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Beyond Wrapping: Canonical and Noncanonical Functions of Schwann Cells

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Abstract

Schwann cells in the peripheral nervous system (PNS) are essential for the support and myelination of axons, ensuring fast and accurate communication between the central nervous system and the periphery. Schwann cells and related glia accompany innervating axons in virtually all tissues in the body, where they exhibit remarkable plasticity and the ability to modulate pathology in extraordinary, and sometimes surprising, ways. Here, we provide a brief overview of the various glial cell types in the PNS and describe the cornerstone cellular and molecular processes that enable Schwann cells to perform their canonical functions. We then dive into discussing exciting noncanonical functions of Schwann cells and related PNS glia, which include their role in organizing the PNS, in regulating synaptic activity and pain, in modulating immunity, in providing a pool of stem cells for different organs, and, finally, in influencing cancer.

Keywords

Schwann cells; satellite cells; boundary cap cells; terminal Schwann cells

1. DEVELOPMENT AND DIVERSITY OF SCHWANN CELLS

The peripheral nervous system (PNS) conveys bidirectional information between the central nervous system (CNS) and the periphery, thus connecting organisms to the external world. The information is transmitted through axons derived from central and peripheral neurons in cooperation with other cells, including barrier- and structure-forming endoneurial, perineurial, and epineurial cells and vascular, immune, and glial cells, which associate intimately with axons and perikarya (Gerber et al. 2021).

The main glial cells in the PNS are axon-associated Schwann cells (SCs) in nerves, synapse-associated SCs, and perikaryon-associated satellite cells in ganglia. Together, they cover

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most of the functions that oligodendrocytes, microglia, and astrocytes perform in the CNS. SCs are more plastic that CNS glia and maintain the ability to de-/transdifferentiate, even when terminally differentiated. This unique ability provides greater adaptability to stress, disease, and injury, endowing the PNS with great resilience and the capacity for regeneration and repair.

All SCs derive from the neural crest and accompany migrating axons, surrounding their growth cones (Wanner et al. 2006). One of the earliest subpopulations of SCs are boundary cap cells (BCCs), which transiently congregate at the boundary between the CNS and PNS (see below). Later, BCCs migrate along motor and sensory roots and give rise to neurons in sensory ganglia and to most of the SCs in spinal roots. BCCs and neural crest cells also differentiate into satellite cells that surround the somas of sensory and autonomic neurons.

Trunk neural crest cells that migrate ventrally give rise to SCs that surround motor and sensory axons in peripheral nerves (Le Douarin & Teillet 1974) by first generating Schwann cell precursors (SCPs), which differentiate into immature SCs (Figure 1). Immature SCs deposit a basal lamina and begin to separate axons into progressively smaller groups; they first select and sort single large axons (e.g., motor and fusimotor fibers) that become myelinated by myelin-forming SCs, while smaller axons (e.g., afferent fibers to skin, pain fibers, and postganglionic autonomic axons) remain associated with SCs, forming a so-called Remak bundle (reviewed by Jessen et al. 2015).

Neural crest cells that migrate with olfactory nerve fibers give rise to a specialized glial population known as olfactory ensheathing cells (reviewed in Barnett & Chang 2004), which share some molecular characteristics with SCs but do not deposit a basal lamina and do not make myelin. However, olfactory ensheathing cells are extremely plastic and regenerative, as they can myelinate CNS axons after transplantation and contribute to the unique renewal capacity of the olfactory nervous system. Neural crest cells also generate neurons of the enteric ganglia and their axons, which organize into enteric plexi. These plexi are ensheathed by enteric glia, which share many characteristics with Remak SCs (Figure 1) (reviewed in Veiga-Fernandes & Pachnis 2017).

At synapses, SCs specialize to perform different functions, such as the terminal or perisynaptic SCs at the neuromuscular junction (NMJ) (see below). SCs of the skin also originate from the neural crest and are associated with subepidermal nerve plexi and specialized nerve endings.

Three recent articles have illuminated our understanding of peripheral glial diversity and nerve cellular composition, and confirmed the developmental origins and lineage paths of glia (Gerber et al. 2021, Tasdemir-Yilmaz et al. 2021, Yim et al. 2022). These studies indicate that satellite glial cells from dorsal root ganglia (DRG) and auditory ganglia are regionally heterogenous and that there are at least three subtypes of trunk SCs. For a more detailed description of peripheral glial diversity, please refer to Reed et al. (2021).

