown that aglycemic nerves develop conduction failure which is prevented when glucose or lactate is added to the media (Brown et al., 2012; Véga et al., 2003). However, conditional knock-out studies have clearly shown that glial glucose import via GLUT1, lactate transport to axons via glial MCT1 or even glycolysis in SC are all neither essential for myelination nor for axonal integrity (Babetto et al., 2020; Jha et al., 2021). SC *Mct1* deficient mice show only a mild phenotype in aged sensory fibres that are engulfed by non-myelinating Remak SC. It is hence likely that axo-glial energy metabolism is secured by multiple molecular routes and may be difficult to unravel by single target approaches.

2.8. The formation of Remak bundles

Remak SC are non-myelinating SCs and ascend from immature SC by unknown mechanisms. However, cross-graft experiments between myelinated and non-myelinated nerves provided proof that the glial myelination fate is, at least in part, determined by the axon (Aguayo et al., 1973, 1976). In line, NRG1 type III expression by sensory axons is needed for Remak Schwann cell differentiation (Fricker et al., 2009; Taveggia et al., 2005). Remak SCs accommodate and separate several small-diameter axons in shallow troughs along their surface (Jessen and Mirsky, 1999) and wrap them together in one bundle (so-called Remak bundle). These axons typically belong to sensory C fibres and post-ganglionic sympathetic and parasympathetic fibres (Birchmeier and Nave, 2008). The number of ensheathed axons per Remak SC is highly variable, ranges between 1 and ~50, and differs between nerves and even within the longitudinal dimension within the same nerve (Muirnson and Griffin, 2004). Typical Remak bundle pathologies appear as incomplete enwrapping of individual fibers and multiple axons within individual Remak SC pockets (Harty and Monk, 2017). Like myelinating SC, also Remak SC are essential for maintaining axonal integrity and their ablation leads to impaired thermoreception and ultimately loss of sensory axons and neurons (S. Chen et al., 2003; McFerrin et al., 2017). A role of Remak SC in sensory perception (next to specialised SC in the skin, see below) may be suggested by mutants with conditional ablation of *Gabbr1*, where an increased Remak fiber density led to mechanical and thermal allodynia (Faroni et al., 2014). However, direct modulation of sensory information by Remak SC that reside in the nerve (and not at the terminals) remains to be proven. In comparison to myelinated fibres, axons that are engulfed by Remak SCs appear particularly prone to degeneration in mutants where mitochondrial metabolism is disturbed (Beirowski et al., 2014; Pooya et al., 2014; Viader et al., 2011). The predominant sensory phenotype in peripheral neuropathies that result from systemic metabolic alterations may therefore be the consequence of a higher metabolic vulnerability of Remak compared to myelinating SCs.

3. Schwann cell functions in nerve repair

A physical trauma to peripheral nerves induces a sequence of de- and regenerative events that are associated with dramatic changes in nerve architecture, cellular composition and signalling. SC respond to nerve injury with a remarkable cellular plasticity and phenotype adaptation, by which they acquire a new set of cell autonomous and non-cell autonomous functions essential for nerve repair. Indeed, SC play a fundamental role for both, nerve degeneration and regeneration and orchestrate the multicellular microenvironment to promote peripheral nerve repair (Jessen and Mirsky, 2016). Moreover, nerve associated SCs participate in repair processes in other tissues, such as skin wound healing (Parfjejevs et al., 2018), mandibular bone repair (Jones et al., 2019) and regeneration of digit tips (Johnston et al., 2016). For more details on SC in non-neuronal tissue repair, we refer the readers to a respective review on this topic (Stierli et al., 2019). Recently, repair-like

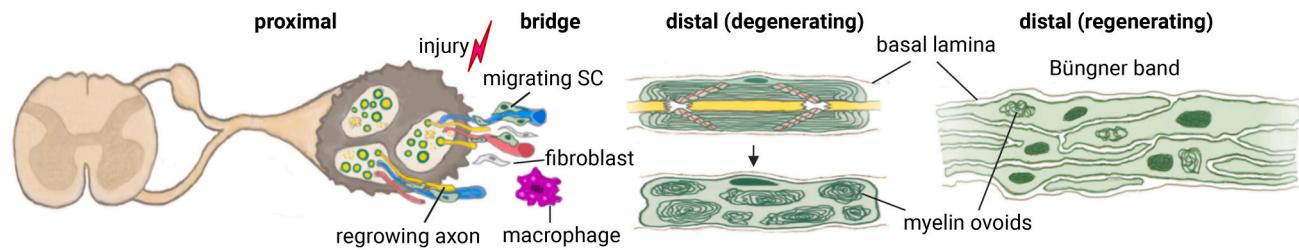
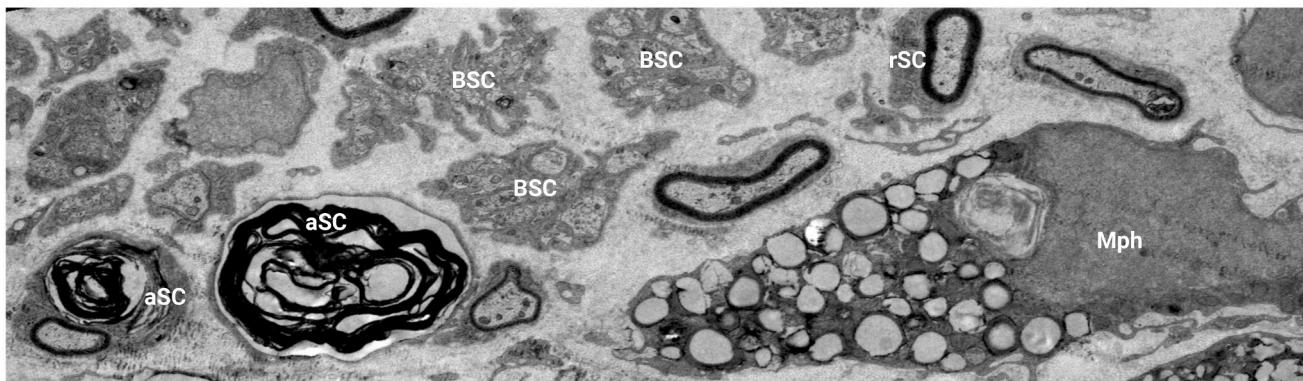
SC have also been shown to serve as guidance tracks for pancreatic tumor cells (Deborde et al., 2022).

An acute injury to the nerve is either the consequence of a neurotmesis (nerve cut) or axonotmesis (nerve crush) (Seddon et al., 1943) and results in a sequence of events referred to as Wallerian degeneration, which comprises the degeneration of the nerve distally from the injury site (*i.e.*, distal stump) and the subsequent clearance of axonal debris (Waller, 1851). In contrast to axons, SC do not degenerate, but transdifferentiate from mature myelinating and non-myelinating SC into an immature-like state - the repair SC. The process of transdifferentiation has been profoundly studied in the past decade and is now understood as a complex adaptive cellular reprogramming process (see Jessen and Arthur-Farrag, 2019; Jessen and Mirsky, 2016; Mirsky et al., 2002 for seminal reviews). The generation of the repair SC is associated with the induction of specific transcription factors, signalling pathways and genes that regulate and control nerve repair (Nocera and Jacob, 2020; Sock and Wegner, 2019). Importantly, the molecular changes of SC precede the morphological fragmentation of axons, however, the mechanisms that are responsible for the initiation of the SC repair response are still unknown (Arthur-Farrag and Coleman, 2021).

As a result of adaptive cellular reprogramming, repair SCs re-enter the cell cycle to proliferate, phagocytose axonal and myelin debris and coordinate the recruitment of immune cells into the injury site (Jessen and Mirsky, 2016). In case of a nerve cut injury, the first and essential process is the bridging of the gap between the proximal and the distal nerve stump, which requires shared labour of SCs together with macrophages, fibroblasts, and endothelial cells (Cattin and Lloyd, 2016; Clements et al., 2017; Dun et al., 2019; Y. Li et al., 2022). In order to facilitate axonal regrowth, SCs in the distal stump adopt an elongated shape and form long columns, the so-called Bands of Büngner, which serve as guidance cues for regrowing axons. Ultimately, SC redifferentiate and remyelinate newly regrown axons and hence contribute to the restoration of nerve function (Fig. 2). Notably, in chronic nerve injury and peripheral neuropathies this sequence of events often fails, and shared glial pathomechanisms may contribute to permanent impairment in these diseases (Stassart and Woodhoo, 2021). In the following sections, we will describe and discuss the most relevant functions of SCs during in acute nerve injury and repair.

3.1. Schwann cell function in Wallerian degeneration and debris removal

Acute axonal injury activates a series of molecular events that lead to the rapid disintegration of the distal nerve stump during the first days after injury. In the last decade, substantial progress has been made in our understanding of the axonal molecular mechanisms that drive Wallerian degeneration, and indeed, the initiation of axon degeneration appears to be mainly axon intrinsic (Arthur-Farrag and Coleman, 2021; Coleman and Höke, 2020). Interestingly, *in vitro*, the presence of SCs alone is sufficient to substantially delay the disintegration of severed axons, which has been suggested to be mediated via an induction of axo-protective metabolic processes (Babetto et al., 2020). Importantly, however, upon committed degeneration, SCs furthermore actively participate in promoting the fragmentation of axons and the breakdown of myelin sheaths. In detail, in the first 2–3 days post injury, Schmidt-Lantermann incisions increase in size (Catenaccio et al., 2017; Ghahreman and Allt, 1979; Jung et al., 2011) and protrude into the axons, leading to axonal segments encapsulated within the inter-incisure myelin fragment (Catenaccio et al., 2017). As these events overlap on molecular level with cellular cytokinesis, the respective process has been suggested to be termed “axokinesis” (Catenaccio et al., 2017). In line, Vaquie and colleagues demonstrated *in vitro* using microfluidic devices that repair SC form constricting actomyosin spheres along not yet fragmented axons distal to the cut, thereby accelerating their disintegration (Vaquie et al., 2019). Notably, the authors found this process to be initiated by a local translation of *Plgf* in the injured axon, which activates the VEGFR1 receptor in SCs. Indeed, *Vegfr1* ablation in SC impaired the formation of

Nerve repair**EM distal nerve****SC function****Autophagic SC**

- axonal fragmentation
- myelin autophagy
- macrophage recruitment

**Büngner SC**

- Büngner band formation
- guidance of regrowing axons

**Remyelinating SC**

- Remyelination
- Re-establishment of myelin functions

Fig. 2. Schwann cells play a key role in peripheral nerve repair after acute nerve injury. In case of nerve transection, SC migrate into the bridge area between proximal and distal nerve stumps. In the bridge, SC interact with fibroblasts, macrophages and blood vessels to facilitate axonal regrowth. In the distal nerve environment (irrespective of the type of injury, crush or cut), SCs transdifferentiate into repair SCs. Initially, these repair SCs aid in the fragmentation of damaged axons into smaller segments by actin constrictions (red) at sites of non-compact myelin. Next, SC perform myelin autophagy and recruit macrophages to the damaged site. Subsequently, SCs proliferate and (within the original basal lamina tubes) align in the bands of Büngner, which provide essential physical tracks for regrowing axons. Finally, SCs remyelinate regrown axons and thus re-establish the functions of a myelinating or Remak SC. The electron micrograph depicts the different functions of SCs during nerve repair: autophagic SCs (aSC), Büngner SC (BSC) and remyelinating SC (rSC). A recruited macrophage (Mph) can also be observed.

actin constriction after nerve injury and slowed nerve repair (Vaquie et al., 2019). Likewise, debris clearance rates have also been shown to depend on the axon fragment size in zebrafish, (Martin et al., 2010) and zebrafish embryos lacking SCs present fewer axonal fragments (Villegas et al., 2012), further demonstrating the active role of SCs in axonal fragmentation (Gonzalez and Allende, 2021).

Next to axonal fragmentation, repair SCs are estimated to be responsible for about 50% of the total myelin debris removal during nerve degeneration and in the first few days after injury, SCs appear to be solely responsible for myelin breakdown and degradation (Perry et al., 1995). Subsequently, resident and infiltrating macrophages contribute to myelin phagocytosis and degradation (Perry et al., 1995). Schwann cell myelin degradation is performed by process termed myelinophagy, which represents a form of selective autophagy and occurs both after nerve crush and cut injury (Brosius Lutz et al., 2017; Gomez-Sanchez et al., 2015; Jang et al., 2016; Reed et al., 2020). In detail, SCs first internalize their own myelin sheath and broken myelin debris is subsequently sequestered by a double membrane autophagophore and delivered into lysosomes for degradation (Jung et al., 2011). At later stages, smaller myelin debris fragments are exposed to the external environment by repair SCs and can subsequently be phagocytosed by infiltrated macrophages or by phagocytosing repair SCs (Brosius Lutz et al., 2017; Hirata and Kawabuchi, 2002). Interestingly, repair SCs upregulate the TAM phagocytic receptors *Axl* and *Mertk* following nerve damage, which allow them to engulf extracellular myelin debris

(Brosius Lutz et al., 2017), while macrophages appear to rather depend on opsonisation of myelin debris by complement component 3 (C3) and the macrophage receptor complement receptor 3 (CR3) (Brück and Friede, 1990). Notably, SC have also been shown to employ the MLKL pseudokinase, known to rupture cell membranes during necroptotic cell death, to promote myelin breakdown (Ying et al., 2018).

However, while the *in vivo* ablation of genes implicated in myelinophagy or phagocytosis all resulted in a delay of myelin clearance, they did not prove limiting for peripheral nerve repair (Brosius Lutz et al., 2017; Gomez-Sanchez et al., 2015; Jang et al., 2016; Reed et al., 2020; Wang et al., 2018). Hence, compensatory SC-intrinsic mechanisms as well as a takeover of myelin degradation by macrophages and potentially other phagocytosing endoneurial cells (Schubert and Friede, 1981) may account for the surprisingly mild phenotypes of respective mouse mutants.

Together, efficient myelin debris removal is believed to be a major premise for subsequent successful axonal growth, and several proteins present in myelin debris are inhibitory for axon growth and may contribute to a non-permissive environment for nerve repair (Bähr and Przyrembel, 1995; Gitik et al., 2011; H. Kang and Lichtman, 2013; McKerracher et al., 1994; Mukhopadhyay et al., 1994; Schäfer et al., 1996; Shen et al., 1998).

3.2. Recruitment and orchestration of the immune response

Nerve injury is associated with an activation of the immune response and an infiltration of different immune cells into the distal stump, including not only macrophages and monocytes, but also mast cells, neutrophils, B cells, T-cells, and natural killer cells (Carr et al., 2019; Lindborg et al., 2017; Martini et al., 2008; Rotshenker, 2011). Repair SCs promote the recruitment and activation of immune cells to the injured tissue via an upregulation of different cytokines and chemokines (Boerboom et al., 2017; Jessen and Mirsky, 2019a; Zigmund and Echevarria, 2019). Particularly, repair SC secrete CCL2 (*i.e.*, MCP-1), which has been suggested to be a major chemoattractant for the recruitment of blood-derived macrophages (Klein and Martini, 2016), although a recent study with a conditional ablation of CCL2 in SC did not detect differences in macrophage infiltration after injury and hence challenges this view (Talsma et al., 2022). However, the presence of and the debris removal by macrophages is essential for efficient nerve repair (Barrette et al., 2008). Recruited immune cells proliferate and respond to the type of injury, and subsequently further secrete inflammatory factors that are also important for nerve repair. Accordingly, proper redifferentiation of repair SC depends on macrophages (Stratton et al., 2018). SC also express toll-like and cytokine receptors (*e.g.*, for TNF- α , LIF and IL-6), which continuously allows them to respond and adapt to the inflammatory milieu (Gaudet et al., 2011; Ozaki et al., 2008; Tzekova et al., 2014; S. H. Zhang et al., 2020). Moreover, repair SC can express genes of the human leukocyte antigen (HLA) system corresponding to molecules of both the major histocompatibility complex (MHC)-I and -II, which has been shown to contribute to T-cell infiltration in a chronic nerve trauma model (Hartlehnert et al., 2017; Meyer Zu Hörste et al., 2010). However, many of the precise molecular interactions between repair SC and immune cells for debris clearance and nerve regeneration remain to be explored.

3.3. The formation of the nerve bridge

In injury cases characterized by a complete transection of the nerve, the proximal and distal stumps are completely separated. For the nerve to regenerate, the formation of a new tissue that reconnects both ends is required. This tissue is called bridge, and it provides a multicellular, initially hostile and nondirectional environment through which regrowing axons need to migrate towards the distal stump (Stierli et al., 2019). Inflammatory cells along with fibroblasts are key initial players in the formation of the bridge. In response to hypoxia, which characterizes the initial bridge tissue, macrophages secrete VEGF which recruits endothelial cells to form a polarized vasculature. The blood vessels are then used by migrating bridge SCs as a track to carry regrowing axons across the bridge (Cattin et al., 2015). Indeed, repair SCs collectively migrate from both tips of the severed stump to infiltrate the bridge (Clements et al., 2017; Parrinello et al., 2010), where they form SC cords to reunite the transected nerve stumps (Cattin and Lloyd, 2016; Jessen and Mirsky, 2019a). The critical value of bridge SCs for axonal regeneration is furthermore illustrated by studies demonstrating that, in the context of nerve transection injuries, regenerating axons lose their directionality and travel along ectopic trajectories if SCs are not present (Dun et al., 2019; Rosenberg et al., 2014). Although several SC-derived signals might participate in the guidance of axons (Min et al., 2021), specific signals that guide axon processes through the bridge tissue have only started to be identified. For instance, in zebrafish models, Netrin1 released by SCs seems to interact with the Netrin1 receptor DCC on regenerating motor axons and direct them toward the correct trajectory across the bridge site (Rosenberg et al., 2014). Vice versa, SCs neighbouring the transection site induce axon destabilisation via expression of collagen4a5 (Isaacman-Beck et al., 2015). Taken together, the repair SC in the bridge acts in a complex cellular interplay in order to invade into the wound microenvironment and to promote axonal regeneration and is hence characterized by specific functions and

cellular interactions. In line, bridge SCs have been shown to be transcriptionally different from repair SC in the distal stump, and to display a strong upregulation in genes involved in cell division, growth, and metabolism (Clements et al., 2017). Furthermore, bridge SCs presented a higher expression in several epithelial-to-mesenchymal transition genes, which has been suggested to reflect the proliferative and invasive role of bridge SCs in early phases after injury (Clements et al., 2017).

3.4. The formation of Büngner bands and axonal regeneration in the distal stump

In the distal stump, once axons and their myelin have degenerated, the emptied endoneurial basal lamina tubes persist and aid in the formation of the Büngner bands by repair SC. Büngner bands were described by Otto von Büngner in the late 19th century as longitudinal cell columns formed by SCs within the original basal lamina tube extending from the injury site to the target tissue (Büngner, 1891). Modern fate mapping experiments revealed that Büngner bands are formed by both Remak and myelinating SCs (Gomez-Sánchez et al., 2017). Interestingly, SCs substantially elongate during the formation of the Büngner bands, and overlap toward the end of their extended processes, thereby forming physical lanes within the basal lamina for guidance of regrowing axons (Gomez-Sánchez et al., 2017). Importantly, mouse mutants with a compromised formation of Büngner Bands suffer from impaired axonal regeneration (Jessen and Mirsky, 2019a; Scheib and Höke, 2016). Indeed, mice with an ablation of *c-Jun*, an essential transcription factor for SCs to acquire the repair phenotype, show flattened and abnormal Bands of Büngner, and are characterized, among others, by defective axonal regeneration (Arthur-Farraj et al., 2012; Fontana et al., 2012).

