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The impact of physical, biochemical, and electrical signaling on Schwann cell plasticity

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ABSTRACT

Peripheral nervous system (PNS) injuries are an ongoing health care concern. While autografts and allografts are regarded as the current clinical standard for traumatic injury, there are inherent limitations that suggest alternative remedies should be considered for therapeutic purposes. In recent years, nerve guidance conduits (NGCs) have become increasingly popular as surgical repair devices, with a multitude of various natural and synthetic biomaterials offering potential to enhance the design of conduits or supplant existing technologies entirely. From a cellular perspective, it has become increasingly evident that Schwann cells (SCs), the primary glia of the PNS, are a predominant factor mediating nerve regeneration. Thus, the development of severe nerve trauma therapies requires a deep understanding of how SCs interact with their environment, and how SC microenvironmental cues may be engineered to enhance regeneration. Here we review the most recent advancements in biomaterials development and cell stimulation strategies, with a specific focus on how the microenvironment influences the behavior of SCs and can potentially lead to functional repair. We focus on microenvironmental cues that modulate SC morphology, proliferation, migration, and differentiation to alternative phenotypes. Promotion of regenerative phenotypic responses in SCs and other non-neuronal cells that can augment the regenerative capacity of multiple biomaterials is considered along with innovations and technologies for traumatic injury.

1. Introduction

The peripheral nervous system (PNS) plays an essential role in connecting the central nervous system (CNS) to tissues throughout the body. Serious injury to peripheral nerves account for approximately 3 % of patients admitted to Level I trauma centers in the US (Foster et al., 2019; Karsy et al., 2019), and often result from automotive accidents, penetrating trauma, or crushing injuries after falls (Kouyoumdjian et al., 2017). Peripheral neuropathies can also arise as a result of conditions such as diabetes, HIV, and cancer (Azhary et al., 2010). PNS injuries present a significant healthcare challenge, as these injuries may result in impaired sensory and motor function, burning or tingling sensations, numbness, and tactile allodynia at the site of the injury. They may also require long term disability care (Bergmeister et al., 2020; Huckhagel et al., 2018).

Minor nerve damage is generally remediated through an innate repair capacity driven by autologous cells, surrounding matrix protein, and a unique inflammatory response by tissue residing macrophages. Vitally important to this response is that Schwann cells (SCs) exhibit a unique plasticity to shift phenotypic expression to provide more favorable regenerative outcomes. As such, minor PNS repair often proceeds without serious medical intervention. However, if the gap between the proximal and distal stumps of the injured nerve is longer than 5 mm, additional medical attention is required to achieve functional recovery (Lotfi et al., 2019). Even still, this is largely remediated by some combination of non-invasive therapy during the repair process. Significant nerve transections typically result in a greater exigency for surgical repair, as the autologous repair response cannot sustain the necessary microenvironment after an initial time frame of 3–4 weeks. In clinical settings, nerve grafting has been repeatedly described as the current "gold standard" in PNS repair. Autografts and allografts supply intact PNS proteins, biological structures, and (in some cases) cells to the injury site. The preservation of key regenerative markers along with robust structural support typically induces sufficient repair. However, grafts have inherent limitations. Autografts require the sacrifice of healthy nerve tissue and may result in surgical complications, while allografts require extended immunosuppression that may increase the potential of infection and tumor formation (Lotfi et al., 2019). An

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alternative technique to nerve grafting is the nerve guidance conduit (NGC), which aims to provide similar mechanical and trophic support through synthetically engineered substrates. NGCs serve as a barrier between regenerating axons and the external environment while also providing physical guidance for regeneration across nerve lesions (Carvalho et al., 2019). Emerging therapeutics work to build upon existing strategies to offer both an alternative approach to PNS repair and a practical supplement to preexisting therapeutics.

Unlike the CNS, injured nerves in the PNS have a robust ability to regenerate and provide functional outcomes, primarily due to the high plasticity of SCs (Nocera and Jacob, 2020). SCs, derived from neural crest cells, are the primary glial cells residing in the PNS. Under healthy conditions, SCs can assume either a myelinating phenotype or a remak (non-myelinating) phenotype. Myelinating SCs secrete lipid-rich myelin protein to coat and insulate axons for the propagation of action potential signaling throughout the nervous system and are characterized by expression of molecules related to myelin sheath synthesis and maintenance such as Erg2 (Krox20), myelin protein zero (MP0), myelin basic protein (MBP), as well as membrane associated proteins such as myelin associated glycoprotein (MAG), PMP22, and periaxin (Jessen and Arthur-Farraj, 2019). Remak SCs, on the other hand, support axonal integrity by ensheathing small caliber axons to form "remak bundles" and exhibit markers also found in immature SCs such as neural cell adhesion molecule (NCAM), p75 neurotrophin receptor (p75NTR) and glial fibrillary acidic protein (GFAP) (Boerboom et al., 2017; Harty and Monk, 2017). While myelinating and remak SCs provide support to healthy axons, during the PNS regeneration process, SCs demyelinate and transdifferentiate into a regenerative phenotype (also sometimes referred to as a repair phenotype) to promote axonal regrowth (Jessen and Arthur-Farraj, 2019; Jessen and Mirsky, 2016; Jessen et al., 2015). Compared with myelinating and remak SC phenotypes, regenerative SCs exhibit gene expression more similar in nature to immature SCs, with L1, NCAM, p75NTR and GFAP being upregulated, while Erg2, P0, MBP, and MAG are downregulated (Jessen and Mirsky, 2016). Regenerative SCs also exhibit phenotypes not observed in either immature or mature SCs, including the upregulation of neurotrophic factors and proteins such as glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), erythropoietin, and N-cadherin (Jessen and Mirsky, 2016). Additionally, inflammatory cytokines including tumor necrosis factor α (TNFα), interleukin-1α (IL-1α), Il-1β, leukaemia inhibitory factor (LIF), and monocyte chemotactic protein 1 (MCF-1) are upregulated in regenerative SCs (Jessen and Mirsky, 2016). Due to these changes in gene expression, regenerative SCs are characterized by low levels of myelination, high proliferative and migratory capacity, and high phagocytic activity (Boerboom et al., 2017). The unique features of the regenerative SC phenotype enable SCs to facilitate the nerve regeneration process. After transdifferentiation, regenerative SCs (in conjunction with macrophages) enable the process of Wallerian degeneration, where damaged axons and myelin debris are cleared from the injury site. After debris clearance, regenerative SCs extend across nerve lesions and begin secreting key extracellular matrix proteins and various neurotrophic factors. Crucially, the formation of dense extracellular matrix fibrils, called Bands of Büngner, is mediated by SCs and neural fibroblasts. The formation of Bands of Büngner is essential to provide regenerating axons, and their growth cones, with biomechanical cues for proper regeneration. Finally, once the axonal lesion has been breached, SCs revert to a myelinating phenotype that helps sustain the regenerated axons (Fig. 1) (Nocera and Jacob, 2020).

