Influence of Mechanical Stimuli on Schwann Cell Biology

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Schwann cells are the glial cells of the peripheral nervous system (PNS). They insulate axons by forming a specialized extension of plasma membrane called the myelin sheath. The formation of myelin is essential for the rapid saltatory propagation of action potentials and to maintain the integrity of axons. Although both axonal and extracellular matrix (ECM) signals are necessary for myelination to occur, the cellular and molecular mechanisms regulating myelination continue to be elucidated. Schwann cells in peripheral nerves are physiologically exposed to mechanical stresses (i.e., tensile, compressive and shear strains), occurring during development, adulthood and injuries. In addition, there is a growing body of evidences that Schwann cells are sensitive to the stiffness of their environment. In this review, we detail the mechanical constraints of Schwann cells and peripheral nerves. We explore the regulation of Schwann cell signaling pathways in response to mechanical stimulation. Finally, we provide a comprehensive overview of the experimental studies addressing the mechanobiology of Schwann cells. Understanding which mechanical properties can interfere with the cellular and molecular biology of Schwann cell during development, myelination and following injuries opens new insights in the regulation of PNS development and treatment approaches in peripheral neuropathies.

Keywords: Schwann cell, mechanobiology, mechanotransducer, mechanosensor, myelin, peripheral nerve

INTRODUCTION

Peripheral nerves are remarkable tissues of tremendous elasticity that propagate action potentials despite developmental growth (Vizoso and Young, 1948; Court et al., 2004; Simpson et al., 2013), stretches associated with movements of the limbs and mechanical compressions from daily activities (Kwan et al., 1992; Phillips et al., 2004). To resist mechanical stress, peripheral nerves are supported by three layers of connective tissues (i.e., epineurium, perineurium and endoneurium). In addition, each axon is individually wrapped by a large extension of modified plasma membrane called myelin sheath. Myelin appeared initially in hinged jaw fishes and was carried out in cartilaginous fishes. It contributed to the evolutionary success of larger vertebrates by allowing a faster and efficient conduction of nerves action potentials (Morell and Quarles, 1999), thus enabling faster predatory and escape maneuvers and the development of large and complex nervous systems (Zalc and Colman, 2000, 2007; Zalc et al., 2008). In addition, to enhance the conduction of electric impulses and protect axons from mechanical stress damage, myelin producing cells also support the exchange of metabolites between the regional vasculature and the axon (Viader et al., 2011; Fünfschilling et al., 2012; Lee et al., 2012).

In the peripheral nervous system (PNS), Schwann cells (SCs) produce the myelin sheath. They are among the largest known cells, with 0.6 mm² of membrane on average (Rosenbluth, 2005). Understanding myelinating SC architecture can be challenging. To initiate myelination, SCs require
an apicobasal polarity created by the axon (apical side) and the extracellular matrix (ECM; basal side). In addition, each myelin segment is flanked by nodes of Ranvier; thus creating a remarkable longitudinal polarity with internodal, juxtaparanodal and paranodal regions (Masaki, 2012; Figure 1). Yet, regardless of their gigantic myelin sheath and complex ultrastructure, SCs have a surprising plasticity. Upon injury to peripheral nerves, myelinated SCs can dedifferentiate and drive the regeneration of peripheral axons (Jessen and Mirsky, 2016; Boerboom et al., 2017). Outstanding reviews on SC development and the regulation of myelination in the PNS have recently been published and may be consulted for comprehensive characterization of SC biology (Kidd et al., 2013; Feltri et al., 2015; Monk et al., 2015; Salzer, 2015). In this review, we will focus on what the environmental constraints are for SCs, how SCs can sense and transduce mechanical signals and the experimental approaches that have started to unveil SC mechanobiology.