2. CANONICAL FUNCTIONS OF SCHWANN CELLS

2.1. Axonal Ensheathment and Support

One of the most important functions of SCs is to support axons. Axons can extend to more than 1 meter in length. This remarkable distance from their cell bodies makes them vulnerable and dependent on axonal transport to survive. Indeed, axon degeneration is an early event of many neurological diseases. SCs are evenly distributed along the entire length of the axon and are therefore perfectly poised to provide local structural and metabolic support to axons, similar to oligodendrocytes in the CNS. This support function is evolutionarily conserved (Nave & Werner 2021), is independent from myelination, and relies on the intimate interaction between SCs and axons. Presumably, SCs in close contact with axons sense their metabolic status. Although the molecular mechanisms that mediate this sensing and energy delivery are still largely unknown, they are the subject of intense investigation, and some aspects of this crucial function are starting to emerge. Earlier investigations indicated that proteins such as myelin-associated protein (MAG), proteolipid protein, and CNPase on the inner SC membrane engage axonal receptors to mediate some of these exchanges (Edgar et al. 2009, Griffiths et al. 1998, Yin et al. 1998). However, the corresponding receptor(s) on the axonal side has been difficult to identify, but there are reports implicating gangliosides such as GD1a and GT1b and Nogo as MAG receptors (Schnaar & Lopez 2009). In the CNS, these molecules may create cytoplasmic channels equipped with gap junctions, which enable the transfer of metabolites to the axon (Rosenbluth et al. 2006, Snaidero et al. 2017). Some of these molecules also form cytoplasmic channels in peripheral myelin called Schmidt-Lanterman incisures, which probably fulfill the same purpose (Balice-Gordon et al. 1998). Ensheathing glia in *Caenorhabditis elegans* and *Drosophila* similarly support axons and form axoglial septate junctions that are similar in morphology and molecular composition to analogous structures that flank the nodes of Ranvier in vertebrate myelinated fibers (reviewed by Nave & Werner 2021). In these regions, close contact between the axolemma and the glial membrane is mediated by several adhesion molecules (see below). Loss of function of these molecules due to autoantibodies or mutations results in demyelinating neuropathies and axonal degeneration in patients, supporting the idea that axo-glia communications at these sites are important for axonal support (reviewed in Fehmi et al. 2018). The nature of the energy that is transferred is also under investigation, and many studies suggest that SCs are metabolically coupled to axons and provide them with energy-rich substrates such as lactose (Boucanova et al. 2021, Funfschilling et al. 2012, Jha et al. 2020), glucose (Saab et al. 2016), glycogen (Brown et al. 2012), and the bioenergetic cofactor NAD^+ (Coleman & Hoke 2020). SCs can also sense axonal injury and respond via mammalian target of rapamycin complex 1 (mTORC1) by upregulating glycolytic enzymes, effectively shifting SC metabolism to support axons (Babetto et al. 2020).

Axonal ensheathment by SCs also serves to recognize and isolate larger axons destined to be myelinated. This process, named radial axonal sorting (Peters & Muir 1959), is essential for the differentiation of small- and large-caliber axons and of SCs. During radial sorting, immature SCs interdigitate lamellipodium-like processes among axons that expose the tyrosine kinase Erb2/3 receptors, which, in turn, sense the amount of axon-bound

neuregulin-1 type III (Nrg1-III) (Taveggia et al. 2005), a key signal for SC terminal differentiation and myelination (see below). This process is modulated by laminins, which are deposited by SCs in the basal lamina and serve different purposes. One purpose is to inhibit PKA-mediated Nrg1-III signaling to prevent myelination until radial sorting is completed (Ghidinelli et al. 2017). The second is to activate the cotranscriptional activators yes-associated protein 1 (YAP1) and WW domain–containing transcription regulator protein 1 (WWTR1 or TAZ), which induce proliferation and the expression of laminin receptors such as dystroglycan and integrin α6β1 and of transcription factors such as Egr2/Krox20 (Poitelon et al. 2016). In turn, laminin receptors activate downstream signaling (e.g., ILK, FAK, Rac1, Cdc42, and PKA) to promote the formation of lamellipodium-like processes, which interdigitate and contact axons (Benninger et al. 2007, Grove & Brophy 2014, Nodari et al. 2007, Pellegatta et al. 2013, Pereira et al. 2009). Experimental deletion of any of the above-mentioned components in SCs or mutations in the human gene coding for laminin 211 prevent radial sorting of axons and peripheral nerve differentiation. For a detailed review on this process, see Feltri et al. (2016).

2.2. Myelination

Among molecules controlling PNS myelination, Nrg1-III represents the best example of a do-it-all signal. Indeed, several studies have demonstrated that the binding of NRG1 to ErbB2/3 receptors is necessary for many steps that lead to PNS myelination (reviewed in Birchmeier & Nave 2008). The relevance of this signaling mechanism (Michailov et al. 2004, Taveggia et al. 2005) is underscored by the fact that its role has been maintained throughout evolution (Lyons et al. 2005). The functionality of NRG1-ErbB receptors in the PNS is strictly regulated, in part by processing mediated by secretases that either activate [the β-secretase BACE1 (Hu et al. 2006, Willem et al. 2006)] or inhibit [the α-secretase ADAM17 (La Marca et al. 2011)] NRG1 activity. The engagement of ErbB receptors on the plasma membrane of SCs activates downstream effectors. Two main pathways are critical for the formation of PNS myelin: the PI3K/AKT/mTOR pathway (Goebbels et al. 2010, Sherman et al. 2012) and the ERK pathway (Ishii et al. 2021, Newbern et al. 2011). A role for a third pathway, calcineurin/NFAT (Kao et al. 2009), has not been confirmed (Reed et al. 2020).