The importance of SC reprogramming as a precursor to successful nerve regeneration has been widely demonstrated. In several studies, it was shown that inhibition of the SC reprogramming process significantly decreased nerve regeneration outcomes, even in cases where neurons, macrophages, and fibroblasts were left unmodified (Arthur-Farraj et al., 2012). Overall, it is crucial that SC reprogramming occurs for nerve regrowth due the role SCs play in initiating Wallerian degeneration, developing the Bands of Büngner, and secreting important neurotrophic factors that sustain axonal regrowth. While the regenerative SC phenotype may be induced experimentally by enforced expression of transcription factors, SCs principally take on a regenerative phenotype as an adaption to the injury environment (Jessen and Mirsky, 2016). Thus, a key strategy for enhancing nerve regeneration lies in understanding the different parameters in the SC microenvironment to control SC behavior and thereby augment the outcomes of tissue engineering applications (Fig. 2). This review details the recent work in biomaterials development and tissue engineering to precisely control the SC microenvironment and ultimately prolong the regenerative phenotype expression of SCs.

2. Physical signaling in the SC microenvironment

Various physical and mechanical parameters in the SC microenvironment have been illustrated to contribute to SC transdifferentiation and nerve regeneration. A key role of the regenerative SC is to extend across the nerve lesion and help secrete and assemble the Band of Büngner matrix that serves as a path for regenerating nerves. To this end, physical signaling of the surrounding ECM plays a key role in the SC

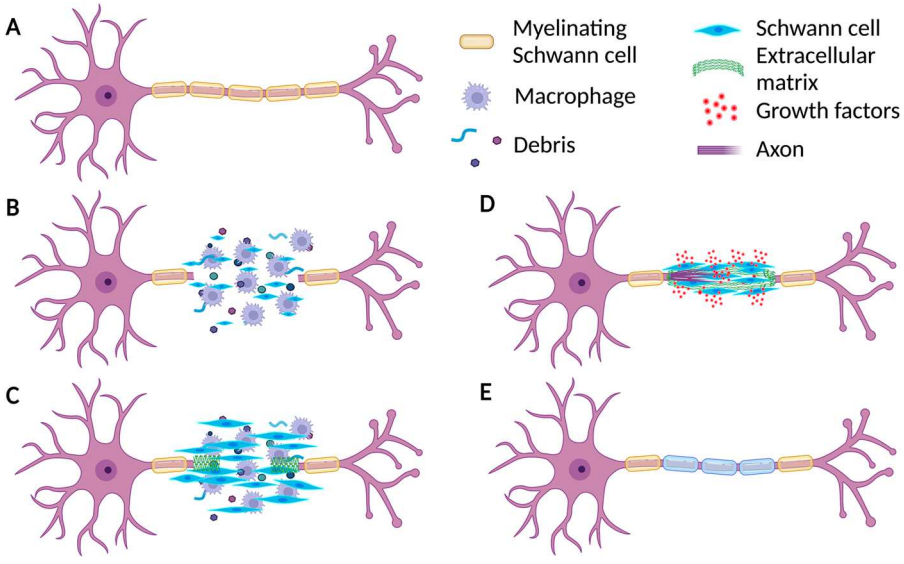

Fig. 1. A schematic overview showing the role of Schwann cells with respect to nerve regeneration. A healthy, myelinated nerve (A) can suffer from physical injury resulting in a nerve gap. Damaged nerves undergo a breakdown of the debris at injury site called Wallerian Degeneration through the recruiting of macrophages and SCs to clear myelination (B). Newly migrated SCs to the lesion site begin elongating, aligning, and proliferating across newly forming ECM to provide guidance cues to regenerating axons (C). SCs begin secreting growth factors to initiate axonal outgrowth to bridge the nerve gap (D). Over time, axons reinnervate and become remyelinated by SCs to form a fully regenerated nerve (E).