PERIPHERAL NERVES AND SCHWANN CELLS RESISTANCE TO MECHANICAL STRESSES

Peripheral nerves and SCs have adapted to sustain constant mechanical constraints. In peripheral nerves, myelinated fibers are surrounded by 6–15 layers of connective tissues (Sunderland, 1990) which shield SCs and axons from strains coming from the external environment (Lundborg and Rydevik, 1973; Rydevik et al., 1990; Wall et al., 1991, 1992; Kwan et al., 1992; Brown et al., 1993). As previously mentioned, the connective tissue in peripheral nerves is constituted of three layers: the epineurium, the perineurium and the endoneurium. The epineurium constitutes a thick layer which surrounds the nerve and contributes to the resilience of the nerve (Peltonen et al., 2013). The perineurium is a strong layer of epithelium-like cells and collagen fibers (Thomas and Jones, 1967). Finally, the endoneurial ECM is found near the myelinated fibers, to protect them further from mechanical stresses. Interestingly, the endoneurial fluid is at a higher pressure than the epineural fluid. An additional role for the perineurium could be to withstand the positive pressure from the endoneurium (Myers et al., 1978; Figure 1).

The stiffness and elasticity of peripheral nerves determine the mechanical cues that SCs are exposed to. They are partially determined by the connective tissue surrounding the nerves. Yet the elastic properties of peripheral nerves are not equal along their length. It is increased near articulations where nerves need to be more elastic, which reveals a more complex tissue architecture than anticipated (Phillips et al., 2004). For many years researchers have observed the undulating course of peripheral nerve fibers, also called spiral bands of Fontana.
(Zachary et al., 1993). Bands of Fontana found in peripheral nerves disappear when nerves are stretched by 10% of their original length (Pourmand et al., 1994). Thus, bands of Fontana are thought to promote peripheral nerve elasticity. In support of this hypothesis, bands of Fontana are absent from nerves not subject to mechanical strain, such as newly regenerated nerves, intracranial nerves or spinal roots (Clarke and Bearn, 1972; Merolli et al., 2012). The mechanism by which bands of Fontana are formed is still unclear (Power et al., 2015).

SCs themselves adapted to endure external mechanical forces. Most of the SC myelin segment consists of compact myelin. Yet, compact myelin is interrupted by regions of uncompact myelin called Schmidt-Lanterman incisures (Small et al., 1987). Thus, it was proposed that incisures are a reservoir of membrane, allowing SCs to respond to a stretch of the myelin segment (Glees, 1943). While Schmidt-Lanterman incisures also have a role to play in SC intracellular transport (Balice-Gordon et al., 1998), it is important to point out that they are found only in the PNS, and their presence is conditional to the expression of P0, a major peripheral myelin protein (Yin et al., 2008, 2015). SCs also contributes to the mechanical resistance of peripheral nerves by secreting the basal lamina. The basal lamina is an essential component of the SC ECM which is critical for SC development, surrounding each myelinated fiber (Feltri et al., 2015; Monk et al., 2015) and is an important component allowing regeneration of the peripheral nerves. The basal lamina organization remains unaffected after a severe mechanical compression on the nerve, or an acute axonal degeneration and is even further maintained after axonal death. As such, the basal lamina is able to be used as a guidance for axonal regrowth (Bunge et al., 1989). More recent methods have confirmed that the basal lamina provides a mechanical resistance to compression (Rosso et al., 2014). Autotypic junctions of SCs, formed between the spiral layers of myelin, have also been hinted to contribute to SC mechanical strength (Poliak et al., 2002). However, several models have shown that disruption of SC autotypic junctions impairs the propagation of action potentials but does not affect the appearance of the myelin sheath (Miyamoto et al., 2005; Denninger et al., 2015). Taken together, these studies suggest that relative elasticity or stiffness of the peripheral nerves influence the mechanical cues that the SCs are exposed to, while SC architecture and basal lamina integrity play key roles in the SC response to mechanical stress.