Other pathways are also critical for peripheral myelination. Among them, the G protein–coupled receptor Gpr126 cell autonomously increases the levels of cAMP and activates PKA signaling in myelinating SCs (Monk et al. 2009). Gpr126 activity requires interaction with molecules in the SC extracellular matrix (Paavola et al. 2014, Petersen et al. 2015). In addition, Gpr44, a receptor of prostaglandin D2, regulates myelination following cleavage of Nrg1-III by the γ-secretase complex (Trimarco et al. 2014). Other molecules important for myelination include those in the Jagged/Delta/Notch signaling pathway (Woodhoo et al. 2009) and members of the Lgi4/ADAM22 complex (Bermingham et al. 2006, Ozkaynak et al. 2010).

The above-mentioned pathways convey signals to the nucleus that control transcription factors, which orchestrate the expression of myelin proteins or enzymes implicated in lipid synthesis. Among them are Yin Yang 1 (He et al. 2010), Zeb2 (Wu et al. 2016),

the sterol regulatory element–binding protein (SREBP) (Verheijen et al. 2009), and early growth response gene 20 (Egr2), also known as Krox-20. Krox-20 is considered the master transcription factor for PNS myelination. Krox-20 is induced in promyelinating SCs, and without its activity, SCs cannot form myelin (Topilko et al. 1994). The timely activation of Krox-20 is under the control of another transcription factor, Pou3f1/Oct6/SCIP (Jaegle et al. 1996), which is expressed in premyelinating SCs; downregulation of Oct6 induces Krox-20 expression. Other important transcription factors belong to the SRY-related HMG box family, including Sox-10, whose expression is maintained in SCs regardless of their stage or phenotype (Woodhoo 2018) and is essential for SCs throughout life (Finzsch et al. 2010). Sox-10 synergizes with Krox-20 to induce myelination (Jagalur et al. 2011, Srinivasan et al. 2012; for comprehensive reviews, see Salzer 2015, Wegner 2000). Future studies should aim to disentangle the complex interconnection occurring between these pathways. It will be similarly important to clarify which of these molecules maintain myelin in adulthood, a critical aspect for the homeostasis of the nervous system.

2.3. Differentiation of Axonal Domains

The textbook function of myelination is to enable fast and reliable conduction of action potentials along axons, which is critical for nervous system function and represents the evolutionary foundation for the complexity of the vertebrate nervous system (Zalc & Colman 2000). The high capacitance of the myelin segments (called internodes) favors regeneration of the action potential exclusively at nodes of Ranvier (Huxley & Stampfli 1949), where there is a high density of voltage-gated sodium channels (Vabnick et al. 1996); voltage-gated potassium channels, which mediate membrane repolarization, are positioned at juxtaparanodes (Arroyo et al. 1999, Einheber et al. 1997). These voltage-gated channel clusters, as well as paranodal junctions, are formed and stabilized by heterotypic adhesion mechanisms, which occur between glial, axonal, and extracellular matrix proteins. In this way, SCs play an active role in the formation of the specific domains (Ching et al. 1999) (Figure 2), where gliomedin and perlecan interact with axonal NrCam and neurofascin 186 at nodes (Colombelli et al. 2015, Eshed et al. 2005, Tait et al. 2000), neurofascin 155 apposes axonal contactin and Caspr at paranodes (Bhat et al. 2001), and Caspr2 interacts with contactin 2–TAG1 at juxtaparanodes (Traka et al. 2003). These complexes in turn are linked to axonal cytoskeletal proteins such as ankyrins and protein 1.4 (Dzhashiashvili et al. 2007; for recent reviews of the process of axonal domain differentiation, see Faivre-Sarrailh 2020, Rasband & Peles 2021).

2.4. Nerve Regeneration and Repair

A characteristic of the PNS that is not shared with the CNS is its capacity to regenerate damaged nerves. If two nerve stumps remain close, a tissue bridge forms through which SCs and axons can regrow (Morris et al. 1972). In the nerve stump distal to the cell body, axons degenerate and trigger a cascade of signals resulting in the transdifferentiation of terminally differentiated SCs into an entirely different phenotype (repair phenotype) (Figure 2), characterized by a high rate of proliferation and the expression of a distinct set of genes (Arthur-Farraj et al. 2017, Stierli et al. 2019). The master regulator of this transition is the transcription factor c-Jun (Arthur-Farraj et al. 2012, Parkinson et al. 2008), but other key factors include STAT3 activation (Benito et al. 2017) and methylation of lysine 27

on histone 3 (Arthur-Farraj et al. 2017, Ma et al. 2016). Collectively, these changes affect the expression of an entire repertoire of molecules that are necessary to activate the repair process and are accompanied by the downregulation of genes encoding myelin proteins (reviewed by Jessen & Arthur-Farraj 2019).

Immediately after damage, repair SCs actively proliferate and initiate to phagocyte myelin (Gomez-Sanchez et al. 2015, Jang et al. 2016). Though the majority of myelin is eventually removed by macrophages that are recruited from the periphery, this initial process is essential, as myelin is inhibitory for axonal regrowth (Filbin 2003). Repair SCs and fibroblasts actively recruit macrophages from the bloodstream by secreting cytokines such as MCP1/CCL2 (Martini et al. 2008). Next, transdifferentiating SCs align to regrowing axons to form the bands of Büngner, regenerative paths that originate along the SC basal lamina and are necessary to support axon regrowth (Weinberg & Spencer 1978). After injury, the recruitment of macrophages is also facilitated by prostaglandin D2, which is also responsible for blood-nerve barrier (BNB) integrity (Forese et al. 2020).