Notably, regenerating axons that accidentally leave the bands of Büngner are likely to stop growing after only a few millimetres within the directly surrounding connective tissue (Ide, 1996; Ramón et al., 1928; Ribeiro-Resende et al., 2009). Next to the provision of physical guidance cues, SCs contribute to the axonal regrowth by the secretion of pro-regenerative factors. For instance, *c-Jun* SC conditional knockout mice are characterized by a decreased expression of proteins such as GDNF, artemin, p75^{NTR} and N-cadherin, which have been implicated in axonal growth (Arthur-Farraj et al., 2012; Fontana et al., 2012; Jessen and Mirsky, 2022). Further insights into the relevance of endogenous neurotrophic factors for axonal regeneration are derived from studies that ablated neurotrophic factor signalling *in vitro* as well as *in vivo*, or, vice versa, from studies that demonstrated improved axonal regeneration upon a treatment with neurotrophic factors after injury. Many such studies have been performed in the field and have been extensively reviewed (Allodi et al., 2012; Boyd and Gordon, 2003; Contreras et al., 2022; Gordon, 2009). Nevertheless, the role of endogenous, SC-derived neurotrophic factors is only partially resolved, especially considering that damaged neurons, and potentially also other cell types within the injured nerve microenvironment, express neurotrophic factors that are likely to contribute to axonal regeneration (Gordon, 2009). Nevertheless, the usage of SC-derived factors as a therapy in cases of SC-caused regeneration failure may be interesting, and GDNF and Artemin have been shown to partially rescue axonal regeneration in mice with a compromised repair SC phenotype due to *c-JUN* ablation (Fontana et al., 2012). In addition, glial p75^{NTR} expression has been implicated in nerve regeneration and grafting experiments with p75^{NTR} knockout SCs revealed a reduced neuronal survival after injury (Gonçalves et al., 2019; Song et al., 2006; Tomita et al., 2007). Notably, also *cJun* mutants demonstrate an increased neuronal death after injury, however, a better understanding of whether and how repair SC provide direct trophic support to neurons whose axons have been injured is needed (Arthur-Farraj et al., 2012; Fontana et al., 2012).

Furthermore, repair SC have been suggested to contribute to the specificity of axonal regeneration and the correct pathfinding of motor and sensory axons towards their original targets. Indeed, the secretion of

neurotrophic factors by SCs has been shown to depend on their localization and repair SCs may keep a molecular identity depending on their motor or sensory specification (Brushart et al., 2013; Contreras et al., 2022; Höke et al., 2006; Martini et al., 1992, 1994; Tham et al., 1997). However, the interpretation of many of these findings is complex and further studies are required to better understand the role of SC for selective axonal pathfinding and regeneration (Bolívar et al., 2020; Brushart et al., 2013; Contreras et al., 2022). Notably, in zebrafish mutants lacking SCs, regenerating axons grow at similar rates to wild types despite following erroneous paths (Rosenberg et al., 2014), suggesting that SCs might be rather involved in the guidance of regrowing axons than in the regulation of their growth rate (Gonzalez and Allende, 2021). Indeed, SC-derived signals, including the glycosyltransferase IH3, an enzyme involved in collagen and ECM modification, have been shown to promote target selective regeneration of axons after injury in zebrafish (Isaacman-Beck et al., 2015; Murphy et al., 2022). In addition, several studies have focused on the role of exosomes secreted by SCs for axonal regeneration. *In vitro*, an uptake of SC-derived exosomes by DRG neurons has been described, and a treatment of injured nerves with glial exosomes enhanced axonal regeneration *in vivo* (Lopez-Verrilli et al., 2013; Lopez-Verrilli and Court, 2013). Indeed, SC exosome cargos have been shown to change along with the acquisition of the SC repair phenotype to specifically modulate axonal growth properties (Ching et al., 2018; López-Leal et al., 2020; Strickland et al., 2011; Wei et al., 2019).

Notably, whether repair SC also contribute to the trophic support of axons during nerve regeneration remains unresolved so far. Indeed, while lactate transport through MCT1 has previously been shown to contribute to nerve repair in full *Mct1* knockout mice (Morrison et al., 2015), a recent study in which *Mct1* was deleted specifically in SC demonstrated glial *Mct1* expression to be dispensable for functional nerve recovery after injury. Instead, this study found that MCT1 is needed by macrophages for optimal nerve repair (Jha et al., 2021).

3.5. Remyelination

SCs eventually enwrap successfully regrown axons with a new myelin sheath. However, remyelinated internodes remain thinner and significantly shorter compared to developmental myelination, leading to an incomplete restoration of nerve function after injury (Schröder, 1972). In order to complete remyelination, SCs need to redifferentiate into myelinating SCs, which is associated with a downregulation of repair SC genes and a concomitant induction of the genes responsible for SC differentiation and myelin synthesis (Fazal et al., 2017; Jessen and Mirsky, 2019a, 2022; Kim et al., 2018). Although many factors and signalling pathways implicated in developmental myelination also contribute to remyelination after peripheral nerve injury, the latter is not a simple recapitulation of peripheral nerve development (Chen et al., 2007; Jessen and Mirsky, 2019a). For instance, in stark contrast to developmental myelination (Michailov et al., 2004; Taveggia et al., 2005), remyelination has been suggested to occur also in the absence of axonal NRG1 signalling after injury, although a transient impairment with thinner and unmyelinated axons has been observed (Fricker et al., 2011, 2013). Nevertheless, axonal NRG1 is able to promote SC redifferentiation and remyelination, and neuronal *Nrg1* overexpression in mice can, in principle, restore myelin sheath thickness of remyelinated axons (Stassart et al., 2013). However, whether altered axon-glia signalling or other alternative mechanisms are responsible for the reduced myelin sheath thickness after nerve injury remains unknown. Importantly, another key difference to developmental myelination is the lack of concomitant body growth, which may, at least in part, explain the insufficient myelin elongation by remyelinating SC after injury (Feltri et al., 2021; Fernando et al., 2016; Tricaud, 2018).

In addition, remyelination efficiency may depend on the permissiveness of the microenvironment, and vice versa, remyelinating SCs start to emerge as active regulators of the resolution of the injury tissue

environment. For instance, a recent study has implicated SC in regulating fibrinolysis via ADAM17 and p75^{NTR} processing, and glial ADAM17 ablation in mice impaired remyelination after injury (Pellegratta et al., 2022). Also, newly synthesized myelin protein MAG has been shown to contribute to macrophages efflux out of the SC basal lamina and into the endoneurial space after injury, although it remains unclear whether this is associated with the migration of macrophages out of the damaged nerve and contributes to inflammation resolution (Fry et al., 2007). However, in contrast to the early phases of nerve injury, the role of SC in regulating the tissue environment during the late phase of peripheral nerve repair are less understood.

3.6. Challenges in peripheral nerve repair

In summary, SCs are of paramount importance for peripheral nerve repair, and the plasticity of SC along with the acquisition of the SC repair phenotype are remarkable (Jessen and Arthur-Farraj, 2019; Jessen and Mirsky, 2016, 2019a). However, many functions of SCs in response to acute nerve injury still remain poorly understood. This holds especially true for their precise molecular role in neuronal survival, axonal regeneration, as well as for a potential trophic support function. Also, although much progress has been made to our understanding of the multicellular environment of the bridge, many aspects of the interaction of SCs with other cell types within the injured nerve during the different phases of nerve de- and regeneration remain to be investigated. Importantly, the specialized pro-regenerative functions of SCs during nerve repair may be restricted to a particular time window and prolonged, chronic nerve injury constitutes a common and severe problem in peripheral nerve injury in humans (Höke et al., 2006; Höke and Brushart, 2010; Jessen and Mirsky, 2019a; Terenghi et al., 1998). In line, the temporal dynamics of nerve regeneration show relevant differences between the rodent (4.5 mm/day) and the human peripheral nerve (1–1.5 mm/day) (Berenberg et al., 1977; Brushart et al., 2002; Gordon, 2016; Meyer Zu Reckendorf et al., 2020; Seddon et al., 1943). Furthermore, human nerve pathology more commonly presents with full nerve transection and is often characterized by long distances between the two stumps, which hampers the formation of the nerve bridge. Moreover, the distal nerve environment may contribute to peripheral nerve regeneration outcome, as suggested by cross suture experiments (Fu and Gordon, 1995; Holmes and Young, 1943; Sulaiman and Gordon, 2000). Indeed, with time, the elicited repair SC response may lose momentum and a fading of the molecular repair phenotype, a decreased expression of growth factors necessary for axonal regeneration as well as drop in the numbers of repair SCs may be responsible for the failure of regeneration in chronically injured nerves (Benito et al., 2017; Höke et al., 2002; Jessen and Mirsky, 2019a; Wagstaff et al., 2021).

4. Glial cell function at specific localizations in the peripheral nervous system

Next to their essential role in peripheral nerve development and their function as myelinating and non-myelinating cells in close apposition to axons, SCs are able to differentiate into specialized glia with distinct functions, such as terminal SCs at both NMJs and sensory end organs. Furthermore, neural crest derived cells give rise to satellite glia cells around sensory and autonomic neurons. In addition, enteric glial cells originate from neural crest cells and are important constituents of the enteric nervous system. Often, the function of these glial cell types is less well understood compared to their counterparts within the long peripheral nerves. Here, we provide an overview of the known roles of terminal SCs at the NMJ and in the skin and discuss the function of satellite and enteric glial cells. For the role of SCs in the CNS, as well as for olfactory ensheathing cells, we refer the reader to respective reviews on this topic (Chen et al., 2021; Reed et al., 2021; Stierli et al., 2019; Ursavas et al., 2021).

4.1. Terminal Schwann cells at the neuromuscular junction

Terminal SCs are specialized non-myelinating SCs that are tightly engaged either as perisynaptic SCs at the NMJ, or as terminal SCs around cutaneous sensory end organs. In the motor system, perisynaptic SCs participate in the development, the functional maintenance, and the repair of the NMJ (Ko and Robitaille, 2015). Perisynaptic SCs can be identified and distinguished from mature myelinating SCs by the co-expression of S100 and NG2 (Castro et al., 2020) and, in mammals, typically 3-5 perisynaptic SCs are closely associated with both the pre- and the postsynaptic components of the NMJ (Darabid et al., 2014; Griffin and Thompson, 2008; Jordan and Williams, 2001; Ko and Robitaille, 2015; Lubischer and Bebinger, 1999). As discussed above, in development, capping SCs around axonal growth cones contribute to axonal pathfinding but are not essential for establishing the initial contact between the axons and the target muscles (Grim et al., 1992; Lin et al., 2000; Morris et al., 1999; Riehmacher et al., 1997; Woldeyesus et al., 1999). However, the subsequent growth and functional maintenance of the synapse is critically dependent on perisynaptic SCs (Griffin and Thompson, 2008; Lubischer and Thompson, 1999). Here, phagocytosing perisynaptic SCs contribute to the elimination of all but one axon terminals from polyneuronally innervated NMJs, which typically occur during mammalian neonatal development (Brill et al., 2011; Lee et al., 2016; Smith et al., 2013). Individual perisynaptic SCs are thereby able to sense the activity of the competing axons (Darabid et al., 2013) but it is still unclear whether they also contribute to the decision of which of the axons ultimately prevail in long term synapse formation.

Next to providing trophic support toward the NMJ and their role in guidance of axonal (re-) innervation and synaptogenesis, perisynaptic SCs also detect and modulate neuromuscular transmission itself (Ko and Robitaille, 2015). The ability to sense and decode synaptic activity is not restricted to development, but is also a feature of adult perisynaptic SC which is realized by intracellular Ca^{2+} signalling downstream of G-protein coupled (Jahromi et al., 1999; Reist and Smith, 1992), muscarinic (M1, M3 or M5; Wright et al., 2009) and purinergic (adenosine A1; Rochon et al., 2001) receptors (GPCRs). In amphibians, GPCR activation in perisynaptic SC has a negative impact on synaptic transmitter release, whereas GPCR inhibition prevented this synaptic depression (Robitaille, 1998). On the other hand, Ca^{2+} chelation in perisynaptic SC has been shown to dissolve synaptic potentiation (Castonguay and Robitaille, 2001), demonstrating that “perisynaptic SC” can both decrease and increase synaptic activity. The type of modulation has been shown to be influenced by the pattern of synaptic firing resulting in distinct “perisynaptic SC” calcium kinetics and an ATP release from perisynaptic SC (Todd et al., 2010). In addition, perisynaptic SC may also release a number of other neuromodulatory molecules, including glutamate, nitric oxide and prostaglandines (Ko and Robitaille, 2015).

After nerve injury, perisynaptic SC emanate long sprouts that can form bridges between neighbouring NMJs (Son and Thompson, 1995). Upon reinnervation, axons can pass these bridges and innervate adjacent endplates (Kang et al., 2003; Love and Thompson, 1999; Reynolds and Woolf, 1993; Son and Thompson, 1995). Perisynaptic SCs have also been shown to promote the functional recovery of injured NMJs via secretion of CXCL12 α and an interaction with CXCR4 on axon terminals (Negro et al., 2017). In line, the ablation of perisynaptic SC in mice impaired the remodelling of the neuromuscular junctions after injury, and limited reinnervation (Hastings et al., 2020). Notably, a recent study demonstrates that injury induced functional changes of perisynaptic SC, assessed as reduced mAChR-mediated Ca^{2+} responses by perisynaptic SC persist for at least 60 days after injury (Perez-Gonzalez et al., 2022).

4.2. Schwann cells of the skin

Schwann cells of the skin are neural crest derived and also originate from boundary-cap cells, the latter giving rise to SC associated with dermal nerve fibers, lanceolate sensory endings around hair follicles and

free nerve endings (Gresset et al., 2015; Radomska and Topilko, 2017). Boundary cap derived SCs in the skin retain furthermore a multipotent capacity and represent a major stem-cell like population in the dermis (Gresset et al., 2015; Radomska and Topilko, 2017).

In general, SCs of the skin accompany the large network of axons within the superficial dermis, that extends into the epidermal layer. While a part of these fibers are myelinated, the majority of axons in the skin is unmyelinated. SC are also associated with the low threshold mechanoreceptors referred to as Meissner, Pacinian and Ruffini corpuscles in the glabrous skin as well as with lanceolate mechanosensors and Merkel's disks at the hair follicle (Handler and Ginty, 2021; Li and Ginty, 2014). Furthermore, SCs form a mesh-like network in the subepidermis and epidermis, where they engulf unmyelinated nerve endings (Abdo et al., 2019). By taking advantage of an optogenetic approach, these „nociceptive“ SCs were identified to contribute to the sensation of mechanical pain and the activation of pain responses (Abdo et al., 2019). In line, SC expression of TRAP1 channels contributes to allodynia and neuroinflammation in neuropathic pain (De Logu et al., 2017), and more recently, SCs have been shown to mediate periorbital mechanical allodynia via a calcitonin gene-related peptide signaling response (De Logu et al., 2022). In general, however, our understanding of the role of SCs for sensory end organ function in the non-pathological skin is still limited.

Studies using diphtheria toxin induced ablation of SC suggest that cutaneous SCs may be important for a preservation of nerve terminals and a sustained innervation of sensory end organs (Li and Ginty, 2014; Rinwa et al., 2021). In addition, the transmembrane protein usherin (USH2A), which appears to be specifically expressed by terminal SC within Meissner corpuscles, has been shown to regulate mechanoreceptor sensitivity and vibration perception in mice, and respective mutations in Usher's syndrome in humans cause an impaired vibrotactile touch sensation (Schwaller et al., 2021). Hence, a role for cutaneous glial cells in actively modulating and mediating sensory responses is emerging, opening many interesting questions on the glial-neuronal interactions as well as the underlying mechanisms such as mechanosensation, in SC of the skin. Moreover, next to the role of sensory SCs in the healthy skin, their function in response to nerve injury remains poorly understood, and the reinnervation of sensory end organs has received much less attention compared to their motor counterparts. Importantly, however, SCs have been implicated in efficient wound healing of the adult skin (Johnston et al., 2013; Parfejevs et al., 2018).

4.3. Satellite glial cells

Satellite glial cells (SGCs) are specialized glial cells that ensheathe sensory, parasympathetic and sympathetic neuron cell bodies (Elfvin and Forsman, 1978; Hanani, 2005; Hanani and Spray, 2020; Pannese, 1981). In general, each individual neuron is completely engulfed by several, flattened satellite glial cells that form ring-like structures, with only a narrow 20nm space between neurons and SGs (Hanani, 2005). As an exception to this rule, a small proportion of DRG neurons seems to be enwrapped as a cluster by a common satellite glial sheath (Hanani and Spray, 2020). In both cases, a single, continuous basal lamina covers these neuron-satellite glia units, which are separated from each other by connective tissue (Pannese, 2010). During development, SGs are derived from neural crest cells and likely furthermore originate from boundary cap cells (Jessen and Mirsky, 2005; Marol et al., 2004). As SGs share several similarities with SC precursor cells, they have been suggested to represent a population of developmentally arrested SCs (George et al., 2018). Though, other studies demonstrate a molecular profile more reminiscent to astrocytes (Avraham et al., 2020; Jager et al., 2020; van Weperen et al., 2021) and emphasize overlapping functions to astrocytes in the CNS (Hanani and Spray, 2020; Huang et al., 2013). However, satellite glial cells were shown to also express unique genes that are absent in SCs and astrocytes (Mapps et al., 2022).

Recent RNA-sequencing studies identified a pronounced

heterogeneity of SGCs and identified different SGCs types depending on their association with either sensory or sympathetic ganglia (Avraham et al., 2021; Mapps et al., 2022; Tasdemir-Yilmaz et al., 2021; van Weperen et al., 2021). Surprisingly, however, only little is known about the function of SGCs in the non-injured nervous system and studies on SGCs are largely restricted to the context of pain and peripheral nerve injury (for an extensive review on this topic see Hanani and Spray, 2020). Briefly, SGCs have been demonstrated in various studies to contribute to changes in neuronal excitability and the development of (chronic) pain by, inter alia, the release of pro-inflammatory cytokines (Afroz et al., 2019; Dubový et al., 2010; Souza et al., 2013), an altered expression of ion channels such as Kir4.1. (Takeda et al., 2011; Tang et al., 2010; Vit et al., 2008), changes in purinergic signaling (Magni et al., 2018; Zhang et al., 2007) and an increased coupling by gap junctions (Hanani and Spray, 2020).

A bidirectional interaction between SGCs and neurons has also been proposed to mediate a spread of depolarization among adjacent neurons after injury (Devor and Wall, 1990; Hanani and Spray, 2020; Kim et al., 2016; Spray et al., 2019). Indeed, there is several evidence that SGCs respond to neuronal stimulation and in turn modulate neuronal activity (Huang et al., 2013; Kim et al., 2016; Spray et al., 2019; Suadicani et al., 2010; Zhang et al., 2007), a function that may not be limited to injury but may likewise be implicated in neuronal function and homeostasis in the developing and mature nervous system. Here, characterizing the specifics of SGCs-neuron units in different types of ganglia will be highly interesting.

Noteworthy, SGCs have also been suggested to represent a multi-potent progenitor population based on the observation that SGCs can differentiate into other cell types *in vitro* (Belzer et al., 2010; Li et al., 2007; Reed et al., 2021; Svenningsen et al., 2004) and the fact that SOX10 overexpression is sufficient to convert SGCs into oligodendroglial like cells (Weider et al., 2015).

4.4. Enteric glia

In addition to glia around sensory and (para)sympathetic neurons, populations of neural crest derived non-myelinating glial cells also surround enteric neurons, which together with their axonal extensions form the myenteric (Auerbach) and the submucosal (Meissner) plexus within the gut wall. Enteric glia have been categorized into different subpopulations depending on their morphology (Hanani and Reichenbach, 1994), their localization (Gulbransen and Sharkey, 2012), immunophenotype (Boesmans et al., 2015; Grundmann et al., 2019; Jessen and Mirsky, 1980; Rao and Gershon, 2015) and, more recently, according to their molecular features in single cell RNA seq (scRNAseq) studies (Baghdadi et al., 2022; Guyer et al., 2022; Howard et al., 2021; Lasrado et al., 2017; Li and Ngan, 2022). Notably, enteric glial cells are interconnected by gap junctions and form a glial network (Hanani et al., 1989; Maudlej and Hanani, 1992). Many studies demonstrated the excitability of enteric glial cells by enteric neurons, which has been suggested to be induced, among others, by neurotransmitters and ATP. However, more studies are required to understand the precise molecular nature of this glia-neuron crosstalk (reviewed in more detail Grundmann et al., 2019; Gulbransen and Sharkey, 2012; McClain et al., 2014).