**MECHANICAL INJURIES TO PERIPHERAL NERVES AND CONSEQUENCE TO SCHWANN CELL BIOLOGY**

The pathological consequences of mechanical peripheral nerves injuries are evident, but their severity can vary. These injuries, were first classified by Seddon et al. (1943) ranked in three degrees: neurotmesis, axonotmesis and neuropraxia. Neurotmesis are dramatic injuries in which axons, connective tissues and basal lamina deposition are disconnected (Figure 2). They cause a complete loss of function. The recovery after neurotmesis is poor. Therapeutic approaches taking advantage of nerve grafts or nerve conduits have been attempted, but the success of such approaches have been mixed with variable improvements in functional recovery (Battiston et al., 2005). On the other hand, axonotmesis are severe compressions of the nerve or stretch-related injuries, and cause a disruption of axons and myelin sheaths with preservation of connective tissues and basal lamina (Figure 2). Distally to the point of trauma, axons degenerate and SCs demyelinate. Within 30 days after injury, peripheral nerves can remarkably recover, with
axon regeneration and SC remyelination. Finally, in neuropraxia peripheral nerves endure more common and less severe trauma that can be caused by mechanical compression of the nerve or ischemia (Ochoa et al., 1971, 1972). In neuropraxia, axon integrity is not primarily disrupted, but demyelination can occur (Figure 2). This injury affects the propagation of action potential, but is fully reversible, as the “Saturday night palsy” (Sunderland, 1990; Lee and Wolfe, 2000). Chronic compressions are another form of injury in peripheral nerves (Brown et al., 2011). They start with the inability of axons to transmit action potentials and as compression become more severe; demyelination follows (Rempel et al., 1999; Burnett and Zager, 2004). The effect of chronic nerve compression has been well characterized (Mackinnon et al., 1985; O’Brien et al., 1987; Dahlin et al., 1993; Pham et al., 2009). Chronic mechanical stimulation induces SC demyelination, as well as an increase in both SC apoptosis and proliferation, in absence of evident axonal injury (Gupta and Steward, 2003; Gupta et al., 2012).

Similarly in vitro shear stress on primary SCs in the form of a laminar fluid flow is sufficient to reduce myelin protein gene expression and promote SC proliferation (Gupta and Steward, 2003; Gupta et al., 2005). Thus, low level mechanical stimuli may activate SC mitogenic pathways, independently from the regulation occurring between SCs and axons after axonal injury (Salzer and Bunge, 1980).

It is also worth mentioning that genetic neuropathies could also be related to mechanical stresses. This appears to be the case with the hereditary neuropathy with liability to pressure palsies (HNPP). In this disease caused by the haploinsufficiency of PMP22, patients are challenged daily by everyday activities. Benign mechanical pressures like crossing the legs can cause weakness or paralysis in the foot for several hours to several months (Earl et al., 1964; Horowitz et al., 2004; Li, 2015). The causes of HNPP are unclear as the exact role and functions of PMP22 are still being deciphered. Yet, a notable observation in HNPP myelinated fibers is the disruption of SCs autotypic junctions (Guo et al., 2014; Hu et al., 2016). Thus, it is possible that in SCs haploinsufficient for PMP22, the myelin is less resilient to mechanical stresses. This hypothesis is supported by atomic force microscopy work on myelinated fibers knock-out for PMP22 (Rosso et al., 2014). Thus, the response of SCs to mechanical stresses plays a role in both traumatic neuropathies and some genetic neuropathies.

**EXTRACELLULAR AND INTRACELLULAR COMPONENTS OF SC MECHANOBIOLOGY**

Mechanobiology refers to how physical and mechanical signals can be sensed by organs, tissues or cells and are converted in specific cellular responses. Many fundamental aspects of cell behavior depend on mechanobiology, including adhesion, spreading, migration, gene expression and cell-cell interactions in multiple cell-types (Jansen et al., 2015). Mechanobiology is based on the existence of two components: (1) mechanosensors, that allow a cell to sense mechanical signals provided by its environment; and (2) mechanotransducers, that allow a cell to transduce mechanical signals into biochemical signals. A large amount of mechanosensors and mechanotransducers from both intra and extracellular compartments have been identified over the last decades (Jansen et al., 2015). However these components are not relevant to all cells (e.g., ciliary bundles on hair cells in the sensory macula, glycocalix presence at the plasma membrane of epithelial cells, etc.; Jaalouk and Lammerding, 2009) and it is still unclear how mechanosensation and -transduction are orchestrated. In SCs, the identity of mechanotransducers and mechanosensors is starting to emerge. In the following section, we will review how physical signals can be transmitted in SCs through ECM, cell adhesion molecules (CAMs) and internal structures such as cortical cytoskeleton and the nucleus.