Repair SCs engage mechanisms similar but complementary to those occurring in development, further underscoring their uniqueness (Jessen et al. 2015). For example, although axonal Nrg1-III is key for myelination, its role is replaced in part by SC-derived Nrg1-I for remyelination (Stassart et al. 2013). Correspondingly, the β-secretase BACE1 promotes nerve remyelination most likely by acting on glial Nrg1-I (reviewed by Pellegatta & Taveggia 2019), which activates glial ErbB receptors and stimulates the ERK1/2 pathway, a response required for the repair process (Napoli et al. 2012).

SCs within the tissue bridge have a higher proliferative capacity (Clements et al. 2017) and acquire a migratory behavior triggered by interactions between Ephrin B2 on fibroblasts and glial EphB2. These interactions relocalize N-cadherin to switch SCs from a repulsive to an attractive phenotype (Parrinello et al. 2010). SCs within the tissue bridge may also acquire mesenchymal characteristics (Arthur-Farraj et al. 2017, Clements et al. 2017).

3. NONCANONICAL FUNCTIONS OF SCHWANN CELLS

3.1. Schwann Cell, Boundary Cap Cell, and Peripheral Nervous System Organization

SCs interact with cells other than neurons to orchestrate nerve architecture, including formation of the BNB, the perineurium, and the boundary between the PNS and the CNS. This boundary comprises BCCs (Figure 2) at regions where axons projecting from CNS-located motor neurons exit the ventral spinal cord [ventral root transitional zone, or motor exit points (MEPs)] and regions where sensory neuron axons enter the dorsal spinal cord (dorsal root transitional zone, or sensory entry points). The BCCs that comprise and maintain this boundary are in part molecularly distinct from SCs and display early and transient expression of Krox-20. Depletion of these cells via Krox-20-Cre enables motor neuron somas to exit the spinal cord (reviewed by Radomska & Topilko 2017). BCCs also share characteristics with MEP cells, which has been shown in the zebrafish (Smith et al. 2014).

Peripheral nerves are surrounded by connective tissue layers, including the perineurium, that form a barrier and a protective layer (Figure 2). In developing mammals, the perineurium is formed by mesenchymal cells that are recruited to embryonic nerves. These cells undergo a mesenchymal-to-epithelial transformation to form tight junctions, deposit a basal lamina and collagen fibers, and form a multilayered tube that is a component of the BNB (Kristensson & Olsson 1971). Recent experiments suggest that at least a subset of perineurial cells originate not from the mesoderm but in the CNS (Clark et al. 2014). Nevertheless, the formation of the perineurium depends on the release of desert hedgehog (Dhh) by developing SCs, which acts on patched receptors on perineurial cells (Parmantier et al. 1999). Pericytes and macrophages that line endothelial blood vessels also contribute to the development of the BNB (Malong et al. 2019). Finally, recent data indicate that Gli1 in endoneurial fibroblasts is also required for development of a normal endoneurium architecture (Zotter et al. 2022). Thus, a series of complex multicellular interactions are necessary for normal nerve formation.

3.2. Schwann Cells and Immunomodulation

SCs are activated in pathological settings in which they express immune-related molecules (Lisak et al. 1997) and act as immune modulators, but they are essentially quiescent under physiological conditions (DeFrancesco-Lisowitz et al. 2015, Stierli et al. 2019). SCs act as immune surveillance cells in Charcot-Marie-Tooth hereditary neuropathies, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy (reviewed by Martini & Willison 2016).

SCs affect both innate and adaptive immune systems, as they express a plethora of molecules directly regulating these systems, including Toll-like receptors, receptors for advanced glycation end products (RAGEs), the mannose receptor, C-type leptin receptor, and the low-density-lipoprotein receptor-related protein-1 (LRP1) (reviewed by Tzekova et al. 2014). These molecules are expressed after injury concomitantly with proinflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF), and IL-6 and chemokines such as leukemia inhibitory factor and monocyte chemoattractant protein (reviewed by Tzekova et al. 2014). SCs also induce the anti-inflammatory cytokine IL-10 to modulate the innate immune response (Siqueira Mietto et al. 2015).

SCs trigger the adaptive immune response by expressing major histocompatibility complex (MHC)-I and MCH-II as well as costimulatory molecules such as CD80, CD86, and CD58 (Murata & Dalakas 2000, Spierings et al. 2001, Van Rhijn et al. 2000). Under pathological conditions, these molecules can reactivate T lymphocytes in peripheral nerves and establish functional immunological synapses on SC plasma membranes (Meyer zu Horste et al. 2010).