Importantly, the best established function of this neuron-glia interaction is the active role of enteric glial cells in regulating intestinal contractility (Delvalle et al., 2018; Grundmann et al., 2019; McClain et al., 2014, 2015; Rao et al., 2017). In line, mouse mutants with an ablation of enteric glial cells demonstrate reduced gut motility (Aubé et al., 2006; Nasser et al., 2006; Rao et al., 2017). Enteric glial cells have furthermore been suggested to be implicated in epithelial differentiation (Bach-Ngohou et al., 2010; Van Landeghem et al., 2009; reviewed in Neunlist et al., 2013; Yu and Li, 2014) as well as in epithelial barrier function in many studies (Aubé et al., 2006; Bush et al., 1998; reviewed in Grundmann et al., 2019), as mucosal enteric glial cells lie close to the epithelial layer, forming a neuron-glia-epithelial unit (Grundmann et al.,

2019; Neunlist et al., 2013). However, a more recent study with an ablation of *Plp* expressing enteric glial cells via diphtheria toxin did not detect a defect in epithelial barrier function upon enteric glial cell loss, and hence questions these earlier findings (Rao et al., 2017). While a potential role for enteric glial cells in electrogenic ion transport and transepithelial resistance under physiological conditions remains unclear, epithelial barrier function may be influenced by enteric glial cells in diseases and under inflammatory conditions (Bach-Ngohou et al., 2010; Grundmann et al., 2019; Liu and Yang, 2022; MacEachern et al., 2015; Neunlist et al., 2013; Pochard et al., 2016; Reed et al., 2021; Savidge et al., 2007). Likewise, enteric glial cells respond to inflammatory stimuli, can act as antigen-presenting cells, activate macrophages and may contribute to both repair and mucosal wound healing as well as to pain in gastrointestinal disorders (Geboes et al., 1992; Grundmann et al., 2019; Morales-Soto and Gulbransen, 2019; Reed et al., 2021; Van Landeghem et al., 2009). Indeed, a recent study revealed a novel role of interferon- γ signalling by enteric glial cells for the regulation of the immune response and tissue repair upon intestinal infection (Progatzky et al., 2021). Finally, another highly interesting function of enteric glial cells emerged recently, which is the contribution of enteric glial cells to the renewal of the intestinal stem cell niche (Baghdadi et al., 2022; Li and Ngan, 2022).

5. Conclusion

In contrast to the many glial functions in the CNS that result from distinct cellular lineages, the functional glial diversity in the PNS is mostly accomplished by Schwann cells, their precursors or descendants. The plethora of specialized Schwann cells throughout the organism highlights their functional flexibility and it is highly likely that many more, e.g., organ-specific, specialized SCs exist which are still unknown today. Recent technical advancements in single cell transcriptomics have shed light on the molecular characteristics of Schwann cells during peripheral nerve development, as well as on the cellular composition of mature nerves, which will help to further untangle the diversity of SC functions and their cellular interactions within the PNS (Gerber et al., 2021; Kastriti et al., 2022a, 2022b; Wolbert et al., 2020; Yim et al., 2022). Although SCs unequivocally interact with various other cell types besides neurons, facilitating axonal function can be considered as a cardinal SC task. In line, while a fine-tuned axon-glia interaction is critical for peripheral nerve development, maintenance and repair, a disturbance of this interaction results in motor and sensory impairment. Indeed, SC malfunction is the cause of many PNS diseases including acquired and inherited peripheral neuropathies and constitutes a pivotal target for therapeutic interventions. However, the regenerative potential of SCs, as particularly seen after acute nerve injury, is captivating and sparks hope for future treatment of these life-burdening diseases.

Author contributions

M.B-Q., R.F. and R.M.S. wrote the review. R.M.S. and R.F. designed and edited the review. Correspondence should be addressed to Ruth.St assart@medizin.uni-leipzig.de or Robert.Fledrich@medizin.uni-leipzig.de.

Declaration of Competing Interest

The authors declare no competing financial interests.

Data availability

Data will be made available on request.

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References

- Abdo, H., Calvo-Enrique, L., Lopez, J.M., Song, J., Zhang, M.D., Usoskin, D., El Manira, A., Adameyko, I., Hjerling-Leffler, J., Ernfors, P., 2019. Specialized cutaneous Schwann cells initiate pain sensation. *Science* (New York, N.Y.) 365 (6454), 695–699. <https://doi.org/10.1126/SCIENCE.AAX6452>.
- Afroz, S., Arakaki, R., Iwasa, T., Oshima, M., Hosoki, M., Inoue, M., Baba, O., Okayama, Y., Matsuka, Y., 2019. CGRP induces differential regulation of cytokines from satellite glial cells in trigeminal ganglia and orofacial nociception. *Int. J. Mol. Sci.* 20 (3) <https://doi.org/10.3390/IJMS20030711>.
- Aguayo, A.J., Peyronnard, J.M., Bray, G.M., 1973. A quantitative ultrastructural study of regeneration from isolated proximal stumps of transected unmyelinated nerves. *J. Neuropathol. Exp. Neurol.* 32 (2), 256–270. <https://doi.org/10.1097/00005072-197304000-00006>.
- Aguayo, A.J., Charron, L., Bray, G.M., 1976. Potential of Schwann cells from unmyelinated nerves to produce myelin: a quantitative ultrastructural and radiographic study. *J. Neurocytol.* 5 (5), 565–573. <https://doi.org/10.1007/BF01175570>.
- Allodi, I., Udina, E., Navarro, X., 2012. Specificity of peripheral nerve regeneration: Interactions at the axon level. *Prog. Neurobiol.* 98 (1), 16–37. <https://doi.org/10.1016/J.PNEUROBIO.2012.05.005>.
- Amor, V., Feinberg, K., Eshed-Eisenbach, Y., Vainshtein, A., Frechter, S., Grumet, M., Rosenbluth, J., Peles, E., 2014. Long-term maintenance of Na⁺ channels at nodes of Ranvier depends on glial contact mediated by gliomedin and NrCAM. *J. Neurosci.* 34 (15), 5089–5098. <https://doi.org/10.1523/JNEUROSCI.4752-13.2014>.
- Arthur-Farraj, P., Coleman, M.P., 2021. Lessons from injury: how nerve injury studies reveal basic biological mechanisms and therapeutic opportunities for peripheral nerve diseases. *Neurotherapeutics* 18 (4), 2200–2221. <https://doi.org/10.1007/s13311-021-01125-3>.
- Arthur-Farraj, P., Moyon, S., 2020. DNA methylation in Schwann cells and in oligodendrocytes. *Glia* 68 (8), 1568–1583. <https://doi.org/10.1002/glia.23784>.
- Arthur-Farraj, P.J., Latouche, M., Wilton, D.K., Quintes, S., Chabrol, E., Banerjee, A., Woodhoo, A., Jenkins, B., Rahman, M., Turmaine, M., Wicher, G.K., Mitter, R., Greensmith, L., Behrens, A., Raivich, G., Mirsky, R., Jessen, K.R., Jun, C.-Jun reprograms Schwann cells of injured nerves to generate a repair cell essential for regeneration. *Neuron* 75 (4), 633–647. <https://doi.org/10.1016/J.NEURON.2012.06.021>.
- Aubé, A.C., Cabarracas, J., Bauer, J., Philippe, D., Aubert, P., Doulay, F., Liblau, R., Galmiche, J.P., Neunlist, M., 2006. Changes in enteric neurone phenotype and intestinal functions in transgenic mouse model of enteric glia disruption. *Gut* 55 (5), 630–637. <https://doi.org/10.1136/GUT.2005.067595>.
- Avraham, O., Deng, P.Y., Jones, S., Kuruvilla, R., Semenkovich, C.F., Klyachko, V.A., Cavalli, V., 2020. Satellite glial cells promote regenerative growth in sensory neurons. *Nat. Commun.* 11 (1) <https://doi.org/10.1038/S41467-020-18642-Y>.
- Avraham, O., Feng, R., Ewan, E.E., Rustenhoven, J., Zhao, G., Cavalli, V., 2021. Profiling sensory neuron microenvironment after peripheral and central axon injury reveals key pathways for neural repair. *Elife* 10. <https://doi.org/10.7554/ELIFE.68457>.
- Babetto, E., Wong, K.M., Beirowski, B., 2020. A glycolytic shift in Schwann cells supports injured axons. *Nat. Neurosci.* 23 (10), 1215–1228. <https://doi.org/10.1038/s41593-020-0689-4>.
- Bach-Ngohou, K., Mahé, M.M., Aubert, P., Abdo, H., Boni, S., Bourreille, A., Denis, M.G., Lardeux, B., Neunlist, M., Masson, D., 2010. Enteric glia modulate epithelial cell proliferation and differentiation through 15-deoxy-12,14-prostaglandin J2. *J. Physiol.* 588 (Pt 14), 2533–2544. <https://doi.org/10.1113/JPHYSIOL.2010.188409>.
- Baghdadi, M.B., Ayyaz, A., Coquenlorge, S., Chu, B., Kumar, S., Streutker, C., Wrana, J.L., Kim, T.H., 2022. Enteric glial cell heterogeneity regulates intestinal stem cell niches. *Cell Stem Cell* 29 (1), 86–100.e6. <https://doi.org/10.1016/J.STEM.2021.10.004>.
- Bähr, M., Przyrembel, C., 1995. Myelin from peripheral and central nervous system is a nonpermissive substrate for retinal ganglion cell axons. *Exp. Neurol.* 134 (1), 87–93. <https://doi.org/10.1006/EXNR.1995.1039>.
- Barrette, B., Hébert, M.A., Filali, M., Lafontaine, K., Vallières, N., Gowing, G., Julien, J.P., Lacroix, S., 2008. Requirement of myeloid cells for axon regeneration. *J. Neurosci.* 28 (38), 9363–9376. <https://doi.org/10.1523/JNEUROSCI.1447-08.2008>.
- Beirowski, B., Babetto, E., Golden, J.P., Chen, Y.J., Yang, K., Gross, R.W., Patti, G.J., Milbrandt, J., 2014. Metabolic regulator LKB1 is crucial for Schwann cell-mediated axon maintenance. *Nat. Neurosci.* 17 (10), 1351–1361. <https://doi.org/10.1038/nrn.3809>.
- Belin, S., Zuloaga, K.L., Poitelon, Y., 2017. Influence of mechanical stimuli on schwann cell biology. *Front. Cell. Neurosci.* 11 <https://doi.org/10.3389/FNCEL.2017.00347>.
- Belzer, V., Shraer, N., Hanani, M., 2010. Phenotypic changes in satellite glial cells in cultured trigeminal ganglia. *Neuron Glia Biol.* 6 (4), 237–243. <https://doi.org/10.1017/S1740925X1100007X>.
- Benito, C., Davis, C.M., Gomez-Sanchez, J.A., Turmaine, M., Meijer, D., Poli, V., Mirsky, R., Jessen, K.R., 2017. STAT3 controls the long-term survival and phenotype of repair schwann cells during nerve regeneration. *J. Neurosci.* 37 (16), 4255–4269. <https://doi.org/10.1523/JNEUROSCI.3481-16.2017>.
- Berenberg, R.A., Forman, D.S., Wood, D.K., DeSilva, A., Demaree, J., 1977. Recovery of peripheral nerve function after axotomy: effect of triiodothyronine. *Exp. Neurol.* 57 (2), 349–363. [https://doi.org/10.1016/0014-4886\(77\)90071-1](https://doi.org/10.1016/0014-4886(77)90071-1).
- Birchmeier, C., Nave, K.A., 2008. Neuregulin-1, a key axonal signal that drives schwann cell growth and differentiation. *Glia* 56 (14), 1491–1497. <https://doi.org/10.1002/glia.20753>.
- Boerboom, A., Dion, V., Chariot, A., Franzen, R., 2017. Molecular mechanisms involved in schwann cell plasticity. *Front. Mol. Neurosci.* 10 <https://doi.org/10.3389/FNMOL.2017.00038>.
- Boesmans, W., Lasrado, R., Vanden Berghe, P., Pachnis, V., 2015. Heterogeneity and phenotypic plasticity of glial cells in the mammalian enteric nervous system. *Glia* 63 (2), 229–241. <https://doi.org/10.1002/GLIA.22746>.
- Bolino, A., 2021. Myelin biology. *Neurotherapeutics* 18, 2169–2184. <https://doi.org/10.1007/s13311-021-01083-w>.
- Bolívar, S., Navarro, X., Udina, E., 2020. Schwann cell role in selectivity of nerve regeneration. *Cells* 9 (9). <https://doi.org/10.3390/cells9092131>.
- Boucanova, F., Chrast, R., 2020. Metabolic interaction between schwann cells and axons under physiological and disease conditions. *Front. Cell. Neurosci.* 14 (May), 1–6. <https://doi.org/10.3389/fncel.2020.00148>.
- Boyd, J.G., Gordon, T., 2003. Neurotrophic factors and their receptors in axonal regeneration and functional recovery after peripheral nerve injury. *Mol. Neurobiol.* 27 (3), 277–323. <https://doi.org/10.1385/MN:27:3:277>.
- Brill, M.H., Waxman, S.G., Moore, J.W., Joyner, R.W., 1977. Conduction velocity and spike configuration in myelinated fibres: computed dependence on internode distance. *J. Neurol. Neurosurg. Psychiatry* 40 (8), 769–774. <https://doi.org/10.1136/JNNP.40.8.769>.
- Brill, M.S., Lichtman, J.W., Thompson, W., Zuo, Y., Misgeld, T., 2011. Spatial constraints dictate glial territories at murine neuromuscular junctions. *J. Cell Biol.* 195 (2), 293–305. <https://doi.org/10.1083/JCB.201108005>.
- Britsch, S., Goerlich, D.E., Riethmacher, D., Peirano, R.I., Rossner, M., Nave, K.A., Birchmeier, C., Wegner, M., 2001. The transcription factor Sox10 is a key regulator of peripheral glial development. *Genes Dev.* 15 (1), 66–78. <https://doi.org/10.1101/GAD.186601>.
- Brosius Lutz, A., Chung, W.S., Sloan, S.A., Carson, G.A., Zhou, L., Lovelett, E., Posada, S., Zuchero, J.B., Barres, B.A., 2017. Schwann cells use TAM receptor-mediated phagocytosis in addition to autophagy to clear myelin in a mouse model of nerve injury. *Proc. Natl. Acad. Sci. U. S. A.* 114 (38), E8072–E8080. <https://doi.org/10.1073/pnas.1710566114>.
- Brown, A.M., Evans, R.D., Black, J., Ransom, B.R., 2012. Schwann cell glycogen selectively supports myelinated axon function. *Ann. Neurol.* 72 (3), 406–418. <https://doi.org/10.1002/ana.23607>.
- Brück, W., Friede, R.L., 1990. Anti-macrophage CR3 antibody blocks myelin phagocytosis by macrophages in vitro. *Acta Neuropathol.* 80 (4), 415–418. <https://doi.org/10.1007/BF00307696>.
- Brushart, T.M., Hoffman, P.N., Royall, R.M., Murinson, B.B., Witzel, C., Gordon, T., 2002. Electrical stimulation promotes motoneuron regeneration without increasing its speed or conditioning the neuron. *J. Neurosci.* 22 (15), 6631–6638. <https://doi.org/10.1523/JNEUROSCI.22-15-06631.2002>.
- Brushart, T.M., Aspalter, M., Griffin, J.W., Redett, R., Hameed, H., Zhou, C., Wright, M., Vyas, A., Höke, A., 2013. Schwann cell phenotype is regulated by axon modality and central-peripheral location, and persists in vitro. *Exp. Neurol.* 247, 272. <https://doi.org/10.1016/J.EXPNEUROL.2013.05.007>.
- Büngner, O.V., 1891. Über die degeneration und regenerationsvorgänge am nerven nach verletzungen. *Beitr. Path. Anat.* 10, 321–390.
- Bush, T.G., Savidge, T.C., Freeman, T.C., Cox, H.J., Campbell, E.A., Mucke, L., Johnson, M.H., Sofroniew, M.V., 1998. Fulminant jejunio-ileitis following ablation of enteric glia in adult transgenic mice. *Cell* 93 (2), 189–201. [https://doi.org/10.1016/S0092-8674\(00\)81571-8](https://doi.org/10.1016/S0092-8674(00)81571-8).
- Carr, M.J., Toma, J.S., Johnston, A.P.W., Steadman, P.E., Yuzwa, S.A., Mahmud, N., Frankland, P.W., Kaplan, D.R., Miller, F.D., 2019. Mesenchymal precursor cells in adult nerves contribute to mammalian tissue repair and regeneration. *Cell Stem Cell* 24 (2), 240–256.e9. <https://doi.org/10.1016/J.STEM.2018.10.024>.
- Castonguay, A., Robitaille, R., 2001. Differential regulation of transmitter release by presynaptic and glial Ca²⁺ internal stores at the neuromuscular synapse. *J. Neurosci.* 21 (6), 1911–1922. <https://doi.org/10.1523/JNEUROSCI.21-06-01911-2001>.
- Castro, R., Taetzsch, T., Vaughan, S.K., Godbe, K., Chappell, J., Settlage, R.E., Valdez, G., 2020. Specific labeling of synaptic schwann cells reveals unique cellular and molecular features. *Elife* 9, 1–19. <https://doi.org/10.7554/ELIFE.56935>.
- Catenaccio, A., Llavoro Hurtado, M., Diaz, P., Lamont, D.J., Wishart, T.M., Court, F.A., 2017. Molecular analysis of axonal-intrinsic and glial-associated co-regulation of axon degeneration. *Cell Death Dis.* 8 (11), e3166. <https://doi.org/10.1038/cddis.2017.489>.
- Cattin, A.L., Lloyd, A.C., 2016. The multicellular complexity of peripheral nerve regeneration. *Curr. Opin. Neurobiol.* 39, 38–46. <https://doi.org/10.1016/j.conb.2016.04.005>.
- Cattin, A.L., Burden, J.J., van Emmenis, L., MacKenzie, F.E., Hoving, J.J.A., Garcia Calavia, N., Guo, Y., McLaughlin, M., Rosenberg, L.H., Quereda, V., Jamecna, D., Napoli, I., Parrinello, S., Enver, T., Ruhrberg, C., Lloyd, A.C., 2015. Macrophage-induced blood vessels guide schwann cell-mediated regeneration of peripheral nerves. *Cell* 162 (5), 1127–1139. <https://doi.org/10.1016/j.cell.2015.07.021>.
- Chen, S., Rio, C., Ji, R.R., Dikkes, P., Coggeshall, R.E., Woolf, C.J., Corfas, G., 2003. Disruption of ErbB receptor signaling in adult non-myelinating Schwann cells causes