**Extracellular Matrix**

ECM acts as a physical support for cells to allow their adhesion and migration, and for tissue to protect their architecture from mechanical stresses. Its composition includes hundreds of proteins (i.e., elastin and collagen), glycoproteins and numerous proteoglycans. In addition, like epithelial cells, SCs secrete a basal lamina, an ECM component composed of laminin and collagen networks cross-linked with proteoglycans and nidogens, which links the extracellular environment to the plasma membrane of SCs (Bunge et al., 1980). The mechanical properties of the ECM are defined mainly by elastic fibers and collagens fibers, which provide respectively resilience (elasticity) and tensile strength (resistance to tensile stress). In peripheral nerves, the proportion of elastic fibers in peripheral nerves is relatively small in comparison to collagen (Sunderland, 1965). In addition, collagen fibers are arranged longitudinally to allow some degree of axial stretch. Thus it was suggested that collagen fibers also contribute to the elastic properties of peripheral nerves (Tassler et al., 1994). Since all Schwann cells are surrounded by ECM, the most intuitive example of mechanotransduction is a transmission of signals through the ECM and the SC basal side. Yet, SCs also have an intimate relationship with axons on their apical side where biochemical signals from neurons are critical for SC migration, proliferation, survival, polarization, differentiation and gene expression (Monk et al., 2015; Salzer, 2015). For example, the myelinating fate of a SC is dictated by the amount of type III neuregulin-1 present on the surface of an axon (Taverggia et al., 2005). However, only membrane-bound type III neuregulin-1 promotes SC differentiation. In addition, a direct axonal contact is required for the deposition of a basal lamina by SCs (Bunge et al., 1982; Poitelon et al., 2015). These reports illustrate the functional need of SC to establish a direct physical contact with axons. Thus, SC fate depends on the formation of adhesion complexes between SCs with both axons and ECM. These adhesion complexes are primary sites of transduction for mechanical signals occurring in SCs and can be considered as mechanosensors.

**Cell Adhesion Molecules**

Major adhesion complexes are formed by CAMs and are implicated at various stages of SC development (Poliak and Peles,
Kong et al., 2009). The behavior of SCs have shown to strengthen under tension (Friedland et al., 2009; Litvinov et al., 2011). In particular, some strain, often these adhesions strengthen or stabilize (Friedland et al., 2015; Monk et al., 2015). Among these receptors, the role of integrin-mediated adhesions in mechanotransduction has been well characterized during the last decades. SCs lacking integrin-ECM interactions weaken when subjected to tension and promotes the formation of actomyosin filaments. In addition, stretch induced injuries could create a conduction block, caused presumably by the shear between axons and SCs at the nodes of Ranvier/paranodal region (Maxwell et al., 1991; Jou et al., 2000; Ichimura et al., 2005). The second group of CAMs, which distinctively interacts with the ECM, includes basal lamina receptors (i.e., integrin, G-protein coupled receptors and Dystroglycan). The role of these molecules has been well characterized during the last decades. SLCs lacking basal lamina receptors experience detachment from the basal lamina and develop arrest or delay in the establishment of the interaction with an axon and its subsequent myelination (Feltri et al., 2015; Monk et al., 2015). Among these receptors, the role of integrin-mediated adhesions in mechanotransduction has been quite studied (Humphrey et al., 2014), and while some integrin-ECM interactions weaken when subjected to tension strain, often these adhesions strengthen or stabilize (Friedland et al., 2009; Litvinov et al., 2011). In particular, some β1 integrins have shown to strengthen under tension (Friedland et al., 2009; Kong et al., 2009). The behavior of SC α3β1, α6β1, α7β1 and α6β4 integrins under strain has not been defined yet (Berti et al., 2006), but is of interest as β1 integrins are essential for SC polarization and proper axonal ensheathment (Feltri et al., 2002).