The inflammatory response is critical in several nerve disorders. For example, studies with animal models of Charcot-Marie-Tooth neuropathies due to genetic defects in SCs revealed that inflammation amplifies the pathological features (Groh et al. 2015), and the ablation of T and B lymphocytes ameliorates the disease course. Similarly, the inflammatory response of enteric glia is critical in gastrointestinal disorders (Seguella & Gulbransen 2021, Veiga-Fernandes & Pachnis 2017). For instance, an IFN-γ, CXCL10 axis in enteric glia is essential to limit inflammation after infection (Progatzky et al. 2021). Furthermore, the migration of

hematopoietic stem cells and leukocytes is in part regulated by sympathetic nerves (Chen et al. 2021). Of note, sensory nerves were also shown to influence the primed immune response via their contribution to lymph node organization (Huang et al. 2021). Results from these studies raise a number of compelling questions; in particular, does the immune system reciprocally influence and shape nerve activity? For a detailed description of the pathogenetic mechanisms at the basis of inflammation in peripheral neuropathies, we refer readers to Martini & Willison (2016) and Ydens et al. (2013).

3.3. Schwann Cell Precursors as Multipotent Progenitors

Recent studies have highlighted new functions for SCPs as a class of multipotent progenitors. A combination of elegant fate mapping studies and single-cell RNA sequencing revealed that SCPs can generate melanocytes (Adameyko et al. 2009, Colombo et al. 2022), endoneurial fibroblasts (Joseph et al. 2004), parasympathetic neurons (Dyachuk et al. 2014, Espinosa-Medina et al. 2014), enteric neurons, dental pulp mesenchymal stromal cells (Kaukua et al. 2014), and adrenal chromaffin cells (Furlan et al. 2017) (Figure 1). For a comprehensive review, we refer the reader to Furlan & Adameyko (2018). SCPs also contribute to the patterning and differentiation of arterial branching, as they can instruct remodeling of the nascent vasculature and guide primitive vessels into arterioles. The relationship between nerve and vasculature is also fundamental to the organization of nascent axons through the bridge after nerve transection (Cattin et al. 2015). The molecular mechanisms regulating the above-described phenomena, which include secreted factors and contact-dependent signals, have been described in reviews (Aquino & Sierra 2018, Furlan & Adameyko 2018, Parfejevs et al. 2018). For the purposes of this review, the multipotent features of SCPs translate as phenotypic characteristics of some PNS tumors such as neurofibromatosis type 1 due to mutation in the neurofibromin 1 gene (*NF1*) (Cram et al. 2022). Likely due to the fact that SCPs can generate melanocytes, almost all neurofibromatosis type 1 patients present pigmented patches on the skin, substantial numbers of melanocytes, and a melanocyte molecular signature in melanotic schwannoma and desmoplastic melanomas (Van Raamsdonk & Deo 2013).

3.4. Modulation of Synaptic and Neuronal Activities by Terminal Schwann Cells and Satellite Cells

One of the best understood synapses in the PNS is the NMJ, formed between motor nerve terminals and the postsynaptic regions of muscle cells. The presynaptic nerve terminal and the postsynaptic muscle are capped by nonmyelin-forming SCs called perisynaptic or terminal SCs (Figure 2). Transcriptomic studies indicate that terminal SCs have unique patterns of gene expression, which include genes known to be important for NMJ and synapse formation (Castro et al. 2020). Terminal SCs are required for the maturation of the NMJ and aid in the regeneration of the nerve terminal after injury (Love & Thompson 1999). Terminal SCs modulate synaptic activity at NMJs and participate in the formation of a bona fide tripartite synapse (Araque et al. 1999). In the frog, ablation of terminal SCs halves synaptic transmission (Reddy et al. 2003). Terminal SCs sense (Jahromi et al. 1992, Reist & Smith 1992) and decode (Todd et al. 2010) synaptic activity via G protein–coupled receptors and regulate the release of calcium via muscarinic and purinergic receptors, which

in turn influences the amount of transmitter released into the synapse (Robitaille 1995). For a comprehensive review, please see Darabid et al. (2014).

Like terminal SCs, satellite cells are also capable of modulating neuronal activities as a result of their contact with the neuronal soma (George et al. 2018) (Figure 2). They also share some functional characteristics with astrocytes (Avraham et al. 2020, Hanani & Spray 2020). For example, satellite cells respond to and modulate sensory neuron stimulation, and experimental manipulation of this bidirectional communication influences neuronal activity (Suadicani et al. 2010, Zhang et al. 2007). For a comprehensive review, we refer readers to Hanani & Spray (2020). Transcriptomic analyses further support the overlapping functions of astrocytes and satellite cells (Avraham et al. 2020, Tasdemir-Yilmaz et al. 2021).

4. PATHOLOGY

4.1. Pathology Due to Defects in Canonical Functions

Defects in the canonical function of SCs cause a plethora of diseases, ranging from inherited Charcot-Marie-Tooth neuropathies to common acquired neuropathies such as diabetic, toxic, and aging-associated neuropathies. We refer the reader to excellent reviews on these topics (Cavaletti & Marmiroli 2010, Laura et al. 2019, Mizukami & Osonoi 2020), as the focus of this review is on normal SC functions and physiopathological noncanonical functions of SCs.

4.2. Pathology Due to Defects in Noncanonical Functions

The noncanonical functions of SCs and related PNS glia described above are required for normal homeostasis of the PNS and other organs. Here, we review some instances in which dysregulation of noncanonical SC functions contributes to disease.