- progressive sensory loss. *Nat. Neurosci.* 6 (11), 1186–1193. <https://doi.org/10.1038/NN1139>.
- Chen, Z.L., Yu, W.M., Strickland, S., 2007. Peripheral regeneration. *Annu. Rev. Neurosci.* 30, 209–233. <https://doi.org/10.1146/ANNUREV.NEURO.30.051606.094337>.
- Chen, C.Z., Neumann, B., Förster, S., Franklin, R.J.M., 2021. Schwann cell remyelination of the central nervous system : why does it happen and what are the benefits ? *Open Biol.* 11, 200352 <https://doi.org/10.1098/rsob.200352>.
- Ching, R.C., Wiberg, M., Kingham, P.J., 2018. Schwann cell-like differentiated adipose stem cells promote neurite outgrowth via secreted exosomes and RNA transfer. *Stem Cell Res Ther* 9 (1). <https://doi.org/10.1186/S13287-018-1017-8>.
- Clements, M.P., Byrne, E., Camarillo Guerrero, L.F., Cattin, A.L., Zakka, L., Ashraf, A., Burden, J.J., Khadate, S., Lloyd, A.C., Marguerat, S., Parrinello, S., 2017. The wound microenvironment reprograms schwann cells to invasive mesenchymal-like cells to drive peripheral nerve regeneration. *Neuron* 96 (1), 98–114.e7. <https://doi.org/10.1016/j.neuron.2017.09.008>.
- Cleveland, D.W., Monteiro, M.J., Wong, P.C., Gill, S.R., Gearhart, J.D., Hoffman, P.N., 1991. Involvement of neurofilaments in the radial growth of axons. *J. Cell Sci. (Supplement_15)*, 85–95. https://doi.org/10.1242/JCS.1991.SUPPLEMENT_15.12.
- Cohen, C.C.H., Popovic, M.A., Klooster, J., Weil, M.T., Möbius, W., Nave, K.A., Kole, M. H.P., 2020. Saltatory conduction along myelinated axons involves a periaxonal nanocircuit. *Cell* 180 (2), 311–322.e15. <https://doi.org/10.1016/J.CELL.2019.11.039>.
- Coleman, M.P., Höke, A., 2020. Programmed axon degeneration: from mouse to mechanism to medicine. *Nat. Rev. Neurosci.* 21 (4), 183–196. <https://doi.org/10.1038/S41583-020-0269-3>.
- Contreras, E., Bolívar, S., Navarro, X., Udina, E., 2022. New insights into peripheral nerve regeneration: The role of secretomes. *Exp. Neurol.* 354 (September 2021), 114069 <https://doi.org/10.1016/j.exppsu.2022.114069>.
- Court, F.A., Sherman, D.L., Pratt, T., Garry, E.M., Ribchester, R.R., Cottrell, D.F., Fleetwood-Walker, S.M., Brophy, P.J., 2004. Restricted growth of Schwann cells lacking Cajal bands slows conduction in myelinated nerves. *Nature* 191–195. <https://doi.org/10.1038/nature02841>.
- Darabid, H., Arbour, D., Robitaille, R., 2013. Glial cells decipher synaptic competition at the mammalian neuromuscular junction. *J. Neurosci.* 33 (4), 1297–1313. <https://doi.org/10.1523/JNEUROSCI.2935-12.2013>.
- Darabid, H., Perez-Gonzalez, A.P., Robitaille, R., 2014. Neuromuscular synaptogenesis: coordinating partners with multiple functions. *Nat. Rev. Neurosci.* 15 (11), 703–718. <https://doi.org/10.1038/nrn3821>.
- Dashiell, S.M., Tanner, S.L., Pant, H.C., Quarles, R.H., 2002. Myelin-associated glycoprotein modulates expression and phosphorylation of neuronal cytoskeletal elements and their associated kinases. *J. Neurochem.* 81 (6), 1263–1272. <https://doi.org/10.1046/J.1471-4159.2002.00927.X>.
- Davies, A.M., 1998. Neuronal survival: Early dependence on Schwann cells. *Curr. Biol.* 8 (1), 15–18. [https://doi.org/10.1016/S0960-9822\(98\)70009-0](https://doi.org/10.1016/S0960-9822(98)70009-0).
- De Logu, F., Nassini, R., Materazzi, S., Carvalho Gonçalves, M., Nosi, D., Rossi Degl'Innocenti, D., Marone, I.M., Ferreira, J., Li Puma, S., Benemei, S., Trevisan, G., Souza Monteiro De Araújo, D., Patacchini, R., Bennett, N.W., Geppetti, P., 2017. Schwann cell TRPA1 mediates neuroinflammation that sustains macrophage-dependent neuropathic pain in mice. *Nat. Commun.* 8 (1) <https://doi.org/10.1038/S41467-017-01739-2>.
- De Logu, F., Nassini, R., Hegron, A., Landini, L., Jensen, D.D., Latorre, R., Ding, J., Marini, M., Monteiro, Souza, de Araujo, D., Ramírez-García, P., Whittaker, M., Retamal, J., Titiz, M., Innocenti, A., Davis, T.P., Veldhuis, N., Schmidt, B.L., Bennett, N.W., Geppetti, P., 2022. Schwann cell endosome CGRP signals elicit periorbital mechanical allodynia in mice. *Nat. Commun.* 13 (1) <https://doi.org/10.1038/S41467-022-28204-Z>.
- de Waegh, S.M., Lee, V.M.Y., Brady, S.T., 1992. Local modulation of neurofilament phosphorylation, axonal caliber, and slow axonal transport by myelinating Schwann cells. *Cell* 68 (3), 451–463. [https://doi.org/10.1016/0092-8674\(92\)90183-D](https://doi.org/10.1016/0092-8674(92)90183-D).
- Deborde, S., Gusain, L., Powers, A., Marcadis, A., Yu, Y., Chen, C.-H., Frants, A., Kao, E., Tang, L.H., Vakiani, E., Amisaki, M., Balachandran, V.P., Calo, A., Omelchenko, T., Jessen, K.R., Reva, B., Wong, R.J., 2022. Reprogrammed schwann cells organize into dynamic tracks that promote pancreatic cancer invasion. *Cancer Discovery* 12 (10), OF1–OF20. <https://doi.org/10.1158/2159-8290.CD-21-1690>.
- Delvalle, N.M., Fried, D.E., Rivera-Lopez, G., Gaudette, L., Gulbransen, B.D., 2018. Cholinergic activation of enteric glia is a physiological mechanism that contributes to the regulation of gastrointestinal motility. *Am. J. Physiol. Gastrointest. Liver Physiol.* 315 (4), G473–G483. <https://doi.org/10.1152/AJPLI.00155.2018>.
- Devor, M., Wall, P.D., 1990. Cross-excitation in dorsal root ganglia of nerve-injured and intact rats. *J. Neurophysiol.* 64 (6), 1733–1746. <https://doi.org/10.1152/JN.1990.64.6.1733>.
- Donaldson, H.H., Hoke, G.W., 1905. On the areas of the axis cylinder and medullary sheath as seen in cross sections of the spinal nerves of vertebrates. *J. Comp. Neurol. Psychol.* 15 (1), 1–16.
- Dubový, P., Klusákov, I., Svízinská, I., Brázda, V., 2010. Satellite glial cells express IL-6 and corresponding signal-transducing receptors in the dorsal root ganglia of rat neuropathic pain model. *Neuron Glia Biol.* 6 (1), 73–83. <https://doi.org/10.1017/S1740925X10000074>.
- Duman, M., Martinez-Moreno, M., Jacob, C., Tapinos, N., 2020. Functions of histone modifications and histone modifiers in Schwann cells. *Glia* 68 (8), 1584–1595. <https://doi.org/10.1002/glia.23795>.
- Duméneu, M., Oulé, M., Kreutz, M.R., Lopez-Rojas, J., 2017. The segregated expression of voltage-gated potassium and sodium channels in neuronal membranes: functional implications and regulatory mechanisms. *Front. Cell. Neurosci.* 11 <https://doi.org/10.3389/FNCEL.2017.00115>.
- Dun, X., Carr, L., Woodley, P.K., Barry, R.W., Drake, L.K., Mindos, T., Roberts, S.L., Lloyd, A.C., Parkinson, D.B., 2019. Macrophage-derived Slit3 controls cell migration and axon pathfinding in the peripheral nerve bridge. *Cell Rep.* 26 (6), 1458–1472.e4. <https://doi.org/10.1016/j.celrep.2018.12.081>.
- Eichel, M.A., Gargareta, V.I., D'Este, E., Fledrich, R., Kungl, T., Buscham, T.J., Lüders, K. A., Miracle, C., Jung, R.B., Distler, U., Kusch, K., Möbius, W., Hülsmann, S., Tenzer, S., Nave, K.A., Werner, H.B., 2020. CMTM6 expressed on the adaxonal Schwann cell surface restricts axonal diameters in peripheral nerves. *Nat. Commun.* 11 (1), 1–12. <https://doi.org/10.1038/s41467-020-18172-7>.
- Elfrin, L.G., Forsman, C., 1978. The ultrastructure of junctions between satellite cells in mammalian sympathetic ganglia as revealed by freeze-etching. *J. Ultrastruct. Res.* 63 (3), 261–274. [https://doi.org/10.1016/S0022-5320\(78\)80051-3](https://doi.org/10.1016/S0022-5320(78)80051-3).
- Eshed, Y., Feinberg, K., Poliak, S., Sabanay, H., Sarig-Nadir, O., Spiegel, I., Bermingham, J.R., Peles, E., 2005. Gliomedin mediates Schwann cell-axon interaction and the molecular assembly of the nodes of Ranvier. *Neuron* 47 (2), 215–229. <https://doi.org/10.1016/J.NEURON.2005.06.026>.
- Eshed, Y., Feinberg, K., Carey, D.J., Peles, E., 2007. Secreted gliomedin is a perinodal matrix component of peripheral nerves. *J. Cell Biol.* 177 (3), 551–562. <https://doi.org/10.1083/JCB.200612139>.
- Faroni, A., Castelnovo, L.F., Procacci, P., Caffino, L., Fumagalli, F., Melfi, S., Gambarotta, G., Bettler, B., Wrabetz, L., Magnaghi, V., 2014. Deletion of GABA-B receptor in Schwann cells regulates remak bundles and small nociceptive C-fibers. *Glia* 62 (4), 548–565. <https://doi.org/10.1002/GLIA.22625>.
- Fazal, S.V., Gomez-Sanchez, J.A., Wagstaff, L.J., Musner, N., Otto, G., Janz, M., Mirsky, R., Jessen, K.R., 2017. Graded elevation of c-jun in schwann cells in vivo: gene dosage determines effects on development, remyelination, tumorigenesis, and hypomyelination. *J. Neurosci.* 37 (50), 12297–12313. <https://doi.org/10.1523/JNEUROSCI.0986-17.2017>.
- Feinberg, K., Eshed-Eisenbach, Y., Frechter, S., Amor, V., Salomon, D., Sabanay, H., Dupree, J.L., Grumet, M., Brophy, P.J., Shrager, P., Peles, E., 2010. A glial signal consisting of gliomedin and NrCAM clusters Axonal Na⁺ channels during the formation of nodes of ranvier. *Neuron* 65 (4), 490–502. <https://doi.org/10.1016/J.NEURON.2010.02.004>.
- Feltri, M.L., Poitelon, Y., Previtali, S.C., 2016. How schwann cells sort axons: new concepts. *Neuroscientist* 22 (3), 252–265. <https://doi.org/10.1177/1073858415572361>.
- Feltri, M.L., Weaver, M.R., Belin, S., Poitelon, Y., 2021. The Hippo pathway: Horizons for innovative treatments of peripheral nerve diseases. *J. Peripher. Nerv. Syst.* 26 (1), 4–16. <https://doi.org/10.1111/jns.12431>.
- Fernando, R.N., Cotter, L., Perrin-Tricaud, C., Berthelot, J., Bartolami, S., Pereira, J.A., Gonzalez, S., Suter, U., Tricaud, N., 2016. Optimal myelin elongation relies on YAP activation by axonal growth and inhibition by Crb3/Hippo pathway. *Nat. Commun.* 7 (1), 1–14. <https://doi.org/10.1038/ncomms12186>.
- Fledrich, R., Akkermann, D., Schütza, V., Abdelaal, T.A., Hermes, D., Schäffner, E., Soto-Bernardini, M.C., Götz, T., Klink, A., Kusch, K., Krueger, M., Kungl, T., Frydrychowicz, C., Möbius, W., Brück, W., Mueller, W.C., Bechmann, I., Sereda, M. W., Schwab, M.H., et al., 2019a. NRG1 type I dependent autocrine stimulation of Schwann cells in onion bulbs of peripheral neuropathies. *Nat. Commun.* 10 (1) <https://doi.org/10.1038/s41467-019-09385-6>.
- Fledrich, R., Kungl, T., Nave, K.A., Stassart, R.M., 2019b. Axo-glial interdependence in peripheral nerve development. *Development* (Cambridge, England) 146 (21), 1–12. <https://doi.org/10.1242/dev.151704>.
- Follis, R.M., Tep, C., Genaro-Mattos, T.C., Lyang Kim, M., Ryu, J.C., Morrison, V.E., Chan, J.R., Porter, N., Carter, B.D., Yoon, S.O., 2021. Metabolic control of sensory neuron survival by the p75 neurotrophin receptor in schwann cells. *J. Neurosci.* 41 (42), 8710–8724. <https://doi.org/10.1523/JNEUROSCI.3243-20.2021>.
- Fontana, X., Hristova, M., Da Costa, C., Patodia, S., Thei, L., Makwana, M., Spencer-Dene, B., Latouche, M., Mirsky, R., Jessen, K.R., Klein, R., Raivich, G., Behrens, A., 2012. c-Jun in Schwann cells promotes axonal regeneration and motoneuron survival via paracrine signaling. *J. Cell Biol.* 198 (1), 127–141. <https://doi.org/10.1083/JCB.201205025>.
- Fontenás, L., Kucenas, S., 2018. Motor exit point (MEP) glia: Novel myelinating glia that bridge CNS and PNS myelin. *Front. Cell. Neurosci.* 12 (October), 1–8. <https://doi.org/10.3389/fncel.2018.00333>.
- Fraher, J., Dockery, P., 1998. A strong myelin thickness-axon size correlation emerges in developing nerves despite independent growth of both parameters. *J. Anat.* 193 (2), 195–201. <https://doi.org/10.1046/j.1469-7580.1998.19320195.x>.
- Fricker, F.R., Zhu, N., Tsantoulas, C., Abrahamsen, B., Nassar, M.A., Thakur, M., Garratt, A.N., Birchmeier, C., McMahon, S.B., Wood, J.N., Bennett, D.L.H., 2009. Sensory axon-derived neuregulin-1 is required for axoglial signaling and normal sensory function but not for long-term axon maintenance. *J. Neurosci.* 29 (24), 7667–7678. <https://doi.org/10.1523/JNEUROSCI.6053-08.2009>.
- Fricker, F.R., Lago, N., Balarajah, S., Tsantoulas, C., Tanna, S., Zhu, N., Fageiry, S.K., Jenkins, M., Garratt, A.N., Birchmeier, C., Bennett, D.L.H., 2011. Axonally derived neuregulin-1 is required for remyelination and regeneration after nerve injury in adulthood. *J. Neurosci.* 31 (9), 3225–3233. <https://doi.org/10.1523/JNEUROSCI.2568-10.2011>.
- Fricker, F.R., Antunes-Martins, A., Galino, J., Paramosothy, R., La Russa, F., Perkins, J., Goldberg, R., Brelstaff, J., Zhu, N., McMahon, S.B., Orengo, C., Garratt, A.N., Birchmeier, C., Bennett, D.L.H., 2013. Axonal neuregulin 1 is a rate limiting but not essential factor for nerve remyelination. *Brain J. Neurol.* 136 (Pt 7), 2279–2297. <https://doi.org/10.1093/BRAIN/AWT148>.
- Fry, E.J., Ho, C., David, S., 2007. A role for nogo receptor in macrophage clearance from injured peripheral nerve. *Neuron* 53 (5), 649–662. <https://doi.org/10.1016/j.neuron.2007.02.009>.