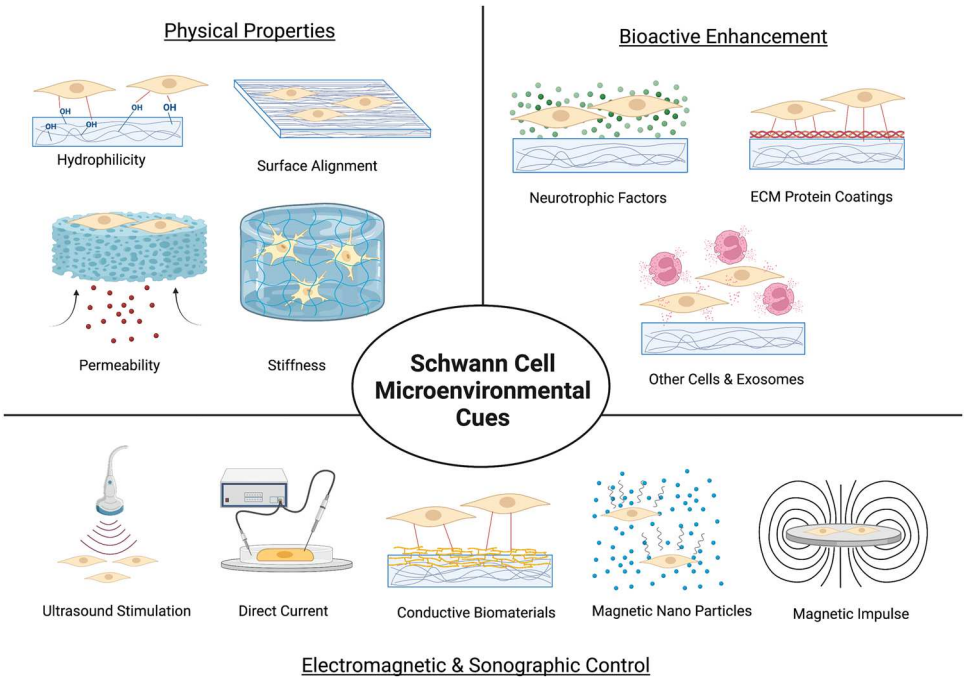

Fig. 2. Schematic detailing the multifaceted microenvironmental components that can impact Schwann cell plasticity. Discussed are physical, bioactive, and electromagnetic and sonographic microenvironmental cues and how they influence Schwann cell behavior and nerve regeneration.

injury response by facilitating the delivery of nutrients to proliferating and migrating SCs. Additionally, the geospatial orientation of the SC physical environment (such as surrounding fibers and channels within the ECM or ECM mimicking biomaterials) has been shown to shape SC morphology and physically guide SC directional migration. In addition to physical support and alignment, SC mechanotransduction is of interest to understanding the interplay of the microenvironment with SC plasticity. Mechanical properties of the SC physical surrounding, such as the stiffness of engineered substrates, have been demonstrated to be influential in regulating the expression of regenerative SC markers such as c-Jun (Xu et al., 2020). Here we look at various physical properties of engineered substrates that have been demonstrated to influence SC transdifferentiation, growth, and migration, as well as different fabrication and substrate modification strategies that have been utilized to tune the physical microenvironment for supporting nerve regeneration.

2.1. *Thickness and porosity of ECM substrate*

Porosity of the substrate plays a key role in promoting both SC viability and migration. Highly porous substrates have been demonstrated to promote SC survival on scaffolds by allowing increased diffusion of nutrients such as oxygen and glucose (Kokai et al., 2009; Li et al., 2012; Naghieh et al., 2019). Porous substrates also promote SC migration by providing a higher surface area for cell attachment (Bhutto et al., 2016). Scaffolds with a porosity of approximately 70–90 % have been demonstrated to support SC viability and proliferation (Bhutto et al., 2016; Orkwis et al., 2020). It was observed that intraluminal fillers in NGCs with an average pore diameter of 20–50 μm were shown to support enhanced nerve regeneration (Bozkurt et al., 2012; Huang et al., 2018; Lietz et al., 2006). In the conduit wall itself, smaller pore sizes are required to prevent the invasion of other support cells into the regenerating axons (Huang et al., 2018). Huang et al., for instance, found that the outer sheaths of NGCs with pore diameters of 6.5 ± 3.3 μm prevented the invasion of fibroblasts (Huang et al., 2018). However, pores that are larger from a cross-sectional view and narrower from a side view may also support SC migration and nerve regeneration. Usal et al. found that SCs cultured on a 3D printed PCL tube with pore diameters of 675 ± 40 μm by 47 ± 16 μm supported SC adhesion, viability, and MPB expression (Dursun Usal et al., 2022). Thus, it may be useful for future work to further examine the effect on SCs of not only the size, but also the shape, directionality, and organization of scaffold pores.

NGC scaffold thickness also plays a role in the dispersion of nutrients to SCs and regenerating axons. In general, thicker scaffolds create a suitable microenvironment for cell growth, as increased thickness provides dimensional stability for tissue growth within the scaffold and prevents structural collapse (Kokai et al., 2009; Ghasemi-Mobarakeh et al., 2009). For example, a PCL conduit with 400 μm wall thickness exhibited sufficient mechanical strength to prevent collapse (0.05–0.065 N/mm at a lateral displacement of 0.3 mm) while supporting SC migration and axon regeneration (Huang et al., 2018). However, excessive thickness may hinder SC proliferation by reducing scaffold permeability and thus decreasing the dispersion of nutrients inside a nerve guidance conduit (Kokai et al., 2009). For instance, increasing wall thickness of a PCL scaffold from 200 to 600 μm resulted in a decrease in permeability of glucose from 82 % to 53 % (Kokai et al., 2009).

2.2. *Topographical cues*

The surface topography of PNS ECM and substrates is another critical parameter that can influence SC plasticity. Physical topography such as grooves, pits, pillars, wells, and other shapes have been used for directing SC reprogramming and migration (Lotfi et al., 2019), with the general consensus that substrates possessing directionally aligned structures provide superior contact guidance to promote SC elongation, alignment, and secretion of neurotrophic factors compared with unaligned substrate topographies (Lotfi et al., 2019). Mechanosensing via an anisotropic surface plays a critical role in SC plasticity because the regulation of SC shape on aligned surfaces has been demonstrated to regulate Rho GTPases such as Rac1 and RhoA, which transduce mechanical cues and regulate SC function (Huang et al., 2010). For example, when Xu et al. investigated the interplay between SC morphology and regenerative behavior on micro-patterned and un-patterned PDMS substrates, it was found that elongated SC

morphology activated Rac1, which in turn activates MAPK kinases 7 (MKK7)/JNK signaling to promote expression of SC demyelination genes such as c-Jun, p75NTR and Sox-2. Conversely, cells that were cultured on un-patterned substrates exhibited a rounded phenotype that inhibited Rac1 and led to a reduction in regenerative signaling. In addition to cell elongation, SCs cultured on substrates that promoted a smaller spreading area showed inhibition of RhoA, which prevented the activation of YAP/TAZ. This is significant for regenerative applications, as YAP/TAZ promotes a myelinating SC phenotype via Krox-20 signaling rather than a regenerative phenotype (Xu et al., 2021). Thus, tuning the specific dimensions and mechanics of the substrates hold promise for harnessing SC mechanosensing to enhance SC reprogramming.