4.2.1. Schwann cells and nerve-cancer interaction.—The plasticity and immunomodulatory function of SCs can influence cancer. Several lines of evidence indicate that nerves play an important role in cancer pathogenesis and dissemination, which is particularly relevant in solid tumors affecting highly innervated organs (Martyn et al. 2019). Seminal studies have demonstrated that nerves stimulate the progression of prostate (Magnon et al. 2013) and gastric (Zhao et al. 2014) cancers. Indeed, denervation experiments in animal models for prostate, gastric, pancreatic, and skin cancer all resulted in reductions of tumor growth. However, denervation could also cause cancer progression (Bunimovich et al. 2017, Dubeykovskaya et al. 2016, Pawlowski & Weddell 1967); thus, the mechanisms regulating the nerve-tumor cross talk are likely context dependent and regulated by the tumor microenvironment, as well as by the neurotransmitters released by the innervating fibers (Gysler & Drapkin 2021, Hayakawa et al. 2017, Renz et al. 2018).

Nerves can directly influence the angiogenic process by enhancing endothelial cell metabolism (Zahalka et al. 2017). Immune cells and fibroblasts, which are part of the tumor microenvironment, can influence both nerves and cancer, as they release factors that activate cancer cells and remodel the extracellular matrix, facilitating the invasion of the tumor by nerves (reviewed by Gysler & Drapkin 2021). Recent studies have shown

that tumor-associated SCs can also modify the ECM upon metabolite-driven epigenetic modifications, ultimately potentiating metastasis formation (Pascual et al. 2021).

Given the centrality of nerves in tumor growth and metastasis, several studies have investigated whether SCs participate in nerve-cancer interactions. Indeed, SCs have a central role in the progression of cancers characterized by perineural invasion, which is defined as the presence of cancer cells along or inside the nerves. Perineural invasion is present in pancreatic adenocarcinoma and in cancers of the prostate and head and neck and is often associated with increased tumor aggressiveness and a poor prognosis (Crippa et al. 2020, Gasparini et al. 2019).

SCs colonize tumors before the onset of cancer invasion (Demir et al. 2014) and actively degrade the extracellular matrix to instruct cancer cell invasion by direct contact (Deborde et al. 2016). Detailed analyses of the molecules expressed by SCs associated with cancer cells have revealed a strong similarity with those expressed in repair SCs (reviewed by Boilly et al. 2017) (Figure 2). Furthermore, nerves growing in the tumor microenvironment undergo sprouting similar to that of regenerating nerves. As during regeneration, SCs may also recruit immune cells to the tumor at the site of nerve invasion. Thus, the contribution of SCs to the nerve-tumor interaction is multifaceted: They can directly affect cancer cell migration and invasion and indirectly modulate the tumor microenvironment by acting on angiogenic processes and the inflammatory milieu.

Despite the recent advances in this field, many issues remain open. It will be important to discover the signal(s) that triggers SC dedifferentiation in early cancer development. Furthermore, whether the molecules that govern the interaction between all the cells implicated in nerve regeneration serve as a platform for perineural invasion and nerve-cancer interaction is poorly understood. Finally, and most important for patients, the essential checkpoints in nerve-cancer interaction and perineurial invasion that could be targeted to develop more-effective treatments need to be deciphered.

4.2.2. Neuropathic pain.—Satellite cells in both the DRG and SCs in peripheral nerves affect neuropathic pain as a result of their influences on neural activity and immune modulation. As mentioned above, satellite cells can modulate the activity of DRG neurons. Experimental evidence and the similarities to CNS astrocytes indicate that SCs are activated after injury or pathology and contribute to the increased neuronal activity that can lead to chronic pain (Figure 2). Experimental blockade of some of these changes is sufficient to reduce the activation of DRG neurons and may provide a target to treat chronic neuropathic pain (De Logu et al. 2022, Grace et al. 2014, Ohara et al. 2008; for an in-depth review of satellite cells in neuropathic pain, see Hanani & Spray 2020).

SCs release factors under pathological conditions that can increase or decrease pain sensitivity. Pain-inducing factors include TNF-α and nitric oxide synthase, whereas protective analgesic factors include SC basal lamina components, erythropoietin, and LRP1. Of note, genetic or pharmacological manipulation of these SC-released factors can induce (Wagner & Myers 1996) or reduce pain (Keswani et al. 2004, Orita et al. 2013) independently from demyelination and axonal degeneration. Deletion of structural genes

in SCs elicits neuropathic behavior in mice (Gillespie et al. 2000, Saito et al. 2003) by unknown mechanisms. Remak SCs modulate neuropathic pain as a result of their association with small pain C fibers (Murinson et al. 2005b) and their exquisite responsiveness to peripheral nerve injuries (Murinson et al. 2005a, Wu et al. 2002; for a more comprehensive review of the role of SCs in neuropathic pain, see Campana 2007).