- Fu, S.Y., Gordon, T., 1995. Contributing factors to poor functional recovery after delayed nerve repair: prolonged denervation. *J. Neurosci.* 15 (5 Pt 2), 3886–3895. <https://doi.org/10.1523/JNEUROSCI.15-05-03886.1995>.
- Fünfschilling, U., Supplie, L.M., Mahad, D., Boretius, S., Saab, A.S., Edgar, J., Brinkmann, B.G., Kassmann, C.M., Tzvetanova, I.D., Möbius, W., Diaz, F., Meijer, D., Suter, U., Hamprecht, B., Sereda, M.W., Moraes, C.T., Frahm, J., Goebels, S., Nave, K.A., 2012. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. *Nature* 485 (7399), 517–521. <https://doi.org/10.1038/nature11007>.
- Furlan, A., Adameyko, I., 2018. Schwann cell precursor: a neural crest cell in disguise? *Dev. Biol.* 444 (Suppl. 1), S25–S35. <https://doi.org/10.1016/J.YDBIO.2018.02.008>.
- Garcia, M.L., Lobsiger, C.S., Shah, S.B., Deerinck, T.J., Crum, J., Young, D., Ward, C.M., Crawford, T.O., Gotow, T., Uchiyama, Y., Ellisman, M.H., Calcutt, N.A., Cleveland, D.W., 2003. NF-M is an essential target for the myelin-directed ‘outside-in’ signaling cascade that mediates radial axonal growth. *J. Cell Biol.* 163 (5), 1011–1020. <https://doi.org/10.1083/JCB.200308159>.
- Gaudet, A.D., Popovich, P.G., Ramer, M.S., 2011. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. *J. Neuroinflammation* 8. <https://doi.org/10.1186/1742-2094-8-110>.
- Geboes, K., Rutgeerts, P., Ectors, N., Mebis, J., Penninckx, F., Vantrappen, G., Desmet, V. J., 1992. Major histocompatibility class II expression on the small intestinal nervous system in Crohn's disease. *Gastroenterology* 103 (2), 439–447. [https://doi.org/10.1016/0016-5085\(92\)90832-J](https://doi.org/10.1016/0016-5085(92)90832-J).
- George, D., Ahrens, P., Lambert, S., 2018. Satellite glial cells represent a population of developmentally arrested Schwann cells. *Glia* 66 (7), 1496–1506. <https://doi.org/10.1002/glia.23320>.
- Gerber, D., Pereira, J.A., Gerber, J., Tan, G., Dimitrieva, S., Yánguez, E., Suter, U., 2021. Transcriptional profiling of mouse peripheral nerves to the single-cell level to build a sciatic nerve ATlas (SNAT). *ELife* 10. <https://doi.org/10.7554/ELIFE.58591>.
- Ghabrial, M.N., Allt, G., 1979. The role of Schmidt-Lanterman incisures in Wallerian degeneration. I. A quantitative teased fibre study. *Acta Neuropathol.* 48 (2), 83–93. <https://doi.org/10.1007/BF00691149>.
- Gitik, M., Liraz-Zaltsman, S., Oldenborg, P.A., Reichert, F., Rotshenker, S., 2011. Myelin down-regulates myelin phagocytosis by microglia and macrophages through interactions between CD47 on myelin and SIRP α (signal regulatory protein- α) on phagocytes. *J. Neuroinflammation* 8 (1), 24. <https://doi.org/10.1186/1742-2094-8-24>.
- Gomez-Sanchez, J.A., Carty, L., Iruarrizaga-Lejarreta, M., Palomo-Irigoyen, M., Varela-Rey, M., Griffith, M., Hantke, J., Macias-Camara, N., Azkargorta, M., Aurrekoetxea, I., De Juan, V.G., Jefferies, H.B.J., Aspichuela, P., Elortza, F., Aransay, A.M., Martínez-Chantar, M.L., Baas, F., Mato, J.M., Mirsky, R., et al., 2015. Schwann cell autophagy, myelinophagy, initiates myelin clearance from injured nerves. *J. Cell Biol.* 210 (1), 153–168. <https://doi.org/10.1083/JCB.201503019>.
- Gomez-Sanchez, J.A., Pilch, K.S., Van Der Lans, M., Fazal, S.V., Benito, C., Wagstaff, L.J., Mirsky, R., Jessen, K.R., 2017. After nerve injury, lineage tracing shows that myelin and remak schwann cells elongate extensively and branch to form repair schwann cells, which shorten radically on remyelination. *J. Neurosci.* 37 (37), 9086–9099. <https://doi.org/10.1523/JNEUROSCI.1453-17.2017>.
- Gonçalves, N.P., Mohseni, S., El Soury, M., Ulrichsen, M., Richner, M., Xiao, J., Wood, R. J., Andersen, S.O.M., Coulson, E.J., Raimondo, S., Murray, S.S., Vægter, C.B., 2019. Peripheral nerve regeneration is independent from Schwann cell p75NTR expression. *Front. Cell. Neurosci.* 13, 235. <https://doi.org/10.3389/FNCEL.2019.00235/BIBTEX>.
- Gonzalez, D., Allende, M.L., 2021. Current advances in comprehending dynamics of regenerating axons and axon–glia interactions after peripheral nerve injury in zebrafish. *Int. J. Mol. Sci.* 22 (5), 1–11. <https://doi.org/10.3390/ijms22052484>.
- Gordon, T., 2009. The role of neurotrophic factors in nerve regeneration. *Neurosurg. Focus* 26 (2), 1–10. <https://doi.org/10.3171/FOC.2009.26.2.E3>.
- Gordon, T., 2016. Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal models and humans. *Neurotherapeutics* 13 (2), 295–310. <https://doi.org/10.1007/S13311-015-0415-1>.
- Gresset, A., Couplier, F., Gerschenfeld, G., Jourdon, A., Matesic, G., Richard, L., Vallat, J. M., Charnay, P., Topilko, P., 2015. Boundary caps give rise to neurogenic stem cells and terminal glia in the skin. *Stem Cell Rep.* 5 (2), 278–290. <https://doi.org/10.1016/J.STEMCR.2015.06.005>.
- Griffin, J.W., Thompson, W.J., 2008. Biology and pathology of nonmyelinating Schwann cells. *Glia* 56 (14), 1518–1531. <https://doi.org/10.1002/GLIA.20778>.
- Grim, M., Halata, Z., Franz, T., 1992. Schwann cells are not required for guidance of motor nerves in the hindlimb in Splotch mutant mouse embryos. *Anat. Embryol.* 186 (4), 311–318. <https://doi.org/10.1007/BF00185979>.
- Grossmann, K.S., Wende, H., Paul, F.E., Cheret, C., Garratt, A.N., Zurborg, S., Feinberg, K., Besser, D., Schulz, H., Peles, E., Selbach, M., Birchmeier, W., Birchmeier, C., 2009. The tyrosine phosphatase Shp2 (PTPN11) directs Neuregulin-1/ErbB signaling throughout Schwann cell development. *Proc. Natl. Acad. Sci. U. S. A.* 106 (39), 16704. <https://doi.org/10.1073/PNAS.0904336106>.
- Grundmann, D., Loris, E., Maas-Omlo, S., Huang, W., Scheller, A., Kirchhoff, F., Schäfer, K.H., 2019. Enteric glia: S100, GFAP, and beyond. *Anat. Rec.* 302 (8), 1333–1344. <https://doi.org/10.1002/AR.24128>.
- Gulbransen, B.D., Sharkey, K.A., 2012. Novel functional roles for enteric glia in the gastrointestinal tract. *Nat. Rev. Gastroenterol. Hepatol.* 9 (11), 625–632. <https://doi.org/10.1038/NRGASTRO.2012.138>.
- Guyer, R.A., Stavely, R.S., Robertson, K., Bhave, S., Hotta, R., Kaltschmidt, J.A., Goldstein, A.M., 2022. Single-cell multiome sequencing clarifies enteric glial cell diversity and identifies an intraganglionic population poised for neurogenesis. *BioRxiv*. <https://doi.org/10.1101/2021.08.24.457368>, 2021.08.24.457368.
- Hanani, M., 2005. Satellite glial cells in sensory ganglia: from form to function. *Brain Res. Brain Res. Rev.* 48 (3), 457–476. <https://doi.org/10.1016/J.BRAINRESREV.2004.09.001>.
- Hanani, M., Reichenbach, A., 1994. Morphology of horseradish peroxidase (HRP)- injected glial cells in the myenteric plexus of the guinea-pig. *Cell Tissue Res.* 278 (1), 153–160. <https://doi.org/10.1007/BF00305787>.
- Hanani, M., Spray, D.C., 2020. Emerging importance of satellite glia in nervous system function and dysfunction. *Nat. Rev. Neurosci.* 21 (9), 485–498. <https://doi.org/10.1038/S41583-020-0333-Z>.
- Hanani, M., Zamir, O., Baluk, P., 1989. Glial cells in the guinea pig myenteric plexus are dye coupled. *Brain Res.* 497 (2), 245–249. [https://doi.org/10.1016/0006-8993\(89\)90269-2](https://doi.org/10.1016/0006-8993(89)90269-2).
- Handler, A., Ginty, D.D., 2021. The mechanosensory neurons of touch and their mechanisms of activation. *Nat. Rev. Neurosci.* 22 (9), 521–537. <https://doi.org/10.1038/S41583-021-00489-X>.
- Hartlehner, M., Derkens, A., Hagenacker, T., Kindermann, D., Schäfers, M., Pawlak, M., Kieseier, B.C., Horste, Meyer Zu, G., 2017. Schwann cells promote post-traumatic nerve inflammation and neuropathic pain through MHC class II. *Sci. Rep.* 7 (1) <https://doi.org/10.1038/S41598-017-12744-2>.
- Hartline, D.K., Colman, D.R., 2007. Rapid conduction and the evolution of giant axons and myelinated fibers. *Current Biology : CB* 17 (1). <https://doi.org/10.1016/J.CUB.2006.11.042>.
- Harty, B.L., Monk, K.R., 2017. Unwrapping the unappreciated: recent progress in Remak Schwann cell biology. *Curr. Opin. Neurobiol.* 47, 131–137. <https://doi.org/10.1016/j.conb.2017.10.003>. Figure 1.
- Hastings, R.L., Mikesh, M., Lee, Y., Thompson, W.J., 2020. Morphological remodeling during recovery of the neuromuscular junction from terminal Schwann cell ablation in adult mice. *Sci. Rep.* 10 (1) <https://doi.org/10.1038/S41598-020-67630-1>.
- Hirata, K., Kawabuchi, M., 2002. Myelin phagocytosis by macrophages and nonmacrophages during Wallerian degeneration. *Microsc. Res. Tech.* 57 (6), 541–547. <https://doi.org/10.1002/JEMT.10108>.
- Höke, A., Brushart, T., 2010. Introduction to special issue: Challenges and opportunities for regeneration in the peripheral nervous system. *Exp. Neurol.* 223 (1), 1–4. <https://doi.org/10.1016/J.EXPNEUROL.2009.12.001>.
- Höke, A., Gordon, T., Zochodne, D.W., Sulaiman, O.A.R., 2002. A decline in glial cell-line-derived neurotrophic factor expression is associated with impaired regeneration after long-term Schwann cell denervation. *Exp. Neurol.* 173 (1), 77–85. <https://doi.org/10.1006/EXNR.2001.7826>.
- Höke, A., Redett, R., Hameed, H., Jari, R., Zhou, C., Li, Z.B., Griffin, J.W., Brushart, T.M., 2006. Schwann cells express motor and sensory phenotypes that regulate axon regeneration. *J. Neurosci.* 26 (38), 9646–9655. <https://doi.org/10.1523/JNEUROSCI.1620-06.2006>.
- Holmes, W., Young, J.Z., 1943. Nerve regeneration after immediate and delayed suture. *Br. Med. Bull.* 1 (7), 82. <https://doi.org/10.1093/oxfordjournals.bmb.a070225>.
- Howard, A.G.A., Baker, P.A., Ibarra-García-padilla, R., Moore, J.A., Rivas, L.J., Tallman, J.J., Singleton, E.W., Westheimer, J.L., Corteguera, J.A., Uribe, R.A., 2021. An atlas of neural crest lineages along the posterior developing zebrafish at single-cell resolution. *ELife* 10, 1–31. <https://doi.org/10.7554/ELIFE.60005>.
- Hsieh, S.T., Crawford, T.O., Griffin, J.W., 1994a. Neurofilament distribution and organization in the myelinated axons of the peripheral nervous system. *Brain Res.* 642 (1–2), 316–326. [https://doi.org/10.1016/0006-8993\(94\)90937-7](https://doi.org/10.1016/0006-8993(94)90937-7).
- Hsieh, S.T., Kidd, G.J., Crawford, T.O., Xu, Z., Lin, W.M., Trapp, B.D., Cleveland, D.W., Griffin, J.W., 1994b. Regional modulation of neurofilament organization by myelination in normal axons. *J. Neurosci.* 14 (11), 6392–6401. <https://doi.org/10.1523/JNEUROSCI.14-11-06392.1994>.
- Huang, L.Y.M., Gu, Y., Chen, Y., 2013. Communication between neuronal somata and satellite glial cells in sensory ganglia. *Glia* 61 (10), 1571–1581. <https://doi.org/10.1002/GLIA.22541>.
- Huxley, A.F., Stämpfli, R., 1949. Evidence for saltatory conduction in peripheral myelinated nerve fibres. *J. Physiol.* 108 (3), 315.
- Ide, C., 1996. Peripheral nerve regeneration. *Neurosci. Res.* 25 (2), 101–121. [https://doi.org/10.1016/0168-0102\(96\)01042-5](https://doi.org/10.1016/0168-0102(96)01042-5).
- Isaacman-Beck, J., Schneiderv, V., Franzini-Armstrong, C., Granato, M., 2015. The Ih3 glycosyltransferase directs target-selective peripheral nerve regeneration. *Neuron* 88 (4), 691–703. <https://doi.org/10.1016/j.neuron.2015.10.004>.
- Jager, S.E., Pallesen, L.T., Richner, M., Harley, P., Hore, Z., McMahon, S., Denk, F., Vægter, C.B., 2020. Changes in the transcriptional fingerprint of satellite glial cells following peripheral nerve injury. *Glia* 68 (7), 1375–1395. <https://doi.org/10.1002/GLIA.23785>.
- Jahromi, B.S., Zhang, L., Carlen, P.L., Pennefather, P., 1999. Differential time-course of slow afterhyperpolarizations and associated Ca $^{2+}$ transients in rat CA1 pyramidal neurons: further dissociation by Ca $^{2+}$ buffer. *Neuroscience* 88 (3), 719–726. [https://doi.org/10.1016/S0306-4522\(98\)00203-6](https://doi.org/10.1016/S0306-4522(98)00203-6).
- Jang, S.Y., Shin, Y.K., Park, S.Y., Park, J.Y., Lee, H.J., Yoo, Y.H., Kim, J.K., Park, H.T., 2016. Autophagic myelin destruction by Schwann cells during Wallerian degeneration and segmental demyelination. *Glia* 64 (5), 730–742. <https://doi.org/10.1002/GLIA.22957>.
- Jessen, K.R., Arthur-Farrar, P., 2019. Repair Schwann cell update: Adaptive reprogramming, EMT, and stemness in regenerating nerves. *Glia* 67 (3), 421–437. <https://doi.org/10.1002/glia.23532>.
- Jessen, K.R., Mirsky, R., 1980. Glial cells in the enteric nervous system contain glial fibrillary acidic protein. *Nature* 286 (5774), 736–737. <https://doi.org/10.1038/286736A0>.
- Jessen, K.R., Mirsky, R., 1999. Schwann cells and their precursors emerge as major regulators of nerve development. *Trends Neurosci.* 22 (9), 402–410. [https://doi.org/10.1016/S0166-2236\(98\)01391-5](https://doi.org/10.1016/S0166-2236(98)01391-5).

- Jessen, K.R., Mirsky, R., 2005. The origin and development of glial cells in peripheral nerves. *Nat. Rev. Neurosci.* 6 (9), 671–682. <https://doi.org/10.1038/NRN1746>.
- Jessen, K.R., Mirsky, R., 2016. The repair Schwann cell and its function in regenerating nerves. *J. Physiol.* 594 (13), 3521–3531. <https://doi.org/10.1113/JP270874>.
- Jessen, K.R., Mirsky, R., 2019a. The success and failure of the schwann cell response to nerve injury. *Front. Cell. Neurosci.* 13 (February), 1–14. <https://doi.org/10.3389/fncel.2019.00033>.
- Jessen, K.R., Mirsky, R., 2019b. Schwann cell precursors; multipotent glial cells in embryonic nerves. *Front. Mol. Neurosci.* 12 <https://doi.org/10.3389/FNMOL.2019.00069>.
- Jessen, K.R., Mirsky, R., 2022. The role of c-jun and autocrine signaling loops in the control of repair schwann cells and regeneration. *Front. Cell. Neurosci.* 15, 581. <https://doi.org/10.3389/FNCEL.2021.820216/BIBTEX>.
- Jessen, K.R., Mirsky, R., Lloyd, A.C., 2015. Schwann cells: Development and role in nerve repair. *Cold Spring Harb. Perspect. Biol.* 7 (7), 1–15. <https://doi.org/10.1101/cshperspect.a020487>.
- Jha, M.K., Passero, J.V., Rawat, A., Ament, X.H., Yang, F., Vidensky, S., Collins, S.L., Horton, M.R., Hoke, A., Rutter, G.A., Latremoliere, A., Rothstein, J.D., Morrison, B.M., 2021. Macrophage monocarboxylate transporter 1 promotes peripheral nerve regeneration after injury in mice. *J. Clin. Investig.* 131 (21), e141964 <https://doi.org/10.1172/jci141964>.
- Johnston, A.P.W., Naska, S., Jones, K., Jinno, H., Kaplan, D.R., Miller, F.D., 2013. Sox2-mediated regulation of adult neural crest precursors and skin repair. *Stem Cell Rep.* 1 (1), 38–45. <https://doi.org/10.1016/J.STEMCR.2013.04.004>.
- Johnston, A.P.W., Yuzwa, S.A., Carr, M.J., Mahmud, N., Storer, M.A., Krause, M.P., Jones, K., Paul, S., Kaplan, D.R., Miller, F.D., 2016. Dedifferentiated schwann cell precursors secreting paracrine factors are required for regeneration of the mammalian digit tip. *Cell Stem Cell* 19 (4), 433–448. <https://doi.org/10.1016/J.CSTEM.2016.06.002>.
- Jones, R.E., Salhotra, A., Robertson, K.S., Ransom, R.C., Foster, D.S., Shah, H.N., Quarto, N., Wan, D.C., Longaker, M.T., 2019. Skeletal stem cell-schwann cell circuitry in mandibular repair. *Cell Rep.* 28 (11), 2757–2766.e5. <https://doi.org/10.1016/J.CELREP.2019.08.021>.
- Jordan, C.L., Williams, T.J., 2001. Testosterone regulates terminal Schwann cell number and junctional size during developmental synapse elimination. *Dev. Neurosci.* 23 (6), 441–451. <https://doi.org/10.1159/000048731>.
- Jung, J., Cai, W., Lee, H.K., Pellegrata, M., Shin, Y.K., Jang, S.Y., Suh, D.J., Wrabetz, L., Feltri, M.L., Park, H.T., 2011. Actin polymerization is essential for myelin sheath fragmentation during Wallerian degeneration. *J. Neurosci.* 31 (6), 2009–2015. <https://doi.org/10.1523/JNEUROSCI.4537-10.2011>.
- Kang, H., Lichtman, J.W., 2013. Motor axon regeneration and muscle reinnervation in young adult and aged animals. *J. Neurosci.* 33 (50), 19480–19491. <https://doi.org/10.1523/JNEUROSCI.4067-13.2013>.
- Kang, P.B., Lidov, H.G.W., David, W.S., Torres, A., Anthony, D.C., Jones, H.R., Darras, B.T., 2003. Diagnostic value of electromyography and muscle biopsy in arthrogryposis multiplex congenita. *Ann. Neurol.* 54 (6), 790–795. <https://doi.org/10.1002/ANA.10769>.
- Kastriti, M.E., Faure, L., Von Ahsen, D., Boudreuil, T.G., Boström, J., Solovieva, T., Jackson, C., Bronner, M., Meijer, D., Hadjeb, S., Lallemend, F., Erickson, A., Kaucka, M., Dyachuk, V., Perlmann, T., Lahti, L., Krivanek, J., Brunet, J., Fried, K., Adameyko, I., 2022a. Schwann cell precursors represent a neural crest-like state with biased multipotency. *EMBO J.* <https://doi.org/10.1525/EMBJ.2021108780>.
- Kastriti, M.E., Faure, L., von Ahsen, D., Boudreuil, T.G., Boström, J., Solovieva, T., Jackson, C., Bronner, M., Meijer, D., Hadjeb, S., Lallemend, F., Erickson, A., Kaucka, M., Dyachuk, V., Perlmann, T., Lahti, L., Krivanek, J., Brunet, J., Fried, K., Adameyko, I., 2022b. Schwann cell precursors represent a neural crest-like state with biased multipotency. *EMBO J.* 41 (17) <https://doi.org/10.1525/EMBJ.2021108780>.
- Kim, Y.S., Anderson, M., Park, K., Zheng, Q., Agarwal, A., Gong, C., Saijilafu Young, L.A., He, S., LaVinka, P.C., Zhou, F., Bergles, D., Hanani, M., Guan, Y., Spray, D.C., Dong, X., 2016. Coupled Activation of Primary Sensory Neurons Contributes to Chronic Pain. *Neuron* 91 (5), 1085–1096. <https://doi.org/10.1016/J.NEURON.2016.07.044>.
- Kim, S., Maynard, J.C., Strickland, A., Burlingame, A.L., Milbrandt, J., 2018. Schwann cell O-GlcNAcylation promotes peripheral nerve remyelination via attenuation of the AP-1 transcription factor JUN. *Proc. Natl. Acad. Sci. U. S. A.* 115 (31), 8019–8024. <https://doi.org/10.1073/PNAS.1805538115>.
- Kirkcaldie, M.T.K., Dwyer, S.T., 2017. The third wave: Intermediate filaments in the maturing nervous system. *Mol. Cell. Neurosci.* 84, 68–76. <https://doi.org/10.1016/J.MCN.2017.05.010>.
- Kirkpatrick, L.L., Brady, S.T., 1994. Modulation of the axonal microtubule cytoskeleton by myelinating Schwann cells. *J. Neurosci.* 14 (12), 7440–7450. <https://doi.org/10.1523/JNEUROSCI.14-12-07440.1994>.
- Klein, D., Martini, R., 2016. Myelin and macrophages in the PNS: An intimate relationship in trauma and disease. In: *Brain Research*, 1641. Elsevier, pp. 130–138. <https://doi.org/10.1016/j.brainres.2015.11.033>.
- Ko, C.P., Robitaille, R., 2015. Perisynaptic schwann cells at the neuromuscular synapse: adaptable, multitasking glial cells. *Cold Spring Harb. Perspect. Biol.* 7 (10) <https://doi.org/10.1101/cshperspect.a020503>.
- Kottmeier, R., Bittern, J., Schoofs, A., Scheiwe, F., Matzat, T., Pankratz, M., Klämbt, C., 2020. Wrapping glia regulates neuronal signaling speed and precision in the peripheral nervous system of *Drosophila*. *Nat. Commun.* 11 (1) <https://doi.org/10.1038/S41467-020-18291-1>.
- Kucenas, S., 2015. Perineurial glia. *Cold Spring Harb. Perspect. Biol.* 7 (6), 1–14. <https://doi.org/10.1101/cshperspect.a020511>.
- Kucenas, S., Takada, N., Park, H.C., Woodruff, E., Broadie, K., Appel, B., 2008. CNS-derived glia ensheath peripheral nerves and mediate motor root development. *Nat. Neurosci.* 11 (2), 143–151. <https://doi.org/10.1038/nn2025>.
- Kumar, S., Yin, X., Trapp, B.D., Paulaitis, M.E., Hoh, J.H., 2002. Role of long-range repulsive forces in organizing axonal neurofilament distributions: evidence from mice deficient in myelin-associated glycoprotein. *J. Neurosci. Res.* 68 (6), 681–690. <https://doi.org/10.1002/JNR.10249>.
- Labasque, M., Devaux, J.J., Lévéque, C., Faivre-Sarrailh, C., 2011. Fibronectin type III-like domains of neurofascin-186 protein mediate gliomedin binding and its clustering at the developing nodes of Ranvier. *J. Biol. Chem.* 286 (49), 42426–42434. <https://doi.org/10.1074/JBC.M111.266353>.
- Lasrado, R., Boesmans, W., Kleijnjung, J., Pin, C., Bell, D., Bhaw, L., McCallum, S., Zong, H., Luo, L., Clevers, H., Vanden Berghe, P., Pachnis, V., 2017. Lineage-dependent spatial and functional organization of the mammalian enteric nervous system. *Science (New York, N.Y.)* 356 (6339), 722–726. <https://doi.org/10.1126/SCIENCE.AAM751>.
- Lee, Y., Morrison, B.M., Li, Y., Lengacher, S., Farah, M.H., Hoffman, P.N., Liu, Y., Tsingalia, A., Jin, L., Zhang, P.W., Pellerin, L., Magistretti, P.J., Rothstein, J.D., 2012. Oligodendroglia metabolically support axons and contribute to neurodegeneration. *Nature* 487 (7408), 443–448. <https://doi.org/10.1038/NATURE11314>.
- Lee, S.H., Kim, Y.J., Choi, S.Y., 2016. BMP signaling modulates the probability of neurotransmitter release and readily releasable pools in *Drosophila* neuromuscular junction synapses. *Biochem. Biophys. Res. Commun.* 479 (3), 440–446. <https://doi.org/10.1016/J.JBRC.2016.09.072>.
- Lewin, G.R., Barde, Y.A., 1996. Physiology of the neurotrophins. *Annu. Rev. Neurosci.* 19, 289–317. <https://doi.org/10.1146/ANNUREV.NE.19.030196.001445>.
- Li, L., Ginty, D.D., 2014. The structure and organization of lanceolate mechanosensory complexes at mouse hair follicles. *ELife* 2014 (3). <https://doi.org/10.7554/ELIFE.01901.001>.
- Li, Z., Ngan, E.S.-W., 2022. New insights empowered by single-cell sequencing: From neural crest to enteric nervous system. *Comput. Struct. Biotechnol. J.* 20, 2464–2472. <https://doi.org/10.1016/J.CSBJ.2022.05.025>.
- Li, H.-Y., Say, E.H.M., Zhou, X.-F., 2007. Isolation and characterization of neural crest progenitors from adult dorsal root ganglia. *Stem Cells (Dayton, Ohio)* 25 (8), 2053–2065. <https://doi.org/10.1634/STEMCELLS.2007-0080>.
- Li, Y., Kang, S., Halawani, D., Wang, Y., Alves, C.J., Ramakrishnan, A., Estill, M., Shen, L., Li, F., He, X., Friedel, R.H., Zou, H., 2022. Macrophages facilitate peripheral nerve regeneration by organizing regeneration tracks through Plexin-B2. *Genes Dev.* 36 (3–4), 133–148. <https://doi.org/10.1101/GAD.349063.121>.
- Lin, W., Sanchez, H.B., Deerinck, T., Morris, J.K., Ellisman, M., Lee, K.F., 2000. Aberrant development of motor axons and neuromuscular synapses in erbB2-deficient mice. *Proc. Natl. Acad. Sci. U. S. A.* 97 (3), 1299–1304. <https://doi.org/10.1073/PNAS.97.3.1299>.
- Lindborg, J.A., Mack, M., Zigmond, R.E., 2017. Neutrophils are critical for myelin removal in a peripheral nerve injury model of wallerian degeneration. *J. Neurosci.* 37 (43), 10258–10277. <https://doi.org/10.1523/JNEUROSCI.2085-17.2017>.
- Liu, C., Yang, J., 2022. Enteric glial cells in immunological disorders of the gut. *Front. Cell. Neurosci.* 0, 210. <https://doi.org/10.3389/FNCEL.2022.895871>.
- López-Leal, R., Díaz-Viráguel, F., Catalán, R.J., Saquel, C., Enright, A., Iraola, G., Court, F. A., 2020. Schwann cell reprogramming into repair cells increases miRNA-21 expression in exosomes promoting axonal growth. *J. Cell Sci.* 133 (12) <https://doi.org/10.1242/JCS.239004>.
- López-Schier, H., Hudspeth, A.J., 2005. Supernumerary neuromasts in the posterior lateral line of zebrafish lacking peripheral glia. *Proc. Natl. Acad. Sci. U. S. A.* 102 (5), 1496–1501. <https://doi.org/10.1073/PNAS.0409361102>.
- López-Verrilli, M.A., Court, F.A., 2013. Exosomes: mediators of communication in eukaryotes. *Biol. Res.* 46 (1), 5–11. <https://doi.org/10.4067/S0716-97602013000100001>.
- López-Verrilli, M.A., Picou, F., Court, F.A., 2013. Schwann cell-derived exosomes enhance axonal regeneration in the peripheral nervous system. *Glia* 61 (11), 1795–1806. <https://doi.org/10.1002/GLIA.22558>.
- Love, F.M., Thompson, W.J., 1999. Glial cells promote muscle reinnervation by responding to activity-dependent postsynaptic signals. *J. Neurosci.* 19 (23), 10390–10396. <https://doi.org/10.1523/JNEUROSCI.19-23-10390.1999>.
- Lubischer, J.L., Bebbinger, D.M., 1999. Regulation of terminal Schwann cell number at the adult neuromuscular junction. *J. Neurosci.* 19 (24) <https://doi.org/10.1523/JNEUROSCI.19-24-00004.1999>.
- Lubischer, J.L., Thompson, W.J., 1999. Neonatal partial denervation results in nodal but not terminal sprouting and a decrease in efficacy of remaining neuromuscular junctions in rat soleus muscle. *J. Neurosci.* 19 (20), 8931–8944. <https://doi.org/10.1523/JNEUROSCI.19-20-08931.1999>.
- Lyons, D.A., Pogoda, H.M., Voas, M.G., Woods, I.G., Diamond, B., Nix, R., Arana, N., Jacobs, J., Talbot, W.S., 2005. erbB3 and erbB2 are essential for schwann cell migration and myelination in zebrafish. *Curr. Biol.* 15 (6), 513–524. <https://doi.org/10.1016/J.CUB.2005.02.030>.
- MacEachern, S.J., Patel, B.A., Keenan, C.M., Dickey, M., Chapman, K., McCafferty, D.M., Savidge, T.C., Beck, P.L., MacNaughton, W.K., Sharkey, K.A., 2015. Inhibiting inducible nitric oxide synthase in enteric glia restores electrogenic ion transport in mice with colitis. *Gastroenterology* 149 (2), 445–455.e3. <https://doi.org/10.1053/J.GASTRO.2015.04.007>.
- Maertens, B., Hopkins, D., Franzke, C.W., Keene, D.R., Bruckner-Tuderman, L., Greenspan, D.S., Koch, M., 2007. Cleavage and oligomerization of gliomedin, a transmembrane collagen required for node of ranvier formation. *J. Biol. Chem.* 282 (14), 10647–10659. <https://doi.org/10.1074/JBC.M611339200>.