While mechanosensing via GTPases and MAPK signaling described previously are common for a variety of cell types, recent work elucidating the specific role of SC signal transduction provides unique therapeutic inferences for the study of nerve tissue repair. Poitelon et al. examined the specific contribution of YAP and TAZ effectors on the hippo pathway during myelination. Mutagenesis studies in mice demonstrated that TAZ, specifically, is responsible for radial sorting in Schwann cells and the upregulation of myelination thereafter (Poitelon et al., 2016). This effect was further examined through the lens of basal lamina receptors, where transcription of receptor associated genes was established as a necessary mediator for the transduction of mechanical stimuli (Poitelon et al., 2016). Experimental techniques have repeatedly highlighted the importance of laminin protein in forming the basement membrane of healthy nerve tissue as well as inducing the desired repair phenotype. Physiologically, these pathways also play important roles in prolonging the repair environment through stress-signaling during neurogenesis. Specifically, YAP activation by axonal growth through regenerating pathways likely helps promote the aforementioned myelinating effect (Fernando et al., 2016). By contrast, this process can also induce deleterious effects related to proliferation of progenitor-like cells into a tumor microenvironment. For instance, Wu et al. showed that Schwann cells can be programed through Lats1/2-Taz/YAP signaling to drive malignant peripheral nerve sheath tumorigenesis (Wu et al., 2018a).

The common approaches for fabricating biomaterials with aligned structure include photolithography, stereolithography, soft lithography, compression molding, injection molding, and 3D printing for hydrogels (Xu et al., 2020; Cady et al., 2020; Papadimitriou et al., 2020; Wu et al., 2018a), as well as self-assembly, electrospraying, and electrospinning for fibrous scaffolds (Orkwis et al., 2020; Papadimitriou et al., 2020) to achieve a desired cell response. Channeled substrates, or grooves in a material, provide one biomaterials engineering approach for achieving an anisotropic geometry to induce a pro-regenerative SC response. Channeled substrates with microscale grooves ranging between 4 and 50 μm in width have been shown to provide a sufficiently oriented structure to promote SC elongation, alignment, oriented migration, remyelination, and NGF secretion (Tang et al., 2021; Wu et al., 2018a; Li et al., 2019; Tonazzini et al., 2015a). Several studies have demonstrated that narrower grooves result in the greatest promotion of regenerative SC behavior and subsequent nerve repair. Zhang et al., for instance, reported that channels formed by thermal pressing of a PDMS stamp with strip patterns against poly(D,L-lactide-co-caprolactone) (PLCL) film, followed by gelatin entrapment significantly regulated SC behaviors, with 3 μm wide channels resulting in higher SC migration rate and extent of elongation compared with 10 μm wide channels (Zhang et al., 2018). Other studies that fabricated channels using poly-L-lysin and laminin coated PDMS or photopolymerization reported similar conclusions that narrow channels promoted SC alignment, migration, elongation, and proliferation compared to wider channels (Wu et al., 2018a; Mitchel and Hoffman-Kim, 2011; Tuft et al., 2013a; Liu et al., 2016)., For example, Tonazzini et. al found that poly-L-lysin and laminin coated PDMS possessing 4 μm channels better promoted SC collective migration and upregulated N-cad expression compared to cells cultured on 20 μm channels. However, using channels that are too narrow (around 1 μm) has been shown to result in decreased cell polarization and migration (Tonazzini et al., 2015b). In terms of the height of channels, scaffolds with microgroove amplitudes of approximately 1–8 μm have been shown to promote SC alignment. It is reported that the alignment of both neurites and SCs is enhanced with increased channel height (Tuft et al., 2013a). For example, Tuft et al. found that SCs and spinal ganglion neurons (SGRNs) cultured on photopolymerized micropatterned methacrylate polymers exhibited greater alignment on scaffolds with 8 μm amplitude channels compared to 3 μm and 1 μm amplitude channels (Tuft et al., 2013b).

In addition to dimensions of substrate channels, the shape of the grooves in the substrate may alter SC behavior. Mobasseri et al. constructed different groove shapes consisting of sloped wall (SL), V-shape (V), square shaped (SQ). It is reported that SL and V grooves enhanced cell alignment, while SL grooves specifically promoted cell attachment. Cell proliferation rate also increased on V and SL grooves compare to SQ grooves (Mobasseri et al., 2015). Moreover, Kim et al. fabricated poly (lactic-co-glycolic acid) into NGCs to form micro-grooves on the inner wall of NGCs. They reported that micro-grooved NGCs resulted in a better functional recovery compared to NGCs with flat inner wall (Kim et al., 2018). These results indicate that channeled topography not only promotes SC regenerative functions in vitro but may also lead to a better nerve regeneration in vivo.

Aligned fibers may also be incorporated into biomaterials to regulate cell behaviors and promote nerve regeneration. Scaffolds constructed with aligned nanofibers have been shown to significantly promote SC migration, proliferation, and elongation (Xia et al., 2016a; Zhang et al., 2016; Xue et al., 2020), which are key features of regenerative SC phenotypes. For instance, when Hu et al. implanted aligned nanofibers into polycaprolactone (PCL) NGCs to bridge a 10-mm rat sciatic nerve gap, it was found that NGCs with nanofibers significantly enhanced axonal regeneration and SC remyelination compared to hollow NGCs (Li et al., 2019). Other in vivo studies that incorporated aligned nanofibers into NGCs also show enhanced nerve regeneration compared to traditional hollow NGCs, which suggests a promising future for the combination of NGCs and aligned nanofibers to promote peripheral nerve regeneration (Frost et al., 2018; Schlatter et al., 2018).