Specialized SCs in skin can respond directly to mechanical stimuli and trigger neuropathic pain. The skin derma is innervated by a plexus of myelinated and unmyelinated fibers, some of which project to the epidermis. Some SCs associated with these fibers form an extensive network of processes in the subepidermal region and can be activated directly by optogenetic stimulation, which results in a pain response and increased nociceptor firing rates. Neurophysiological studies determined that these skin SCs respond directly to mechanical stimuli and are necessary and sufficient for propagating action potentials in associated axons, thus initiating mechanical pain sensation (Abdo et al. 2019) (Figure 2). Finally, SCs associated with skin mechanoreceptors, but not their afferent DRG neurons, express the protein usherin, the gene for which is mutated in a genetic syndrome that includes impaired touch and pallesthesic (vibratory) sensation (Schwaller et al. 2021). Thus, the participation of PNS glial cells in the transduction of sensory inputs may be substantially greater than previously appreciated.

5. CONCLUDING REMARKS

Our increasing understanding of the multifaceted role of SCs and nerves raises many questions that trigger new opportunities for research. For instance, as nerves reach all organs, does SC plasticity also influence other body systems? Is it possible, for example, that SCs provide immunological surveillance in the skin, as enteric glia do in the gut? If so, is this system affected in dermatological disorders? Do SCs and nerves play additional roles in the gastrointestinal tract; for example, do they influence the action of the local microbiota? Can glial cells influence the specialization of different neuronal subtypes in ganglia similarly to their actions in the auditory system? Given the remarkable plasticity of SCPs and their role as a stem cell reservoir, can we exploit SCPs to develop new treatments? Answering these questions will further reveal the centrality of peripheral nerves in shaping and maintaining multiple biological systems.

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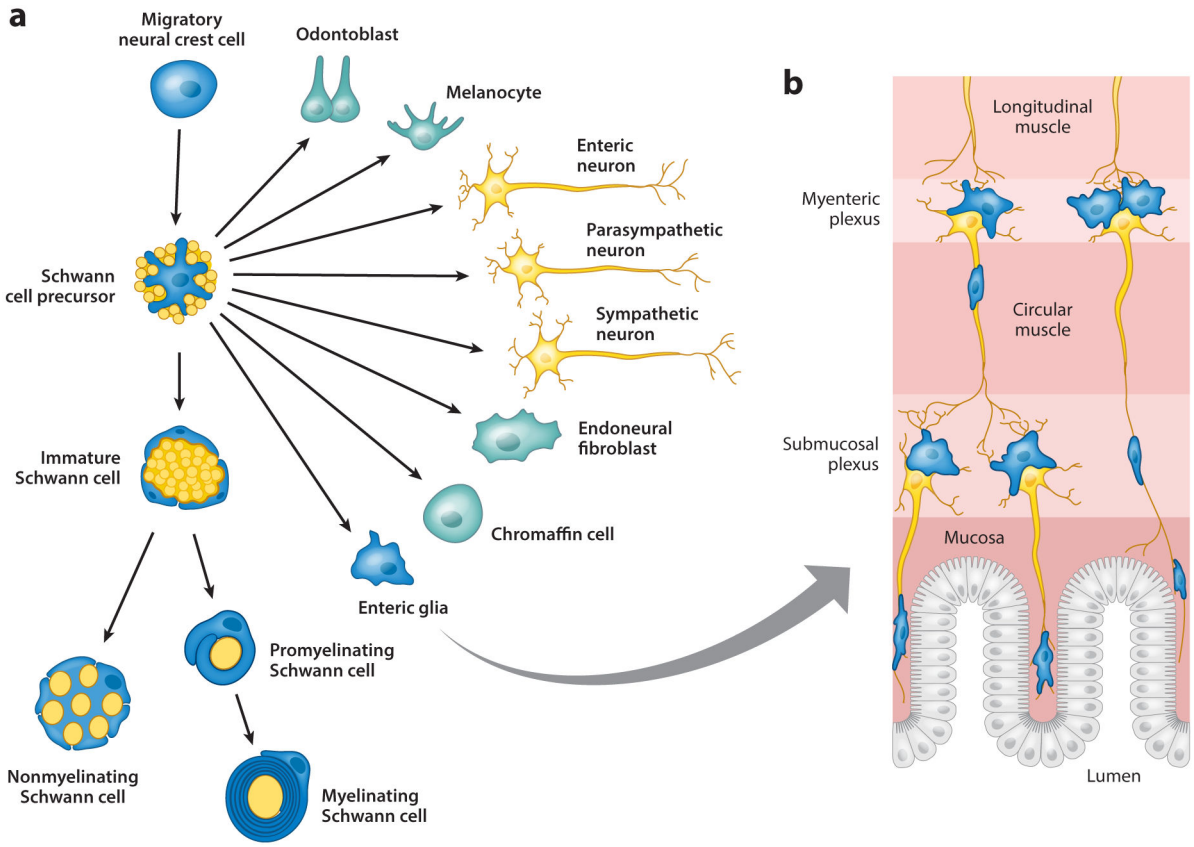

Figure 1.