- Magni, G., Riccio, D., Ceruti, S., 2018. Tackling Chronic Pain and Inflammation through the Purinergic System. *Curr. Med. Chem.* 25 (32), 3830–3865. <https://doi.org/10.2174/092986732466170710110630>.
- Mapa, A.A., Thomsen, M.B., Boehm, E., Zhao, H., Hattar, S., Kuruvilla, R., 2022. Diversity of satellite glia in sympathetic and sensory ganglia. *Cell Rep.* 38 (5) <https://doi.org/10.1016/J.CELREP.2022.110328>.
- Marol, G.S., Vermeren, M., Voiculescu, O., Melton, L., Cohen, J., Charnay, P., Topilko, P., 2004. Neural crest boundary cap cells constitute a source of neuronal and glial cells of the PNS. *Nat. Neurosci.* 7 (9), 930–938. <https://doi.org/10.1038/NN1299>.
- Martin, S.M., O'Brien, G.S., Portera-Cailliau, C., Sagasti, A., 2010. Wallerian degeneration of zebrafish trigeminal axons in the skin is required for regeneration and developmental pruning. *Development (Cambridge, England)* 137 (23), 3985–3994. <https://doi.org/10.1242/DEV.053611>.
- Martini, R., 2001. The effect of myelinating Schwann cells on axons. *Muscle Nerve* 24 (4), 456–466. <https://doi.org/10.1002/MUS.1027>.
- Martini, R., Xin, Y., Schmitz, B., Schachner, M., 1992. The L2/HNK-1 carbohydrate epitope is involved in the preferential outgrowth of motor neurons on ventral roots and motor nerves. *Eur. J. Neurosci.* 4 (7), 628–639. <https://doi.org/10.1111/J.1460-9568.1992.TB00171.X>.
- Martini, R., Schachner, M., Brushart, T.M., 1994. The L2/HNK-1 carbohydrate is preferentially expressed by previously motor axon-associated Schwann cells in reinnervated peripheral nerves. *J. Neurosci.* 14 (11 Pt 2), 7180–7191. <https://doi.org/10.1523/JNEUROSCI.14-11-07180.1994>.
- Martini, R., Fischer, S., López-Vales, R., David, S., 2008. Interactions between Schwann cells and macrophages in injury and inherited demyelinating disease. *Glia* 56 (14), 1566–1577. <https://doi.org/10.1002/GLIA.20766>.
- Mata, M., Kupina, N., Fink, D.J., 1992. Phosphorylation-dependent neurofilament epitopes are reduced at the node of Ranvier. *J. Neurocytol.* 21 (3), 199–210. <https://doi.org/10.1007/BF01194978>.
- Maudlej, N., Hanani, M., 1992. Modulation of dye coupling among glial cells in the myenteric and submucosal plexuses of the guinea pig. *Brain Res.* 578 (1–2), 94–98. [https://doi.org/10.1016/0006-8993\(92\)90234-Z](https://doi.org/10.1016/0006-8993(92)90234-Z).
- McClain, J.L., Grubišić, V., Fried, D., Gomez-Suarez, R.A., Leininger, G.M., Sévigny, J., Parpura, V., Gulbransen, B.D., 2014. Ca²⁺ responses in enteric glia are mediated by connexin-43 hemichannels and modulate colonic transit in mice. *Gastroenterology* 146 (2). <https://doi.org/10.1053/J.GASTRO.2013.10.061>.
- McClain, J.L., Fried, D.E., Gulbransen, B.D., 2015. Agonist-evoked Ca²⁺ signaling in enteric glia drives neural programs that regulate intestinal motility in mice. *Cell. Mol. Gastroenterol. Hepatol.* 1 (6), 631–645. <https://doi.org/10.1016/J.JCMGH.2015.08.004>.
- McFerrin, J., Patton, B.L., Sunderhaus, E.R., Kretschmar, D., 2017. NTE/PNPLA6 is expressed in mature Schwann cells and is required for glial ensheathment of Remak fibers. *Glia* 65 (5), 804–816. <https://doi.org/10.1002/GLIA.23127>.
- McKerracher, L., David, S., Jackson, D.L., Kottis, V., Dunn, R.J., Braun, P.E., 1994. Identification of myelin-associated glycoprotein as a major myelin-derived inhibitor of neurite growth. *Neuron* 13 (4), 805–811. [https://doi.org/10.1016/0896-6273\(94\)90247-X](https://doi.org/10.1016/0896-6273(94)90247-X).
- Meyer Zu Hörste, G., Heidenreich, H., Mausberg, A.K., Lehmann, H.C., ten Asbroek, A.L., M.A., Saavedra, J.T., Baas, F., Hartung, H.P., Wiendl, H., Kieseier, B.C., 2010. Mouse Schwann cells activate MHC class I and II restricted T-cell responses, but require external peptide processing for MHC class II presentation. *Neurobiol. Dis.* 37 (2), 483–490. <https://doi.org/10.1016/J.NBD.2009.11.006>.
- Meyer Zu Reckendorf, S., Brand, C., Pedro, M.T., Hegler, J., Schilling, C.S., Lerner, R., Bindila, L., Antoniadis, G., Knöll, B., 2020. Lipid metabolism adaptations are reduced in human compared to murine Schwann cells following injury. *Nat. Commun.* 11 (1) <https://doi.org/10.1038/s41467-020-15915-4>.
- Michailov, G.V., Sereda, M.W., Brinkmann, B.G., Fischer, T.H., Haug, B., Birchmeier, C., Role, L., Lai, C., Schwab, M.H., Nave, K.A., 2004. Axonal neuroregulin-1 regulates myelin sheath thickness. *Science* 304 (5671), 700–703. <https://doi.org/10.1126/science.1095862>.
- Min, Q., Parkinson, D.B., Dun, X.P., 2021. Migrating Schwann cells direct axon regeneration within the peripheral nerve bridge. *Glia* 69 (2), 235–254. <https://doi.org/10.1002/glia.23892>.
- Mirsky, R., Parmantier, E., McMahon, A.P., Jessen, K.R., 1999. Schwann cell-derived desert hedgehog signals nerve sheath formation. *Ann. N. Y. Acad. Sci.* 883 (1), 196–202. <https://doi.org/10.1111/j.1749-6632.1999.tb08582.x>.
- Mirsky, R., Jessen, K.R., Brennan, A., Parkinson, D., Dong, Z., Meier, C., Parmantier, E., Lawson, D., 2002. Schwann cells as regulators of nerve development. *J. Physiol. Paris* 96 (1–2), 17–24. [https://doi.org/10.1016/S0928-4257\(01\)00076-6](https://doi.org/10.1016/S0928-4257(01)00076-6).
- Monk, K.R., Feltri, M.L., Taveggia, C., 2015. New insights on schwann cell development. *Glia* 63 (8), 1376–1393. <https://doi.org/10.1002/glia.22852>.
- Monsma, P.C., Li, Y., Daniel Fenn, J., Jung, P., Brown, A., 2014. Local regulation of neurofilament transport by myelinating cells. *J. Neurosci.* 34 (8), 2979–2988. <https://doi.org/10.1523/JNEUROSCI.4502-13.2014>.
- Moore, J.W., Joyner, R.W., Brill, M.H., Waxman, S.D., Najjar-Joa, M., 1978. Simulations of conduction in uniform myelinated fibers. Relative sensitivity to changes in nodal and internodal parameters. *Biophys. J.* 21 (2), 147–160. [https://doi.org/10.1016/S0006-3495\(78\)85515-5](https://doi.org/10.1016/S0006-3495(78)85515-5).
- Morales-Soto, W., Gulbransen, B.D., 2019. Enteric glia: a new player in abdominal pain. *Cell. Mol. Gastroenterol. Hepatol.* 7 (2), 433–445. <https://doi.org/10.1016/J.JCMGH.2018.11.005>.
- Morris, J.K., Weichun, L., Hauser, C., Marchuk, Y., Getman, D., Kuo-Fen, L., 1999. Rescue of the cardiac defect in erbB2 mutant mice reveals essential roles of erbB2 in peripheral nervous system development. *Neuron* 23 (2), 273–283. [https://doi.org/10.1016/S0896-6273\(00\)80779-5](https://doi.org/10.1016/S0896-6273(00)80779-5).
- Morrison, B.M., Tsingalia, A., Vidensky, S., Lee, Y., Jin, L., Farah, M.H., Lengacher, S., Magistretti, P.J., Pellerin, L., Rothstein, J.D., 2015. Deficiency in monocarboxylate transporter 1 (MCT1) in mice delays regeneration of peripheral nerves following sciatic nerve crush. *Exp. Neurol.* 263, 325–338. <https://doi.org/10.1016/J.EXPNEUROL.2014.10.018>.
- Mukhopadhyay, G., Doherty, P., Walsh, F.S., Crocker, P.R., Filbin, M.T., 1994. A novel role for myelin-associated glycoprotein as an inhibitor of axonal regeneration. *Neuron* 13 (3), 757–767. [https://doi.org/10.1016/0896-6273\(94\)90042-6](https://doi.org/10.1016/0896-6273(94)90042-6).
- Mukouyama, Y.S., Shin, D., Britsch, S., Taniguchi, M., Anderson, D.J., 2002. Sensory nerves determine the pattern of arterial differentiation and blood vessel branching in the skin. *Cell* 109 (6), 693–705. [https://doi.org/10.1016/S0092-8674\(02\)00757-2](https://doi.org/10.1016/S0092-8674(02)00757-2).
- Murinson, B.B., Griffin, J.W., 2004. C-fiber structure varies with location in peripheral nerve. *J. Neuropathol. Exp. Neurol.* 63 (3), 246–254. <https://doi.org/10.1093/JNEN/63.3.246>.
- Murphy, P.L., Isaacman-Beck, J., Granato, M., 2022. Robo2 drives target-selective peripheral nerve regeneration in response to glia-derived signals. *J. Neurosci.* 42 (5), 762–776. <https://doi.org/10.1523/JNEUROSCI.1528-21.2021>.
- Nasser, Y., Fernandez, E., Keenan, C.M., Ho, W., Oland, L.D., Tibbles, L.A., Schemann, M., MacNaughton, W.K., Rühl, A., Sharkey, K.A., 2006. Role of enteric glia in intestinal physiology: effects of the gliotoxin fluorocitrate on motor and secretory function. *Am. J. Physiol. Gastrointest. Liver Physiol.* 291 (5) <https://doi.org/10.1152/AJGGL.00067.2006>.
- Nave, K.A., 2010. Myelination and the trophic support of long axons. *Nat. Rev. Neurosci.* 11 (4), 275–283. Nature Publishing Group. <https://doi.org/10.1038/nrn2797>.
- Nave, K.A., Werner, H.B., 2021. Ensheathment and myelination of axons: evolution of glial functions. *Annu. Rev. Neurosci.* 44, 197–219. <https://doi.org/10.1146/ANNUREV-NEURO-100120-122621>.
- Negro, S., Lessi, F., Duregotti, E., Aretini, P., La Ferla, M., Franceschi, S., Menicagli, M., Bergamini, E., Radice, E., Thelen, M., Megighian, A., Pirazzini, M., Mazzanti, C.M., Rigoni, M., Montecucco, C., 2017. CXCL12α/SDF-1 from perisynaptic Schwann cells promotes regeneration of injured motor axon terminals. *EMBO Mol. Med.* 9 (8), 1000–1010. <https://doi.org/10.1525/EMMM.201607257>.
- Neunlist, M., Van Landeghem, L., Mahé, M.M., Derkinderen, P., Des Varannes, S.B., Roll-Derkinderen, M., 2013. The digestive neuronal-glia-epithelial unit: a new actor in gut health and disease. *Nat. Rev. Gastroenterol. Hepatol.* 10 (2), 90–100. <https://doi.org/10.1038/NGASTRO.2012.221>.
- Newbern, J.M., 2015. Molecular control of the neural crest and peripheral nervous system development. *Curr. Top. Dev. Biol.* 111, 201. <https://doi.org/10.1016/BS.CTDB.2014.11.007>.
- Newbern, J.M., Li, X., Shoemaker, S.E., Zhou, J., Zhong, J., Wu, Y., Bonder, D., Hollenback, S., Copolla, G., Geschwind, D.H., Landreth, G.E., Snider, W.D., 2011. Specific functions for ERK/MAPK signaling during PNS development. *Neuron* 69 (1), 91–105. <https://doi.org/10.1016/J.NEURON.2010.12.003>.
- Nocera, G., Jacob, C., 2020. Mechanisms of Schwann cell plasticity involved in peripheral nerve repair after injury. *Cell. Mol. Life Sci.* 77 (20), 3977–3989. <https://doi.org/10.1007/s00018-020-03516-9>.
- Obremski, V.J., Wood, P.M., Bunge, M.B., 1993. Fibroblasts promote Schwann cell basal lamina deposition and elongation in the absence of neurons in culture. *Dev. Biol.* 160 (1), 119–134. <https://doi.org/10.1006/DBIO.1993.1291>.
- Ozaki, A., Nagai, A., Lee, Y.B., Myong, N.H., Kim, S.U., 2008. Expression of cytokines and cytokine receptors in human Schwann cells. *Neuroreport* 19 (1), 31–35. <https://doi.org/10.1097/WNR.0B013E3282F27E60>.
- Pan, B., Fromholt, S.E., Hess, E.J., Crawford, T.O., Griffin, J.W., Sheikh, K.A., Schnaar, R.L., 2005. Myelin-associated glycoprotein and complementary axonal ligands, gangliosides, mediate axon stability in the CNS and PNS: Neuropathology and behavioral deficits in single- and double-null mice. *Exp. Neurol.* 195 (1), 208–217. <https://doi.org/10.1016/J.EXPNEUROL.2005.04.017>.
- Pannese, E., 1981. The satellite cells of the sensory ganglia. *Adv. Anat. Embryol. Cell Biol.* 65 <https://doi.org/10.1007/978-3-642-67750-2>.
- Pannese, E., 2010. The structure of the perineuronal sheath of satellite glial cells (SGCs) in sensory ganglia. *Neuron Glia Biol.* 6 (1), 3–10. <https://doi.org/10.1017/S1740925X10000037>.
- Parfejevs, V., Debbache, J., Shakhova, O., Schaefer, S.M., Glausch, M., Wegner, M., Suter, U., Riekstina, U., Werner, S., Sommer, L., 2018. Injury-activated glial cells promote wound healing of the adult skin in mice. *Communications* 9 (1). <https://doi.org/10.1038/S41467-017-01488-2>.
- Parmantier, E., Lynn, B., Lawson, D., Turmaine, M., Namini, S.S., Chakrabarti, L., McMahon, A.P., Jessen, K.R., Mirsky, R., 1999. Schwann cell-derived desert hedgehog controls the development of peripheral nerve sheaths. *Neuron* 23 (4), 713–724. [https://doi.org/10.1016/S0896-6273\(01\)80030-1](https://doi.org/10.1016/S0896-6273(01)80030-1).
- Parrinello, S., Napoli, I., Ribeiro, S., Digby, P.W., Fedorova, M., Parkinson, D.B., Doddrell, R.D.S., Nakayama, M., Adams, R.H., Lloyd, A.C., 2010. EphB signaling directs peripheral nerve regeneration through Sox2-dependent Schwann cell Sorting. *Cell* 143 (1), 145–155. <https://doi.org/10.1016/j.cell.2010.08.039>.
- Pellegatta, M., Canevazzi, P., Forese, M.G., Podini, P., Valenzano, S., Del Carro, U., Quattrini, A., Taveggia, C., 2022. ADAM17 Regulates p75 NTR-Mediated Fibrinolysis and Nerve Remyelination. *J. Neurosci.* 42 (12), 2433–2447. <https://doi.org/10.1523/JNEUROSCI.1341-21.2022>.
- Perez-Gonzalez, A.P., Provost, F., Rousse, I., Piovesana, R., Benzina, O., Darabid, H., Lamoureux, B., Wang, Y.S., Arbour, D., Robitaille, R., 2022. Functional adaptation of glial cells at neuromuscular junctions in response to injury. *Glia*. <https://doi.org/10.1002/GLIA.24184>.
- Perry, V.H., Tsao, J.W., Feam, S., Brown, M.C., 1995. Radiation-induced reductions in macrophage recruitment have only slight effects on myelin degeneration in sectioned peripheral nerves of mice. *Eur. J. Neurosci.* 7 (2), 271–280. <https://doi.org/10.1111/J.1460-9568.1995.TB01063.X>.