When designing aligned fiber-related biomaterials, the diameter of fibers plays a critical role in regulating SC regenerative functions. Gnavi et al. reported that using SC-DRG co-culture and gelatin fibers, nanofibers (300 and 600 nm) were able to promote SC adhesion and proliferation, whereas microfibers (1.0 and 1.3 μm) were able to promote SC migration (Gnavi et al., 2015). Similarly, when Usal et al. constructed a NGC using electrospun Gelatin-PHBV fibers with a fiber diameter of 1.5 $\pm$ 0.4 μm, the scaffolds supported the attachment and proliferation of both SCs and PC12 cells, and also enhanced nerve conduction velocities (NCVs) (Dursun Usal et al., 2022). Wang et al., using poly-L-lactic acid (PLLA) fibers, reported that modifications to fiber diameters were not able to regulate SC migration. However, large (1325 $\pm$ 383 nm) and intermediate (759 $\pm$ 179 nm) diameter fibers were able to enhance neurite extension (Wang et al., 2010). When considering fiber diameter that was much larger than 1 μm, it was reported that large diameter (13.5 $\pm$ 2.3 μm) fibers constructed with polyhydroxyalkanoates (PHAs) promoted neuronal cell alignment and survival within a neuronal/SC co-culture system compared to small diameter fibers (Lizarraga-Valderrama et al., 2019). However, Daud et al. constructed PCL fibers with a smaller mean diameter (1 μm) which supported better neurite outgrowth, SC migration, and SC elongation compared to large diameter (5 and 8 μm) fibers (Daud et al., 2012). However, this difference may have been due to the use of different fiber materials in addition to diameters. When using microfibers, SC plasticity may also be enhanced through nanopatterning of fibers, as nanoscale patterns provide sensing targets and contact areas that promote axon guidance (Wu et al., 2020). For example, engraving the surface of electrospun PCL microfibers with nanoscale grooves (239 $\pm$ 54 nm in width) resulted in increased SC migration, with the thinnest ridges on the microfibers

providing the most optimal substrate for migration (Wu et al., 2020). Overall, both aligned channels and fibers have been illustrated to provide important topographical cues to SCs during regeneration.

Recent work has also demonstrated the impact of substrate mechanics on modifying SC behavior. For peripheral nerve injuries, softer substrates have been shown to promote higher SC viability and regenerative phenotype expression compared with stiffer substrates (Xu et al., 2020; Naghieh et al., 2019). Soft substrates have been demonstrated to promote a regenerative SC phenotype through regulation of RhoA and YAP/TAZ. Both RhoA and YAP/TAZ promote a mature myelinating SC phenotype (Wu et al., 2018a; Tang et al., 2021), and consequently their upregulation can inhibit regenerative SC behavior during the Wallerian degeneration process. For example, Mindos et al. reported that YAP/TAZ activation by merlin deletion downregulated SC regenerative markers such as c-Jun, and therefore caused a failure in axonal regeneration and SC remyelination (Huang et al., 2018; Ryan et al., 2017). The regulation of RhoA/YAP/TAZ signaling using soft substrates has been studied using a variety of soft materials. For example, SCs seeded on soft PDMS or polyacrylamide substrates exhibited lower RhoA and YAP/TAZ activities, resulting in higher migration rate, proliferation rate and regenerative marker expression (Xu et al., 2020; Rosso et al., 2017; Gu et al., 2012). NGCs constructed with poly(glycerol sebacate methacrylate) (PGSm) and collagen exhibited significantly lower scaffold stiffness compared to clinically used and synthetic polymer-based NGCs (Ryan et al., 2017; Singh et al., 2018). Implanting PGSm-based NGC to injury sites resulted in comparable functional recovery to allograft repair. Other NGCs constructed with soft materials such as hyaluronic acid (HyA) sponges, polyvinyl alcohol (PVA) and polyacrilyamide (PAAm) have also been used to promote SC proliferation, maturation and nerve regeneration (Entekhabi et al., 2021; Stocco et al., 2018; Rosso et al., 2022). For example, Rosso et. al found that PAAm substrates with an elastic modulus of 1.1 kPa resulted in increased c-Jun expression in SCs and a downregulation in Krox20 expression compared with scaffolds with a 27.2 kPa stiffness (Rosso et al., 2022). Soft NGCs could also prevent RhoA induced myofibroblast formation, which hinders nerve outgrowth (Chamberlain et al., 2000; Huang et al., 2012). However, decreasing the stiffness of scaffolds could compromise the structural rigidity and lead to collapse of NGCs, thereby pinching the regenerating nerve tissue. Additionally, stiffer substrates may play a role in promoting SC migration and fibronectin deposition. SC fibronectin expression and fibrillogenesis are essential for SC alignment and directional migration (Torres-Mejía et al., 2020). Both fibronectin and fibronectin fibrillogenesis have been shown to be directly controlled by Sox2, which is upregulated on stiffer substrates (27.7 kPa) (Torres-Mejía et al., 2020). Regardless, extremes in either stiffness or softness may adversely affect SCs (Xu et al., 2020). For example, decreasing the elastic modulus of PDMS substrates from 1119 to 8.67 kPa resulted in higher SC viability, proliferation, and c-Jun expression for softer substrates, but when the stiffness was 3.85 kPa it resulted in decreased proliferation and c-Jun expression (Xu et al., 2020).