Integrins are central to mechanosensation as they are connected both to the ECM and the actomyosin cytoskeleton, in clusters called focal adhesions. The structure of focal adhesions is complex and constitutes of numerous proteins. Thus, it is difficult to integrate the contribution of each one during mechanosensation. However, possible mechanically-induced stimulation of the focal adhesion complexes, could regulate important signaling pathways for SC biology, (i.e., downstream of FAK or ILK; Grove et al., 2007; Pereira et al., 2009; Grove and Brophy, 2014; Love et al., 2017), and stimulate the actin cytoskeleton in SCs. Indeed, Rac1 acts downstream of integrin β1 to drive actomyosin activity (Benninger et al., 2007; Nodari et al., 2007). The important role of actin in SC myelination was shown through the deletion of N-Wasp and Profilin1, regulators of actin polymerization (Jin et al., 2011; Novak et al., 2011; Montani et al., 2014). Yet, filaments of actin, linked to focal adhesions, also play a direct role in mechanosensation. The application of tensile force to cells increases their F- /G-actin ratio and promotes the formation of actomyosin filaments. In addition to the actin assembly, activation of myosin II or myosin light chain kinase is critical for SC myelination (Fernandez-Valle et al., 1997; Melendez-Vasquez et al., 2004; Wang et al., 2008; Leitman et al., 2011; Montani et al., 2014). Thus, integrins can affect SC mechanobiology via their actions as mechanosensors and via changes in actomyosin activity.

Mechanotransduction Pathways

Although incompletely understood, the responses of the actomyosin cytoskeleton together with the activation of focal adhesion signaling induce several mechanotransducing pathways. The most notable are YAP and TAZ, two transcriptional activators of the Hippo pathway. Indeed, several works have shown that YAP can be activated through the Hippo pathway in SCs by Crb/Amolt proteins (Colciago et al., 2015; Fernando et al., 2016). In addition, mechanical stimulation through a signaling cascade involving FAK, Src, PI3K, JNK pathways (Codelia et al., 2014; Mohseni et al., 2014; Kim and Gumbiner, 2015; Elbediwy et al., 2016), or formation of actomyosin filaments and presence of F-actin (Dupont et al., 2011; Aragona et al., 2013) can regulate YAP and TAZ. Upon stimulation, YAP and TAZ are translocated to the nucleus to regulate gene transcription. In addition to regulating YAP and TAZ, F-/G-actin ratio also regulates the translocation of myocardin-related transcription factors (MRTFs) from the cytosol into the nucleus to activate serum response factor (SRF)-dependent transcription (Olson and Nordheim, 2010). While YAP/TAZ and MRTF transcriptional targets overlap (Esnault et al., 2014), MRTFs have also been shown to be upstream of YAP and TAZ and to facilitate the YAP/TAZ response (Cui et al., 2015). Mechanotransduction by YAP and TAZ is critical to SC development and will be discussed in depth later in this review; however, the functions of MRTFs in the peculiar architecture of SC remain to be explored. The application of forces, including high density plating and mechanical compression, acts on the actin cytoskeleton and can lead to deformation of the nucleus and influence chromatin organization (Hernandez et al., 2016). The Linker of Nucleoskeleton and Cytoskeleton complex (LINC)
bends the nuclear envelope and the actin cytoskeleton fulfilling a role of mechanotransducer between the cell inner membrane and its nucleus (Baarlink et al., 2013; Isermann and Lammerding, 2013; Plessner et al., 2015). Epigenetic modulators of chromatin structures, such as histone deacetylases, have been shown to be extremely important for SC myelination (Chen et al., 2011; Jacob et al., 2011; Brügger et al., 2015; Wu et al., 2016), but the exact function of LINC in SC development is unclear.

Mechanosensitive Ion Channels

Although much emphasis has been placed on cell adhesion complexes as force sensors, mechanosensitive ion channels contribute both to mechanosensation and transduction. Over the past few years, a number of advances have been made through the identification of new ion channels, expressed in nearly all cell types, such as mechanosensitive potassium channels and Piezo ion channels (Coste et al., 2010; Ranade et al., 2015). They showed that conformational changes in the lipid bilayer of the plasma membrane, such as shear or membrane curvatures, can be converted directly in electric or biochemical signals (Brohawn et al., 2014). This is particularly of interest in the SC, which function is to wrap their membrane around an axon. Interestingly, the importance of membrane curvature during myelination has already been suggested in previous works, which have highlighted the role of lipids in plasma membrane (Ohler et al., 2004; Shaharabani et al., 2016) or N-Wasp (Novak et al., 2011). Considering that SCs express ion channels (Gray et al., 1984; Barres et al., 1990), the role of potential mechanosensitive ion channels in SC should be considered. In summary, SC mechanobiology can be influenced by both extracellular and intracellular cues. Particularly important regulators are the ECM, CAMs, YAP/TAZ signaling and the cortical cytoskeleton.