- Pochard, C., Coquenlorge, S., Jaulin, J., Cenac, N., Vergnolle, N., Meurette, G., Freyssinet, M., Neunlist, M., Rolli-Derkinderen, M., 2016. Defects in 15-HETE production and control of epithelial permeability by human enteric glial cells from patients with Crohn's disease. *Gastroenterology* 150 (1), 168–180. <https://doi.org/10.1053/J.GASTRO.2015.09.038>.
- Poitelon, Y., Lopez-Anido, C., Catignas, K., Berti, C., Palmisano, M., Williamson, C., Ameroso, D., Abiko, K., Hwang, Y., Gregorjeff, A., Wrana, J.L., Asmani, M., Zhao, R., Sim, F.J., Wrabetz, L., Svaren, J., Feltri, M.L., 2016. YAP and TAZ control peripheral myelination and the expression of laminin receptors in Schwann cells. *Nat. Neurosci.* 19 (7), 879–887. <https://doi.org/10.1038/NN.4316>.
- Poliak, S., Peles, E., 2003. The local differentiation of myelinated axons at nodes of Ranvier. *Nat. Rev. Neurosci.* 4 (12), 968–980. <https://doi.org/10.1038/nrn1253>.
- Pooya, S., Liu, X., Kumar, V.B.S., Anderson, J., Imai, F., Zhang, W., Ciraolo, G., Ratner, N., Setchell, K.D.R., Yutaka, Y., Jankowski, M.P., Dasgupta, B., 2014. The tumour suppressor LKB1 regulates myelination through mitochondrial metabolism. *Nat. Commun.* 5. <https://doi.org/10.1038/NCOMMS5993>.
- Porrello, E., Rivellini, C., Dina, G., Triolo, D., Del Carro, U., Ungaro, D., Panattoni, M., Feltri, M.L., Wrabetz, L., Pardi, R., Quattrini, A., Previtali, S.C., 2014. Jab1 regulates Schwann cell proliferation and axonal sorting through p27. *J. Exp. Med.* 211 (1), 29–43. <https://doi.org/10.1084/JEM.20130720>.
- Previtali, S.C., 2021. Peripheral Nerve Development and the Pathogenesis of Peripheral Neuropathy: the Sorting Point. *Neurotherapeutics* 18 (4), 2156–2168. <https://doi.org/10.1007/s13311-021-01080-z>.
- Previtali, S.C., Zambon, A.A., 2020. LAMA2 neuropathies: human findings and pathomechanisms from mouse models. *Front. Mol. Neurosci.* 0, 60. <https://doi.org/10.3389/FMOL.2020.00060>.
- Progatzky, F., Shapiro, M., Chng, S.H., Garcia-Cassani, B., Classon, C.H., Sevgi, S., Laddach, A., Bon-Frauches, A.C., Lasrado, R., Rahim, M., Amaniti, E.M., Boeing, S., Shah, K., Entwistle, L.J., Suárez-Bonnet, A., Wilson, M.S., Stockinger, B., Pachnis, V., 2021. Regulation of intestinal immunity and tissue repair by enteric glia. *Nature* 599 (7883), 125–130. <https://doi.org/10.1038/S41586-021-04006-Z>.
- Radomska, K.J., Topilko, P., 2017. Boundary cap cells in development and disease. *Curr. Opin. Neurobiol.* 47, 209–215. <https://doi.org/10.1016/j.conb.2017.11.003>.
- Ramón, Y., De Felipe, J., Jones, E.G., May, R.M., 1928. Cajal's degeneration and regeneration of the nervous system. In: Cajal's Degeneration and Regeneration of the Nervous System. Oxford University Press. <https://doi.org/10.1093/acprof:oso/9780195065169.001.0001>.
- Rao, M., Gershon, M.D., 2015. Bugs, guts, and glia: how microbiota influence enteric gliogenesis and migration. *Neuron* 85 (2), 229–230. <https://doi.org/10.1016/J.NEURON.2014.12.066>.
- Rao, M.V., Campbell, J., Yuan, A., Kumar, A., Gotow, T., Uchiyama, Y., Nixon, R.A., 2003. The neurofilament middle molecular mass subunit carboxyl-terminal tail domains is essential for the radial growth and cytoskeletal architecture of axons but not for regulating neurofilament transport rate. *J. Cell Biol.* 163 (5), 1021–1031. <https://doi.org/10.1083/JCB.200308076>.
- Rao, M., Rastelli, D., Dong, L., Chiu, S., Setlik, W., Gershon, M.D., Corfas, G., 2017. Enteric glia regulate gastrointestinal motility but are not required for maintenance of the epithelium in mice. *Gastroenterology* 153 (4), 1068–1081.e7. <https://doi.org/10.1053/J.GASTRO.2017.07.002>.
- Raphael, A.R., Talbot, W.S., 2011. New insights into signaling during myelination in zebrafish. *Curr. Top. Dev. Biol.* 97, 1. <https://doi.org/10.1016/B978-0-12-385975-4.00007-3>.
- Raphael, A.R., Perlin, J.R., Talbot, W.S., 2010. Schwann cells reposition a peripheral nerve to isolate it from postembryonic remodeling of its targets. *Development* 137 (21), 3643–3649. <https://doi.org/10.1242/DEV.057521>.
- Rasband, M.N., Peles, E., 2021. Mechanisms of node of Ranvier assembly. *Nat. Rev. Neurosci.* 22 (1), 7–20. <https://doi.org/10.1038/s41583-020-00406-8>.
- Reed, C.B., Frick, L.R., Weaver, A., Sidoli, M., Schlant, E., Feltri, M.L., Wrabetz, L., 2020. Deletion of calcineurin in schwann cells does not affect developmental myelination, but reduces autophagy and delays myelin clearance after peripheral nerve injury. *J. Neurosci.* 40 (32), 6165–6176. <https://doi.org/10.1523/JNEUROSCI.0951-20.2020>.
- Reed, C.B., Feltri, M.L., Wilson, E.R., 2021. Peripheral glia diversity. *J. Anat.* (February), 1–16. <https://doi.org/10.1111/joa.13484>.
- Reist, N.E., Smith, S.J., 1992. Neurally evoked calcium transients in terminal Schwann cells at the neuromuscular junction. *Proc. Natl. Acad. Sci. U. S. A.* 89 (16), 7625–7629. <https://doi.org/10.1073/PNAS.89.16.7625>.
- Reles, A., Friede, R.L., 1991. Axonal cytoskeleton at the nodes of Ranvier. *J. Neurocytol.* 20 (6), 450–458. <https://doi.org/10.1007/BF01252273>.
- Reynolds, M.L., Woolf, C.J., 1993. Reciprocal Schwann cell-axon interactions. *Curr. Opin. Neurobiol.* 3 (5), 683–693. [https://doi.org/10.1016/0959-4388\(93\)90139-P](https://doi.org/10.1016/0959-4388(93)90139-P).
- Ribeiro-Resende, V.T., Koenig, B., Nichterwitz, S., Oberhoffner, S., Schlosshauer, B., 2009. Strategies for inducing the formation of bands of Büngner in peripheral nerve regeneration. *Biomaterials* 30 (29), 5251–5259. <https://doi.org/10.1016/J.BIOMATERIALS.2009.07.007>.
- Riethmacher, D., Sonnenberg-Riethmacher, E., Brinkmann, V., Yamaai, T., Lewin, G.R., Birchmeier, C., 1997. Severe neuropathies in mice with targeted mutations in the ErbB3 receptor. *Nature* 389 (6652), 725–730. <https://doi.org/10.1038/39593>.
- Rinwa, P., Calvo-Enrique, L., Zhang, M.D., Nyengaard, J.R., Karlsson, P., Ernfors, P., 2021. Demise of nociceptive Schwann cells causes nerve retraction and pain hyperalgesia. *Pain* 162 (6), 1816–1827. <https://doi.org/10.1097/J.PAIN.0000000000002169>.
- Robitaille, R., 1998. Modulation of synaptic efficacy and synaptic depression by glial cells at the frog neuromuscular junction. *Neuron* 21 (4), 847–855. [https://doi.org/10.1016/S0896-6273\(00\)80600-5](https://doi.org/10.1016/S0896-6273(00)80600-5).
- Rochon, D., Rousse, I., Robitaille, R., 2001. Synapse-glia interactions at the mammalian neuromuscular junction. *J. Neurosci.* 21 (11), 3819–3829. <https://doi.org/10.1523/JNEUROSCI.21-11-03819.2001>.
- Rosenberg, A.F., Isaacman-Beck, J., Franzini-Armstrong, C., Granato, M., 2014. Schwann cells and deleted in colorectal carcinoma direct regenerating motor axons towards their original path. *J. Neurosci.* 34 (44), 14668–14681. <https://doi.org/10.1523/JNEUROSCI.2007-14.2014>.
- Rosenbluth, J., 2009. Multiple functions of the paranodal junction of myelinated nerve fibers. *J. Neurosci. Res.* 87 (15), 3250–3258. <https://doi.org/10.1002/JNR.22013>.
- Rosso, G., Liashkovich, I., Young, P., Röhr, D., Shahin, V., 2017a. Schwann cells and neurite outgrowth from embryonic dorsal root ganglia are highly mechanosensitive. *Nanomedicine* 13 (2), 493–501. <https://doi.org/10.1016/J.NANO.2016.06.011>.
- Rosso, G., Young, P., Shahin, V., 2017b. Mechanosensitivity of Embryonic Neurites Promotes Their Directional Extension and Schwann Cells Progenitors Migration. *Cell. Physiol. Biochem.* 44 (4), 1263–1270. <https://doi.org/10.1159/000485485>.
- Rotshenker, S., 2011. Wallerian degeneration: the innate-immune response to traumatic nerve injury. *J. Neuroinflammation* 8 (109). <https://doi.org/10.1186/1742-2094-8-109>.
- Sahenk, Z., Brady, S.T., 1987. Axonal tubulin and microtubules: morphologic evidence for stable regions on axonal microtubules. *Cell Motil. Cytoskeleton* 8 (2), 155–164. <https://doi.org/10.1002/CM.970080207>.
- Sakaguchi, T., Okada, M., Kitamura, T., Kawasaki, K., 1993. Reduced diameter and conduction velocity of myelinated fibers in the sciatic nerve of a neurofilament-deficient mutant quail. *Neurosci. Lett.* 153 (1), 65–68. [https://doi.org/10.1016/0304-3940\(93\)90078-Y](https://doi.org/10.1016/0304-3940(93)90078-Y).
- Salzer, J.L., 2003. Polarized Domains of Myelinated Axons. *Neuron* 40 (2), 297–318. [https://doi.org/10.1016/S0896-6273\(03\)00628-7](https://doi.org/10.1016/S0896-6273(03)00628-7).
- Salzer, J.L., 2015. Schwann cell myelination. *Cold Spring Harb. Perspect. Biol.* 7 (8) <https://doi.org/10.1101/cshperspect.a020529>.
- Salzer, J.L., Brophy, P.J., Peles, E., 2008. Molecular domains of myelinated axons in the peripheral nervous system. *Glia* 56 (14), 1532–1540. <https://doi.org/10.1002/GLIA.20750>.
- Savidge, T.C., Newman, P., Pothoulakis, C., Ruhl, A., Neunlist, M., Bourreille, A., Hurst, R., Sofroniew, M.V., 2007. Enteric glia regulate intestinal barrier function and inflammation via release of S-nitrosoglutathione. *Gastroenterology* 132 (4), 1344–1358. <https://doi.org/10.1053/J.GASTRO.2007.01.051>.
- Schäfer, M., Fruttiger, M., Montag, D., Schachner, M., Martini, R., 1996. Disruption of the gene for the myelin-associated glycoprotein improves axonal regrowth along myelin in C57BL/6J mice. *Neuron* 16 (6), 1107–1113. [https://doi.org/10.1016/S0896-6273\(00\)80137-3](https://doi.org/10.1016/S0896-6273(00)80137-3).
- Scheibl, J., Höke, A., 2016. Impaired regeneration in aged nerves: Clearing out the old to make way for the new. *Exp. Neurol.* 284, 79–83. <https://doi.org/10.1016/j.expneurol.2016.07.010>.
- Schröder, J.M., 1972. Altered ratio between axon diameter and myelin sheath thickness in regenerated nerve fibers. *Brain Res.* 45 (1), 49–65. [https://doi.org/10.1016/0006-8993\(72\)90215-6](https://doi.org/10.1016/0006-8993(72)90215-6).
- Schubert, T., Friede, R.L., 1981. The role of endoneurial fibroblasts in myelin degradation. *J. Neuropathol. Exp. Neurol.* 40 (2), 134–154. <https://doi.org/10.1097/00005072-19810300-00006>.
- Schwaller, F., Bégy, V., García-García, G., Taberner, F.J., Moshourab, R., McDonald, B., Docter, T., Kühnemund, J., Ojeda-Alonso, J., Paricio-Montesinos, R., Lechner, S.G., Poulet, J.F.A., Millan, J.M., Lewin, G.R., 2021. USH2A is a Meissner's corpuscle protein necessary for normal vibration sensing in mice and humans. *Nat. Neurosci.* 24 (1), 74–81. <https://doi.org/10.1038/S41593-020-00751-Y>.
- Seddon, H.J., Medawar, P.B., Smith, H., 1943. Rate of regeneration of peripheral nerves in man. *J. Physiol.* 102 (2), 191–215. <https://doi.org/10.1113/JPHYSIOL.1943.SP04027>.
- Shackleford, G., Marziali, L.N., Sasaki, Y., Weinstock, N.I., Rossor, A.M., Silvestri, N.J., Wilson, E.R., Hurley, E., Kidd, G.J., Manohar, S., Ding, D., Salvi, R.J., Laura Feltri, M., D'Antonio, M., Wrabetz, L., 2022. MPZ-T124M mouse model replicates human axonopathy and suggest alteration in axo-glia communication. *BioRxiv*. <https://doi.org/10.1101/2022.05.09.491190>, 2022.05.09.491190.
- Shanthaveerappa, T.R., Bourne, G.H., 1966. Perineural epithelium: a new concept of its role in the integrity of the peripheral nervous system. *Science (New York, N.Y.)* 154 (3755), 1464–1467. <https://doi.org/10.1126/SCIENCE.154.3755.1464>.
- Sharghi-Namini, S., Turnaime, M., Meier, C., Sahni, V., Umehara, F., Jessen, K.R., Mirsky, R., 2006. The structural and functional integrity of peripheral nerves depends on the glial-derived signal desert hedgehog. *J. Neurosci.* 26 (23), 6364–6376. <https://doi.org/10.1523/JNEUROSCI.0157-06.2006>.
- Shen, Y.J., DeBellard, M.E., Salzer, J.L., Roder, J., Filbin, M.T., 1998. Myelin-associated glycoprotein in myelin and expressed by Schwann cells inhibits axonal regeneration and branching. *Mol. Cell. Neurosci.* 12 (1–2), 79–91. <https://doi.org/10.1006/MCNE.1998.0700>.
- Sherman, D.L., Brophy, P.J., 2005. Mechanisms of axon ensheathment and myelin growth. *Nat. Rev. Neurosci.* 6 (9), 683–690. <https://doi.org/10.1038/nrn1743>.
- Simons, M., Lyons, D.A., 2013. Axonal selection and myelin sheath generation in the central nervous system. *Curr. Opin. Cell Biol.* 25 (4), 512–519. <https://doi.org/10.1016/j.ceb.2013.04.007>.
- Smith, R.S., Koles, Z.J., 1970. Myelinated nerve fibers: computed effect of myelin thickness on conduction velocity. *Am. J. Phys.* 219 (5), 1256–1258. <https://doi.org/10.1152/AJLEGACY.1970.219.5.1256>.
- Smith, I.W., Mikes, M., Lee, Y. Il, Thompson, W.J., 2013. Terminal Schwann cells participate in the competition underlying neuromuscular synapse elimination. *J. Neurosci.* 33 (45), 17724–17736. <https://doi.org/10.1523/JNEUROSCI.3339-13.2013>.