In addition to scaffold stiffness, the stiffness of the NGC intraluminal filler may also be tuned to promote SC regenerative phenotype and nerve regeneration. Hydrogels are excellent substrates for intraluminal fillers due to the capacity for enhanced bioactivity, stability and hydrophilicity (Dietzmeyer et al., 2020). Hydrogel intraluminal filler can be constructed via various materials such as elastin, fibrin, gelatin/chitosan and peptide amphiphile, with each having been shown to enhance nerve regeneration (Du et al., 2017; Black et al., 2015; Suhar et al., 2020; Hsu et al., 2019). Critically, the Young's moduli (E) of these hydrogels, approximately 1–1.5 kPa, are much lower than native peripheral nerve with a Young's moduli at approximately 6–50 kPa throughout development (Urbanski et al., 2016). Other low stiffness intraluminal fillers such as Hyaluronic acid ($E < 1$ kPa) and collagen-chitosan ($E = 2$ kPa) have also been introduced to NGCs to promote nerve regeneration (Huang et al., 2018; Ryan et al., 2017).

3. Bioactive enhancement of natural and synthetic scaffolds

While physical cues in the SC microenvironment play a significant role in altering SC behavior post injury, various biological parameters also create a cascade of vital signals that regulate SC plasticity. The biochemical composition of the SC's ECM has been demonstrated to influence the expression of several key regulators of SC myelination and demyelination, such as c-Jun, Krox20, and Pmp22 (Xu et al., 2020; Orkwis et al., 2020; Ning et al., 2016). After SC transdifferentiation and myelin clearance post-injury, SCs secrete growth factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which promote the survival and extension of regenerating axons (Jessen and Mirsky, 2016). This growth factor secretion by SCs has also been enhanced through manipulation of the biochemical properties of SCs surroundings (Li et al., 2022a; Liu et al., 2020), highlighting the importance in understanding biological influences within the SC microenvironment to enhance SC response to injury. Biological cues have also been demonstrated to modulate SC proliferation, elongation, and migratory capacity, which are critical characteristics for the formation of the Bands of Büngner by SCs (Xu et al., 2020; Basu et al., 2022; Ko et al., 2018).

SCs sense their biochemical environment through a variety of cell adhesion molecules (CAMs), with the basal lamina receptors (including integrins, G-protein coupled receptors, and Dystroglycan) specifically playing an important role in SC-ECM interactions (Belin et al., 2017). To manipulate SC response to biochemical cues, engineered biomaterials are often derived from a multitude of natural and synthetic sources. In many cases, this ensures that the resulting scaffold can be tailored to compliment a variety of cell microenvironments. Soft tissue biomaterials can often be augmented by fabrication in conjunction with bioactive modifications that better emulate the native regenerative environment, including ECM-constituent proteins, protein fragments, and whole ECM (Xu et al., 2020; Orkwis et al., 2020; Chen et al., 2019a; Nune et al., 2022; Xue et al., 2022; Yu et al., 2021). Additionally, the application of soluble signaling factors has been utilized to induce regenerative SC behavior (Basu et al., 2022; Ko et al., 2018; Li et al., 2022b, 2020a; Liu et al., 2021). The addition of these biomolecules in conjunction with ECM mimics how the native regenerative environment relies on constant communication between cells, matrix, and soluble signals to ensure the regenerative microenvironment is maintained. Here we will discuss the recent efforts to converge these bioactive principles to help facilitate biomaterials that recreate the native environment and enhance SC regenerative activity.

3.1. ECM based biomaterials

ECM derived materials such as proteins and protein fragments have been previously used to promote SC adhesion, elongation, proliferation, growth factor deposition, and remyelination (Orkwis et al., 2020; Li et al., 2019; Wu et al., 2020; Ning et al., 2016; Yu et al., 2021). Three ECM proteins relevant to SC differentiation and nerve regeneration are collagen I, fibronectin, and laminin (Wu et al., 2020; Harris et al., 2017). SCs interact with these ECM proteins via cell surface integrins, with α1β1 and α2 β1 binding collagens, α2 β1 and α6 β1 binding laminin, and α 5 β1 and αv β3 binding fibronectin (Chernousov and Carey, 2000). All three of these proteins have been shown to promote SC spreading, elongation, and proliferation, with this effect promoted by the activation of Rac1 signaling (Chakraborty et al., 2017). Additionally, it has been demonstrated that coatings of all three proteins on a soft PDMS substrate (with elastic modulus 8.96 kPa) each upregulated c-Jun expression (Wu et al., 2020). While ECM proteins have been shown to upregulate regenerative SC markers, there are limitations to using ECM proteins as coatings for bioactive enhancement of scaffolds. Namely, when peptides or proteins are simply mixed with or coated onto scaffolds, the effect on SC behavior may be diminished due to unstable concentrations of the peptide (Ning et al., 2016). To improve the even distribution and stability of ECM

protein coatings, ECM protein derived peptides may be chemically immobilized to scaffold surfaces. For example, when Ning et al. utilized a functionalized alginate hydrogel bound with RGD peptide (a fragment of fibronectin), the peptide coating provided cues for cell attachment on the scaffold via α5 and β6 integrins, thus increasing SC recruitment and adhesion on the scaffold (Ning et al., 2016). SCs cultured on the functionalized substrates also exhibited higher Pmp22 and Krox20 expression, as well as improved proliferation, elongation, migration, and laminin expression compared with scaffolds that had simply been mixed or coated with peptide (Ning et al., 2016). Similarly, Li et al. found that immobilizing YIGSR peptide (a fragment of laminin) on polyacrylamide (PAM) hydrogels promoted SC alignment, elongation, oriented growth, and secretion of NGF, BDNF, and GDNF (Li et al., 2019), while Yu et al. found that functionalization of poly(D,L-lactide-co-caprolactone) (PLCL) scaffolds with KHIFSDDSSE peptides increased SC adhesion and elongation (Yu et al., 2021).