EXPERIMENTAL APPROACHES TO SC MECHANOBIOLOGY

Experimental approaches to study SC mechanobiology need to account for a variety of factors to model accurately the in vivo environment of peripheral nerves. During adult life, peripheral nerves are constantly subjected to mechanical stresses. In addition, the elasticity of peripheral nerves varies greatly along development, from 6 kPa after birth, when myelination is starting, to 50 kPa in adult nerves (Urbanski et al., 2016). This prompted the engineering community to investigate the response of SCs to their environment, in order to improve the design of nerve conduits used after injury (Gu et al., 2012; López-Fagundo et al., 2014). Isolated SCs grown on soft substrates (from 0.5 to 4 kPa) are rounded and present a low motility and a low proliferation rate (Gu et al., 2012; Poitelon et al., 2016). On stiffer substrates (≥40 kPa), SCs become bipolar and have an increased motility and proliferation (Gu et al., 2012; Poitelon et al., 2016). Surprisingly, SCs appear to be relatively insensitive to variations in stiff substrates, showing slight variations in morphology and no variations in the activation in YAP/TAZ mechanotransducers from 40 kPa to 4 MPa (Poitelon et al., 2016). However, when substrates are enriched with laminin, SC response is vastly different. On soft substrate coated with laminin (around 1 kPa), SCs are able to maintain a cytoskeletal architecture and form actomyosin filaments (López-Fagundo et al., 2014; Poitelon et al., 2016; Urbanski et al., 2016). In addition, the presence of laminin in stiff substrate (40 kPa) affects SC morphology, allowing them to spread, and activate YAP/TAZ mechanotransducers, as characterized by the transfer of YAP and TAZ in SC nucleus (Poitelon et al., 2016; Urbanski et al., 2016). These data show that, in contrast to most anchorage-dependant cells, SCs require laminin to respond to the stiffness of their substrate. The use of static two-dimensional monoculture to study the response of SCs to their environment remains limited. Peripheral nerves are continuously stimulated by stretched movements of the limbs and we do not know how compression, demyelination or loss of axons affects the stiffness of peripheral nerves.

Advances in Understanding SC Mechanobiology in Vivo

The first reports that studied YAP/TAZ in SCs in vivo confirmed that both mechanotransducers are active in SCs during axon-SC recognition, while SCs are myelinating and after completion of myelination (Poitelon et al., 2016; Deng et al., 2017; Grove et al., 2017). During development, YAP/TAZ regulates SC proliferation, differentiation and myelination programs (López-Anido et al., 2016; Poitelon et al., 2016; Deng et al., 2017; Grove et al., 2017). SCs ablated for both YAP/TAZ show an arrest of proliferation, fail to associate with an axon and do not initiate myelination (Poitelon et al., 2016; Deng et al., 2017; Grove et al., 2017). The role of YAP/TAZ after myelination remains unclear as reports conflict on their requirements in adult SCs (Deng et al., 2017; Grove et al., 2017). Interestingly, YAP/TAZ regulates in concert several pathways including lipid or sterol biosynthesis in SCs but also integrins (i.e., integrin α6) and G-protein signaling (i.e., Gas), suggesting respectively positive and negative feedback loops (Poitelon et al., 2016; Deng et al., 2017). YAP and TAZ are functionally redundant, yet it appears that TAZ has a more prominent role in SC development (Poitelon et al., 2016; Deng et al., 2017). Recent findings showed that after nerve injury TAZ levels are increased (Mindos et al., 2017). On the other hand, YAP levels remain stable in control animals and ablation of YAP alone does not affect peripheral nerve remyelination (Mindos et al., 2017). These data hint toward a specific role for TAZ in peripheral nerve remyelination. On the other hand, independent work demonstrated that YAP alone plays a role in the modulation of internodal length and positively regulates myelination and myelin elongation (Fernando et al., 2016). Interestingly, in a model deficient for the laminin receptor Dystroglycan, the amount of active YAP is reduced and internodes are shorter. However upon bone expansion, the peripheral nerves are stretched, the activity of YAP in SCs is increased and myelination appears to be improved (Fernando et al., 2016). These data suggest that physical stretch of the nerve could be a new therapeutic path to improve myelination. It is unclear if the physical stimulation provided by the stretch comes from CAMs at the axon interface, at the ECM interface or both. However, as myelin internodal length is...
known to grow together with limbs (Thomas and Young, 1949), it will be important to assess if the stretch affects also myelin thickness.