Schwann cells and Schwann cell precursors are endowed with significant plasticity. (*a*) Schwann cell precursors derive from the neural crest and maintain some of the neural crest's multipotency. They can act as multipotent progenitors for several glia and nonglial cell types such as odontoblasts, melanocytes, autonomic neurons, chondrocytes, endoneurial fibroblasts, chromaffin cells, and enteric glia. Enteric glia are shown in detail in panel *b*. Schwann cell precursors' main function is to develop into immature and then myelinating or nonmyelinating Schwann cells, which fulfill the canonical functions of axonal ensheathment and myelination. In a process known as axonal sorting, large axons that are destined to be myelinated, such as motor axons or sensory axons that transmit positional information, are segregated by immature Schwann cells from axon bundles into a 1:1 Schwann cell relationship (promyelinating Schwann cells) and finally wrapped by multiple layers of membrane to form the myelin sheath. Nonmyelinating Schwann cells form Remak bundles by ensheathing the small-caliber axons (e.g., sensory axons that transmit pain and temperature information) that remain after the large axons have been sorted out.

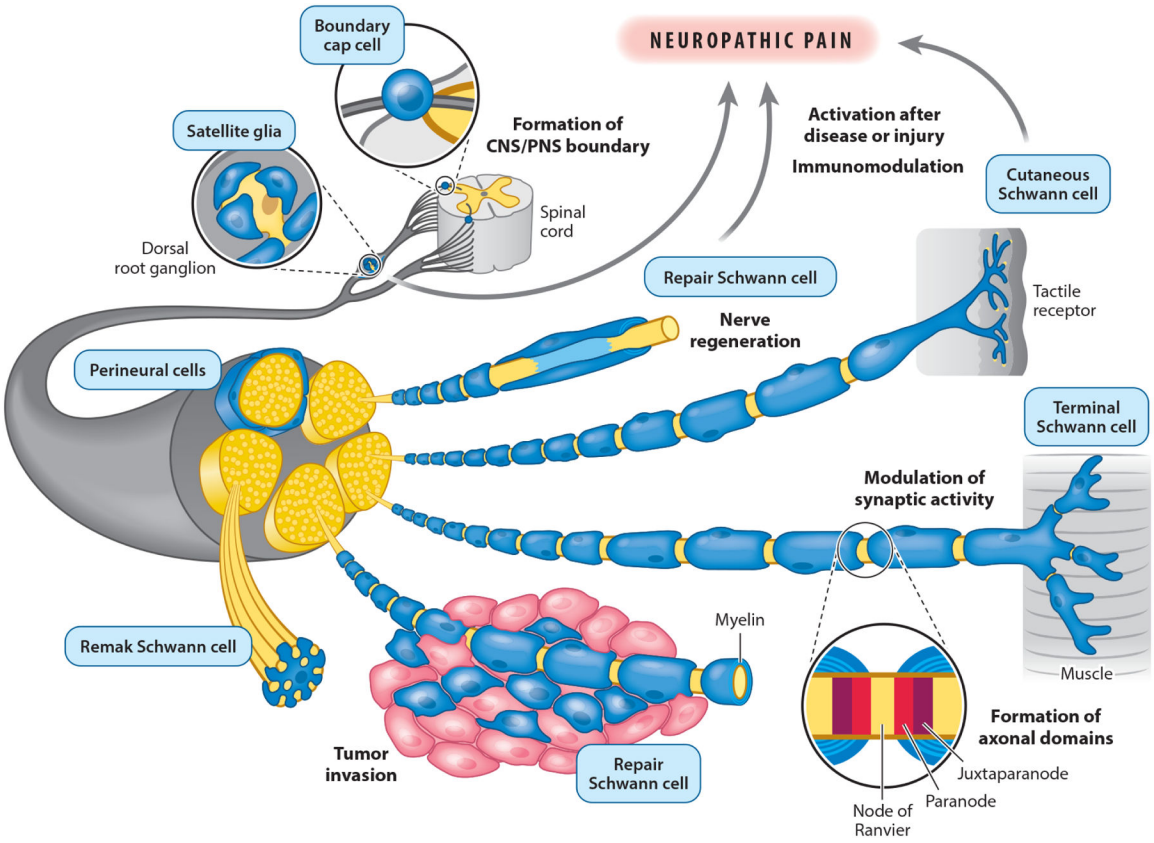

Figure 2.

Schwann cell functions in physiological and pathological conditions. In addition to canonical functions such as wrapping and myelinating axons and instructing the formation of the node of Ranvier, Schwann cells exert other functions that are required for the physiological function of several organs. For example, a subset of Schwann cells called boundary cap cells actively contribute to the formation of the boundary between the central and peripheral nervous systems (CNS and PNS). Another subset called satellite glia surround neuronal cell bodies in ganglia, such as dorsal root sensory ganglia, where they modulate neuronal activity. Terminal Schwann cells surround the pre- and postsynaptic portion of the neuromuscular junction and actively regulate the activity of this synapse. Other noncanonical Schwann cell functions include the modulation of the innate and adaptive immune response, and the formation and regulation of tactile receptors in the epidermis. Due to their remarkable plasticity, fully differentiated myelinating, nonmyelinating (Remak), and terminal Schwann cells are able to transdifferentiate after injury into repair Schwann cells, which actively contribute to the process of nerve regeneration by clearing myelin and cellular debris and creating basal lamina tracks used by axons to regrow. In pathological conditions, the plasticity, immunomodulatory, and neuromodulatory activities of Schwann cells contribute to neuropathic pain and to the invasion and spreading of cancer cells, the latter likely by dedifferentiating to a phenotype resembling that of repair Schwann cells. Figure adapted with permission from Reed et al. (2021).