3.2. Treatment with growth factors

In addition to ECM proteins, treatment of scaffolds with growth factors may be used to upregulate regenerative SC markers. Neurotrophic factors such as nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF), normally secreted by SCs during regeneration to promote axonal growth, may be exogenously administered to promote SC proliferation and induce expression of a regenerative phenotype. For example, Li et al. found that treatment of SCs with NGF resulted in NGF activation through the p75NTR/AMPK/mTOR signaling pathway (Li et al., 2020a). This effect ultimately increased SC autophagy and myelin clearance (Li et al., 2020a). Other work showed that the administration of hepatocyte growth factor (HGF), which binds to the receptor c-met, increased GDNF, LIF, and TNF-alpha expression, and that exogenous introduction of HGF to an injury site by intramuscular injection of plasmid DNA increased the myelin thickness of injured nerves (Ko et al., 2018). In addition to promoting cell proliferation and protein secretion, application of neurotrophic factors may also be used to regulate SC response to a pro-inflammatory environment after injury. Basu et al., for instance, found that treatment of SCs with platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) enhanced the phagocytic activity of SCs in pro-inflammatory conditions (Basu et al., 2022). PDGF is proposed to increase SC phagocytotic clearance of myelin through activating the Erk pathway via TAM receptors (Tyro 3, Axl, Mertk), while VEGF binds to VEGFR-1 in SCs to activate the PI3k signaling pathway, thus dampening the phagocytic effect (Basu et al., 2022).

While exogenously applied neurotrophic factors have been shown to have positive effects on beneficial SC function, there are some limitations for their in vivo application due to high costs and rapid degradability (Li et al., 2022a). Because of this, recent efforts have begun to look towards utilizing growth factor mimicking peptides for the bioactive enhancement of bioengineered materials. For example, Li et al. loaded polydopamine-modified chitin conduits with RGIDKRHWNSG (RGI) and KLTWQULQLKYKGI (KLT) peptides, which mimic BDNF and VEGF respectively. The RGI and KLT peptides synergistically promoted c-Jun and Sox2 expression in SCs, while downregulating MPB and Krox2, indicating the promotion of a regenerative SC phenotype (Li et al., 2022a). The functionalization of the scaffold with RGI/KLT also increased SC proliferation and secretion of CTNF, BDNF, VEGF, and NGF (Li et al., 2022a). Future studies may further examine the use of peptides in place of different growth factors as a more efficient method of biologically enhancing the SC microenvironment for in vivo applications. (Table 1).

3.3. Decellularized ECM

While the application of individual growth factors and ECM proteins is useful for enhancing specific SC behaviors, more focus has recently been placed on the use of a decellularized nerve matrix as a source of natural biochemical cues for regenerative SCs. Decellularized nerve ECM (dECM) closely mimics the native tissue environment, as it contains all key bioactive molecules including collagens, fibronectins, laminins, polysaccharides, cytokines and growth factors (Xue et al., 2022; Harris et al., 2018). Various forms of decellularized nerve matrix have been used to enhance SC proliferation, migration, and myelination (Xue et al., 2022; Chen et al., 2019b; Wu et al., 2018b). Xue et al., for instance, found that hydrogels containing decellularized nerve increased Pu3f1, Egr2, and MPB expression of SCs, indicating that the decellularized nerve hydrogels promoted a myelinating SC phenotype (Xue et al., 2022). Chen et al. found that decellularized nerve matrix may also be used to promote SC migration and neurite growth, with PLLA electronspun scaffolds treated with decellularized nerve matrix facilitating further SC migration as well as faster axonal extension compared to untreated scaffolds (Chen et al., 2019a). In addition to decellularized nerve tissue, decellularized SC ECM has also been applied to scaffolds to support SC viability and elongation (Nune et al., 2022).

Despite many clear advantages to using dECM for promoting SC transdifferentiation and nerve regeneration, the process of synthesizing dECM with biomaterials to create a functional NGC composite material remains a challenge. This is because application of high concentrations of bioactive coatings such as decellularized dECM or ECM proteins has been shown to cause scaffolds to lose the patterned physical topography, resulting in a tradeoff between physical cues and bioactivity of scaffolds (Deng et al., 2022; Zheng et al., 2021). For example, Zheng et al. showed that depositing a dECM coating of more than 1 % (w/v) concentration onto aligned PLLA nanofibrous scaffolds caused SCs to lose the directional alignment provided by the aligned fibers (Zheng et al., 2021). Because of these limitations, future work should be applied to developing scaffold fabrication methods that account for both physical and biochemical parameters in the SC's microenvironment simultaneously. For example, electrospun scaffolds fabricated with pre-blended or co-axially electrospun dECM/synthetic polymer composites have shown promise for generating scaffolds with optimal physical, mechanical, and biochemical properties for nerve regeneration (Deng et al., 2022).

3.4. Support cells and Co-cultured cells

A variety of cell types have also been incorporated into the SC microenvironment to provide biochemical cues for nerve repair. Adipose derived stem cells (ADSCs) are one cell type that has been investigated as a potential avenue for promoting regenerative SCs following PNS injury. For example, Liu et al. found that SCs harvested from spinal cord injuries (SCI) that were cocultured with ADSCs experienced lower levels of SCI-induced apoptosis and higher levels of proliferation compared to the control (Liu et al., 2020). Co-culture with endothelial cells has been shown to promote SC proliferation and migration, with Meng et al. finding that SC/endothelial cell co-cultures resulted in an upregulation in SC Ki67, glial fibrillary acidic protein (GFAP), and NGR1 expression (Meng et al., 2022). Future works may further examine how co-cultures with multiple different cell types may have a synergistic effect on SC behavior and nerve regeneration.

3.5. Other bioactive treatments

In addition to ECM derived materials and growth factors from various support cells, other bioactive materials may be used to enhance SC response to injury. Certain bacteria derived protein toxins have been shown to promote a regenerative SC phenotype, such as Bolulinum Neurotoxin A (BoNT/A). It has been shown that injecting 15 pg BoNT/A into the injured hindlimb of a mouse resulted in the upregulation of GFAP and S100 calcium binding protein-β (S100β) in SCs and increased SC proliferation (Adler et al., 2022). It has also been observed that BoNT/A application enhanced nerve regeneration via the increased expression of nerve regeneration marker cyclin-dependent kinase-2

Table 1
How each physical, biochemical, and electromagnetic signal aspect from the microenvironment influences Schwann cells.