- Snider, W.D., 1994. Functions of the neurotrophins during nervous system development: what the knockouts are teaching us. *Cell* 77 (5), 627–638. [https://doi.org/10.1016/0092-8674\(94\)90048-5](https://doi.org/10.1016/0092-8674(94)90048-5).
- Sock, E., Wegner, M., 2019. Transcriptional control of myelination and remyelination. *Glia* 67 (11), 2153–2165. <https://doi.org/10.1002/glia.23636>.
- Son, Y.J., Thompson, W.J., 1995. Nerve sprouting in muscle is induced and guided by processes extended by Schwann cells. *Neuron* 14 (1), 133–141. [https://doi.org/10.1016/0896-6273\(95\)90247-3](https://doi.org/10.1016/0896-6273(95)90247-3).
- Song, X.Y., Zhou, F.H.H., Zhong, J.H., Wu, L.L.Y., Zhou, X.F., 2006. Knockout of p75 (NTR) impairs re-myelination of injured sciatic nerve in mice. *J. Neurochem.* 96 (3), 833–842. <https://doi.org/10.1111/j.1471-4159.2005.03564.x>.
- Souza, G.R., Talbot, J., Lotufo, C.M., Cunha, F.Q., Cunha, T.M., Ferreira, S.H., 2013. Fractalkine mediates inflammatory pain through activation of satellite glial cells. *Proc. Natl. Acad. Sci. U. S. A.* 110 (27), 11193–11198. <https://doi.org/10.1073/pnas.1307445110>.
- Spray, D.C., Iglesias, R., Shraer, N., Suadicani, S.O., Belzer, V., Hanstein, R., Hanani, M., 2019. Gap junction mediated signaling between satellite glia and neurons in trigeminal ganglia. *Glia* 67 (5), 791–801. <https://doi.org/10.1002/GLIA.23554>.
- Stassart, R.M., Woodhoo, A., 2021. Axo-axial interaction in the injured PNS. *Dev. Neurobiol.* 81 (5), 490–506. <https://doi.org/10.1002/dneu.22771>.
- Stassart, R.M., Fledrich, R., Velanovic, V., Brinkmann, B.G., Schwab, M.H., Meijer, D., Sereda, M.W., Nave, K.A., 2013. A role for Schwann cell-derived neuregulin-1 in remyelination. *Nat. Neurosci.* 16 (1), 48–54. <https://doi.org/10.1038/nn.3281>.
- Stassart, R.M., Möbius, W., Nave, K.A., Edgar, J.M., 2018. The Axon-Myelin unit in development and degenerative disease. *Front. Neurosci.* 12 (JUL) <https://doi.org/10.3389/fnins.2018.00467>. Frontiers Media S.A.
- Sterli, S., Imperatore, V., Lloyd, A.C., 2019. Schwann cell plasticity-roles in tissue homeostasis, regeneration, and disease. *Glia* 67 (11), 2203–2215. <https://doi.org/10.1002/glia.23643>.
- Stratton, J.A., Holmes, A., Rosin, N.L., Sinha, S., Vohra, M., Burma, N.E., Trang, T., Midha, R., Biernaskie, J., 2018. Macrophages regulate schwann cell maturation after nerve injury. *Cell Rep.* 24 (10), 2561–2572.e6. <https://doi.org/10.1016/j.celrep.2018.08.004>.
- Strickland, I.T., Richards, L., Holmes, F.E., Wynnick, D., Uney, J.B., Wong, L.F., 2011. Axotomy-induced miR-21 promotes axon growth in adult dorsal root ganglion neurons. *PLoS One* 6 (8). <https://doi.org/10.1371/journal.pone.0023423>.
- Sudanic, S.O., Cherkas, P.S., Zuckerman, J., Smith, D.N., Spray, D.C., Hanani, M., 2010. Bidirectional calcium signaling between satellite glial cells and neurons in cultured mouse trigeminal ganglia. *Neuron Glia Biol.* 6 (1), 43–51. <https://doi.org/10.1017/S1740925X09900408>.
- Sulaiman, O., Gordon, T., 2000. Effects of short- and long-term Schwann cell denervation on peripheral nerve regeneration, myelination, and size. *Glia* 32 (3), 234–246. [https://doi.org/10.1002/1098-1136\(200012\)32:3<234::aid-glia40>3.0.co;2-3](https://doi.org/10.1002/1098-1136(200012)32:3<234::aid-glia40>3.0.co;2-3).
- Svaren, J., 2014. MicroRNA and transcriptional crosstalk in myelinating glia. *Neurochem. Int.* 77, 50–57. <https://doi.org/10.1016/j.neuint.2014.06.010>.
- Svenningsen, A.F., Colman, D.R., Pedraza, L., 2004. Satellite cells of dorsal root ganglia are multipotential glial precursors. *Neuron Glia Biol.* 1 (1), 85–93. <https://doi.org/10.1017/S1740925X04000110>.
- Taib, S., Lamandé, N., Martin, S., Couplier, F., Topilko, P., Brunet, I., 2022. Myelinating Schwann cells and Netrin-1 control intra-nervous vascularization of the developing mouse sciatic nerve. *ELife* 11. <https://doi.org/10.7554/ELIFE.64773>.
- Takeda, M., Takahashi, M., Nasu, M., Matsumoto, S., 2011. Peripheral inflammation suppresses inward rectifying potassium currents of satellite glial cells in the trigeminal ganglia. *Pain* 152 (9), 2147–2156. <https://doi.org/10.1016/j.pain.2011.05.023>.
- Talsma, A.D., Niemi, J.P., Pachter, J.S., Zigmond, R.E., 2022. The primary macrophage chemokine, CCL2, is not necessary after a peripheral nerve injury for macrophage recruitment and activation or for conditioning lesion enhanced peripheral regeneration. *J. Neuroinflammation* 19 (1), 179. <https://doi.org/10.1186/S12974-022-02497-9>.
- Tang, X., Schmidt, T.M., Perez-Leighton, C.E., Kofuji, P., 2010. Inwardly rectifying potassium channel Kir4.1 is responsible for the native inward potassium conductance of satellite glial cells in sensory ganglia. *Neuroscience* 166 (2), 397–407. <https://doi.org/10.1016/j.neuroscience.2010.01.005>.
- Tao-Cheng, J.H., Rosenbluth, J., 1983. Axolemmal differentiation in myelinated fibers of rat peripheral nerves. *Brain Res.* 285 (3), 251–263. [https://doi.org/10.1016/0165-3806\(83\)90023-8](https://doi.org/10.1016/0165-3806(83)90023-8).
- Tasaki, I., 1939. The electro-saltatory transmission of the nerve impulse and the effect of narcosis upon the nerve fiber. *Am. J. Physiol. Legacy Content* 127 (2), 211–227. <https://doi.org/10.1152/ajiplegacy.1939.127.2.211>.
- Tasdemir-Yilmaz, O.E., Druckenbrod, N.R., Olukoya, O.O., Dong, W., Yung, A.R., Bastille, I., Pazyra-Murphy, M.F., Sitko, A.A., Hale, E.B., Vigneau, S., Gimelbrant, A.A., Kharchenko, P.V., Goodrich, L.V., Segal, R.A., 2021. Diversity of developing peripheral glia revealed by single-cell RNA sequencing. *Dev. Cell* 56 (17), 2516–2535.e8. <https://doi.org/10.1016/j.devcel.2021.08.005>.
- Taveggia, C., Zanazzi, G., Petrylak, A., Yano, H., Rosenbluth, J., Einheber, S., Xu, X., Esper, R.M., Loeb, J.A., Shrager, P., Chao, M.V., Falls, D.L., Role, L., Salzer, J.L., 2005. Neuregulin-1 type III determines the ensheathment fate of axons. *Neuron* 47 (5), 681–694. <https://doi.org/10.1016/j.neuron.2005.08.017>.
- Terenghi, G., Calder, J.S., Birch, R., Hall, S.M., 1998. A morphological study of Schwann cells and axonal regeneration in chronically transected human peripheral nerves. *J. Hand Surgery (Edinburgh, Scotland)* 23 (5), 583–587. [https://doi.org/10.1016/S0266-7681\(98\)80006-5](https://doi.org/10.1016/S0266-7681(98)80006-5).
- Tham, S., Dowsing, B., Finkelstein, D., Donato, R., Cheema, S.S., Bartlett, P.F., Morrison, W.A., 1997. Leukemia Inhibitory Factor Enhances the Regeneration of Transected Rat Sciatic Nerve and the Function of Reinnervated Muscle, 215, pp. 208–215. August 1996.
- Todd, K.J., Darabid, H., Robitaille, R., 2010. Perisynaptic glia discriminate patterns of motor nerve activity and influence plasticity at the neuromuscular junction. *J. Neurosci.* 30 (35), 11870–11882. <https://doi.org/10.1523/JNEUROSCI.3165-10.2010>.
- Tomita, K., Kubo, T., Matsuda, K., Fujiwara, T., Yano, K., Winograd, J.M., Tohyama, M., Hosokawa, K.O., 2007. The neurotrophin receptor p75NTR in Schwann cells is implicated in remyelination and motor recovery after peripheral nerve injury. *Glia* 55 (11), 1199–1208. <https://doi.org/10.1002/GLIA.20533>.
- Tricaud, N., 2018. Myelinating schwann cell polarity and mechanically-driven myelin sheath elongation. *Front. Cell. Neurosci.* 11 (January), 1–12. <https://doi.org/10.3389/fncel.2017.00041>.
- Tzekova, N., Heinen, A., Küry, P., 2014. Molecules involved in the crosstalk between immune- and peripheral nerve Schwann cells. *J. Clin. Immunol.* 34 (Suppl. 1), 86–104. <https://doi.org/10.1007/S10875-014-0015-6/FIGURES/2>.
- Ursavas, S., Darici, H., Karaoz, E., 2021. Olfactory ensheathing cells: Unique glial cells promising for treatments of spinal cord injury. *J. Neurosci. Res.* 99 (6), 1579–1597. <https://doi.org/10.1002/JNR.24817>.
- Van Landeghem, L., Mahé, M.M., Teusau, R., Léger, J., Guisle, I., Houlgate, R., Neunlist, M., 2009. Regulation of intestinal epithelial cells transcriptome by enteric glial cells: impact on intestinal epithelial barrier functions. *BMC Genomics* 10, 507. <https://doi.org/10.1186/1471-2164-10-507>.
- van Weperen, V.Y.H., Littman, R.J., Arneson, D.V., Contreras, J., Yang, X., Ajijola, O.A., 2021. Single-cell transcriptomic profiling of satellite glial cells in stellate ganglia reveals developmental and functional axial dynamics. *Glia* 69 (5), 1281–1291. <https://doi.org/10.1002/GLIA.23965>.
- Vaquié, A., Sauvain, A., Duman, M., Nocera, G., Egger, B., Meyenhofer, F., Falquet, L., Bartesaghi, L., Chrast, R., Lamy, C.M., Bang, S., Lee, S.R., Jeon, N.L., Ruff, S., Jacob, C., 2019. Injured axons instruct schwann cells to build constricting actin spheres to accelerate axonal disintegration. *Cell Rep.* 27 (11), 3152–3166.e7. <https://doi.org/10.1016/j.celrep.2019.05.060>.
- Végá, C., Martiel, J.L., Drouhault, D., Burckhart, M.F., Coles, J.A., 2003. Uptake of locally applied deoxyglucose, glucose and lactate by axons and schwann cells of rat vagus nerve. *J. Physiol.* 546 (2), 551–564. <https://doi.org/10.1113/JPHYSIOL.2002.029751>.
- Vermeren, M., Maro, G.S., Bron, R., McGonnell, I.M., Charnay, P., Topilko, P., Cohen, J., 2003. Integrity of developing spinal motor columns is regulated by neural crest derivatives at motor exit points. *Neuron* 37 (3), 403–415. [https://doi.org/10.1016/S0896-6273\(02\)01188-1](https://doi.org/10.1016/S0896-6273(02)01188-1).
- Viader, A., Golden, J.P., Baloh, R.H., Schmidt, R.E., Hunter, D.A., Milbrandt, J., 2011. Schwann cell mitochondrial metabolism supports long-term axonal survival and peripheral nerve function. *J. Neurosci.* 31 (28), 10128–10140. <https://doi.org/10.1523/JNEUROSCI.0884-11.2011>.
- Viader, A., Sasaki, Y., Kim, S., Strickland, A., Workman, C.S., Yang, K., Gross, R.W., Milbrandt, J., 2013. Aberrant Schwann cell lipid metabolism linked to mitochondrial deficits leads to axon degeneration and neuropathy. *Neuron* 77 (5), 886–898. <https://doi.org/10.1016/J.NEURON.2013.01.012>.
- Villegas, R., Martin, S.M., O'Donnell, K.C., Carrillo, S.A., Sagasti, A., Allende, M.L., 2012. Dynamics of degeneration and regeneration in developing zebrafish peripheral axons reveals a requirement for extrinsic cell types. *Neural Dev.* 7 (1) <https://doi.org/10.1186/1749-8104-7-19>.
- Vit, J.P., Ohara, P.T., Bhargava, A., Kelley, K., Jasmin, L., 2008. Silencing the Kir4.1 potassium channel subunit in satellite glial cells of the rat trigeminal ganglion results in pain-like behavior in the absence of nerve injury. *J. Neurosci.* 28 (16), 4161–4171. <https://doi.org/10.1523/JNEUROSCI.5053-07.2008>.
- Wagstaff, L.J., Gomez-Sanchez, J.A., Fazal, S.V., Otto, G.W., Kilpatrick, A.M., Michael, K., Wong, L.Y.N., Ma, K.H., Turmaine, M., Svaren, J., Gordon, T., Arthur-Farraj, P., Velasco-Avilés, S., Cabedo, H., Benito, C., Mirsky, R., Jessen, K.R., 2021. Failures of nerve regeneration caused by aging or chronic denervation are rescued by restoring schwann cell c-jun. *ELife* 10, 1–32. <https://doi.org/10.7554/ELIFE.62232>.
- Waller, A., 1851. Experiments on the Section of the Glosso-Pharyngeal and Hypoglossal Nerves of the Frog, and Observations of the Alterations Produced Thereby in the Structure of Their Primitive Fibres. *Edinburgh Med. Surg. J.* 76 (189), 369–376.
- Wang, Y., Wu, W., Wu, X., Sun, Y., Zhang, Y.P., Deng, L.X., Walker, M.J., Qu, W., Chen, C., Liu, N.K., Han, Q., Dai, H., Shields, L.B.E., Shields, C.B., Sengelaub, D.R., Jones, K.J., Smith, G.M., Xu, X.M., 2018. Remodeling of lumbar motor circuitry remote to a thoracic spinal cord injury promotes locomotor recovery. *ELife* 7. <https://doi.org/10.7554/ELIFE.39016>.
- Wanner, I.B., Mahoney, J., Jessen, K.R., Wood, P.M., Bates, M., Bunge, M.B., 2006. Invariant mantling of growth cones by Schwann cell precursors characterize growing peripheral nerve fronts. *Glia* 54 (5), 424–438. <https://doi.org/10.1002/GLIA.20389>.
- Waxman, S.G., 1980. Determinants of conduction velocity in myelinated nerve fibers. *Muscle Nerve* 3 (2), 141–150. <https://doi.org/10.1002/MUS.880030207>.
- Webster, H., Martin, J.R., O'Connell, M.F., 1973. The relationships between interphase Schwann cells and axons before myelination: a quantitative electron microscopic study. *Dev. Biol.* 32 (2), 401–416. [https://doi.org/10.1016/0012-1606\(73\)90250-9](https://doi.org/10.1016/0012-1606(73)90250-9).
- Wei, Z., Fan, B., Ding, H., Liu, Y., Tang, H., Pan, D., Shi, J., Zheng, P., Shi, H., Wu, H., Li, A., Feng, S., 2019. Proteomics analysis of Schwann cell-derived exosomes: a novel therapeutic strategy for central nervous system injury. *Mol. Cell. Biochem.* 457 (1–2), 51–59. <https://doi.org/10.1007/S11010-019-03511-0/TABLES/2>.
- Weider, M., Wegener, A., Schmitt, C., Küspert, M., Hillgärtner, S., Bösl, M.R., Hermans-Borgmeyer, I., Nait-Oumesmar, B., Wegner, M., 2015. Elevated in vivo levels of a single transcription factor directly convert satellite glia into oligodendrocyte-like cells. *PLoS Genet.* 11 (2), 1–21. <https://doi.org/10.1371/JOURNAL.PGEN.1005008>.

- Wolbert, J., Li, X., Heming, M., Mausberg, A.K., Akkermann, D., Frydrychowicz, C., Fledrich, R., Groeneweg, L., Schulz, C., Stettner, M., Gonzalez, N.A., Wiendl, H., Stassart, R., zu Hörste, G. M., 2020. Redefining the heterogeneity of peripheral nerve cells in health and autoimmunity. *Proc. Natl. Acad. Sci. U. S. A.* 117 (17), 9466–9476. <https://doi.org/10.1073/PNAS.1912139117/-DCSUPPLEMENTAL>.
- Woldeyesus, M.T., Britsch, S., Riethmacher, D., Xu, L., Sonnenberg-Riethmacher, E., Abou-Rebyeh, F., Harvey, R., Caroni, P., Birchmeier, C., 1999. Peripheral nervous system defects in erbB2 mutants following genetic rescue of heart development. *Genes Dev.* 13 (19), 2538. <https://doi.org/10.1101/GAD.13.19.2538>.
- Wolpowitz, D., Mason, T.B.A., Dietrich, P., Mendelsohn, M., Talmage, D.A., Role, L.W., 2000. Cysteine-rich domain isoforms of the neuregulin-1 gene are required for maintenance of peripheral synapses. *Neuron* 25 (1), 79–91. [https://doi.org/10.1016/S0896-6273\(00\)80873-9](https://doi.org/10.1016/S0896-6273(00)80873-9).
- Wright, M.C., Potluri, S., Wang, X., Dentcheva, E., Gautam, D., Tessler, A., Wess, J., Rich, M.M., Son, Y.J., 2009. Distinct muscarinic acetylcholine receptor subtypes contribute to stability and growth, but not compensatory plasticity, of neuromuscular synapses. *J. Neurosci.* 29 (47), 14942–14955. <https://doi.org/10.1523/JNEUROSCI.2276-09.2009>.
- Wu, L.M.N., Williams, A., Delaney, A., Sherman, D.L., Brophy, P.J., 2012. Increasing internodal distance in myelinated nerves accelerates nerve conduction to a flat maximum. *Curr. Biol.* 22 (20), 1957–1961. <https://doi.org/10.1016/J.CUB.2012.08.025>.
- Yim, A.K.Y., Wang, P.L., Bermingham, J.R., Hackett, A., Strickland, A., Miller, T.M., Ly, C., Mitra, R.D., Milbrandt, J., 2022. Disentangling glial diversity in peripheral nerves at single-nuclei resolution. *Nat. Neurosci.* 25 (2), 238–251. <https://doi.org/10.1038/S41593-021-01005-1>.
- Yin, X., Crawford, T.O., Griffin, J.W., Tu, P.H., Lee, V.M.Y., Li, C., Roder, J., Trapp, B.D., 1998. Myelin-associated glycoprotein is a myelin signal that modulates the caliber of myelinated axons. *J. Neurosci.* 18 (6), 1953–1962. <https://doi.org/10.1523/JNEUROSCI.18-06-01953.1998>.
- Ying, Z., Pan, C., Shao, T., Liu, L., Li, L., Guo, D., Zhang, S., Yuan, T., Cao, R., Jiang, Z., Chen, S., Wang, F., Wang, X., 2018. Mixed lineage kinase domain-like protein MLKL breaks down myelin following nerve injury. *Mol. Cell* 72 (3), 457–468.e5. <https://doi.org/10.1016/J.MOLCEL.2018.09.011>.
- Yu, Y.B., Li, Y.Q., 2014. Enteric glial cells and their role in the intestinal epithelial barrier. *World J. Gastroenterol.* 20 (32), 11273–11280. <https://doi.org/10.3748/WJG.V20.I32.11273>.
- Zhang, X., Chen, Y., Wang, C., Huang, L.Y.M., 2007. Neuronal somatic ATP release triggers neuron-satellite glial cell communication in dorsal root ganglia. *Proc. Natl. Acad. Sci. U. S. A.* 104 (23), 9864–9869. <https://doi.org/10.1073/PNAS.0611048104>.
- Zhang, S.H., Shurin, G.V., Khosravi, H., Kazi, R., Kruglov, O., Shurin, M.R., Bunimovich, Y.L., 2020. Immunomodulation by Schwann cells in disease. *Cancer Immunol. Immunother.* 69 (2), 245–253. <https://doi.org/10.1007/s00262-019-02424-7>.
- Zigmond, R.E., Echevarria, F.D., 2019. Macrophage biology in the peripheral nervous system after injury. *Prog. Neurobiol.* 173, 102–121. <https://doi.org/10.1016/J.PNEUROBIO.2018.12.001>.