**USING SC MECHANOBIOLOGY IN THERAPEUTIC APPROACHES FOR PERIPHERAL NEUROPATHIES**

An exceptional quality of SCs is their ability to dedifferentiate from myelinated SCs to become repair SCs. After neurotmesis or axonotmesis, repair SCs are able to remylinate newly regenerated axons, but most importantly, they provide the necessary tracks for axon guidance and support axonal regeneration. The function of repair SCs is highly considered in peripheral nerves injuries, but also in spinal cord injuries (Xu et al., 1995; Rutkowski et al., 2004; Oudega and Xu, 2006; Kanno et al., 2015). The non-invasive stimulations of SCs at the point of injury, or through the peripheral nerve in peripheral neuropathies, could be an approach to stimulate repair SCs to enhance recovery. The application of pulsed ultrasound on SCs in vitro appears to promote SC proliferation and prevent SC differentiation (Zhang et al., 2009; Tsuang et al., 2011). In vivo application of ultrasound after axonotmesis, also showed that SCs appeared to be affected, promoting an acceleration of peripheral nerve regeneration (Chang and Hsu, 2004; Raso et al., 2005; Jiang et al., 2016). Contrastingly, a most recent report showed that in SCs alone or in co-culture with neurons, ultrasonic stimulation promotes myelination signaling, with the increase of EGR2 levels in SCs (Yue et al., 2016). Thus it remains indispensable to precisely elucidate the influence of the ultrasound on SCs and peripheral nerves as well as the level and frequency of the ultrasound application. Another approach to stimulate SCs mechanically is the use of electromagnetic fields. Less studied, the stimulation of SCs by electromagnetic fields also opens interesting perspectives in peripheral nerve regeneration (Sisken et al., 1989; Kanje, 1992). Indeed, application of an electromagnetic field to cultured SCs promotes their proliferation and migration, presumably through YAP/TAZ (Colciago et al., 2015). Finally, physical therapy has also been considered as a therapeutic approach to stimulate tensile strain on peripheral nerves. Tensile stimulation, under a certain magnitude, appears to improve the regeneration of peripheral nerves (Bueno and Shah, 2008). However, much of this evidence is empirical and it is unclear how tension strain would stimulate axonal regrowth directly, or indirectly through SCs. In addition, the precise stresses required on a particular injured nerve are difficult to evaluate and could be more damaging. Thus patients could undergo such procedures only once the axon regeneration of nerve is completed (Suszynski et al., 2015).

**CONCLUSION**

SCs are poised to be the target of non-invasive mechanical therapies. Mechanically stimulating SCs could be of interest in traumatic neuropathies and demyelinating peripheral neuropathies, such as Charcot-Marie-Tooth disease, chronic inflammatory demyelinating polyradiculoneuropathy or Guillain-Barré syndrome. Yet, there is first a critical need to better understand SC mechanobiology. Determining the identity of the SC mechanosensors and mechanotransducers will define the signaling pathways and biochemical targets downstream of mechanical stress and help establish multidisciplinary approaches toward remyelination. Such research will also have the potential to be extended to strategies at reducing aberrant proliferation of SCs occurring in Schwannomas or neurofibromas.

**AUTHOR CONTRIBUTIONS**

SB and YP wrote the manuscript; SB, KLZ and YP revised the manuscript; YP created the figures. All authors approved the final version of the manuscript for publication.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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