Category	Microenvironmental Cue	Condition	Property of Influence	Impact on SC Behavior	References
Physical Cues	Scaffold Alignment	Aligned microfibers (~1–13.5 μm diameter)	– oriented structure – less porous than unaligned scaffold – - upregulates MAG & P0	– promotes SC adhesion, alignment, elongation, migration – promotes mature SC phenotype – effect varies with scaffold material	Wu et al. (2018),Orkwis et al. (2020), Chew et al. (2008),Daud et al. (2012), Lizarraga-Valderrama (2019), Roca et al. (2022),Wu et al. (2020)
		Aligned microfibers with nanoscale grooves (239 ± 54 nm width)	– oriented structure – grooves may be used as carriers for encapsulation and controlled release of proteins, growth factors	– increases SC migration compared with smooth microfibers	Wu et al. (2020)
		Aligned microscale grooves (4–50 μm width; 0.85–8 μm depth)	– oriented structure – increases Krox20 expression	– promotes SC elongation, alignment, oriented growth, migration, and myelination – promotes SC soma and neurite elongation – promotes NGF expression	Tang et al. (2021), Tonazzini et al. (2015),Li et al. (2019), Wu et al. (2018)
		Aligned nanofibers (~300–1325 nm diameter)	– nanoscale network provides more FA points compared to microfibers	– promotes SC adhesion and proliferation – smaller diameter decreases SC spreading, promotes elongation and proliferation	Gnavi et al. (2015),Wang et al. (2010),Nune et al. (2022)
	Scaffold Mechanical Properties	Soft Hydrogel (Youngs Modulus 8.96 kPa, 1.17–2.62 kPa)	– mimics native PNS matrix elasticity – increases c-Jun expression – promotes MBP expression when used with laminin or fibronectin coating	– promotes SC spreading, viability, proliferation – promotes secretion of laminin	Xu et al. (2019),Ning et al. (2016)
	Scaffold Permeability	3D Structure (3D printed hydrogels, electrospun mats)	– mimics 3D native ECM environment – reflects biomechanical properties of nerve – more space for cell proliferation	– improves SC viability, proliferation, elongation – increases secretion of NGF, BDNF, GDNF, PDGF	Naghieh et al. (2019), Wu et al. (2019),Ning et al. (2016),Usal et al. (2022)
		Porous Scaffolds (Intraluminal material 20–50 μm pore diameter)	– improves dispersion of nutrients (glucose, oxygen) – higher surface area for cell attachment	– improves SC viability & proliferation	Bhutto et al. (2016),Kokai et al. (2009), Bruzauskaite et al. (2016)
Biochemical Cues	Decellularized ECM	Decellularized nerve hydrogel (dNH)	– preserves key bioactive molecules from native tissue: collagens, fibronectins, laminins, polysaccharides, endogenous cytokines and growth factors – exhibits high tissue specificity – increases Pu3f1, Egr2, MBP expression	– promotes SC proliferation – promotes myelinating SC phenotype	Xue et al. (2022)
		Decellularized nerve matrix (pDNM) (0.25 % w/v)	– preserves key bioactive molecules from native tissue: collagens, fibronectins, laminins, polysaccharides, endogenous cytokines, and growth factors – exhibits high tissue specificity	– promotes SC migration – enhances SC ability to wrap around bundled neurites to trigger axonal remyelination	Chen et al. (2019)
		Decellularized SC matrix (SC-ACM) (227 μg/mL)	– closely mimics native ECM	– supports SC viability and elongation	Nune et al. (2022)
		Matrigel (PBS, 1:40, ~300 μg mL^{-1})	– natural ECM	– promotes SC adhesion, viability, and growth – supports myelination	Wu et al. (2018)
	ECM Proteins	Collagen I (10 μg/mL)	– cell integrins bind and activate Rac1 signaling – upregulates c-Jun on a soft substrate – upregulates MBP on a stiff substrate	– promotes SC spreading, elongation and proliferation	Xu et al. (2019)
		Fibronectin (10 μg/mL)	– cell integrins bind and activate Rac1 signaling	– promotes SC spreading (more effective than laminin or collagen)	Xu et al. (2019)

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Table 1 (*continued*)

Category	Microenvironmental Cue	Condition	Property of Influence	Impact on SC Behavior	References
			– upregulates c-Jun on a soft substrate – upregulates MBP on a stiff substrate	– promotes SC elongation and proliferation	
		Laminin (10 μg/mL)	– primary protein found in basal lamina – cell integrins bind and activate Rac1 signaling – upregulates c-Jun on a soft substrate – - upregulates MBP on a stiff substrate	– promotes SC elongation and proliferation (more effective than fibronectin or collagen) – promotes SC adhesion	Xu et al. (2019),Orkwis et al. (2020)
	ECM Protein Derived Peptides	KHIFSDDSSE (KHI) peptide (4.3 μg/cm2)	– derived from NCAM	– increases SC adhesion and elongation	Yu et al. (2021)
		RGD peptide (1.0 %, 1.5 %, 2.0 %, and 2.5 % w/v)	– fragment of fibronectin – provides cues for cell attachment (α5 and β6 integrins) – upregulates Pmp22 and Krox20 – downregulates NCAM	– improves SC recruitment to injury site – increases cell adhesion, proliferation, elongation, and migration – increases laminin expression – promotes remyelination	Ning et al. (2016)
		YIGSR peptide (0.5, 5, and 50 μg/mL)	– fragment of laminin – provides cues for cell attachment – enhances expression of BDNF and β-actin	– increases SC alignment, elongation, and oriented growth – increases number of neurites on SCs – increases NGF, BDNF, and GDNF secretion	Li et al. (2019)
	Growth Factors and Growth Factor Mimic Peptides	Hepatocyte growth factor (HGF) (10, 25, and 50 ng/mL)	– binds with c-met receptor – induces expression of GDNF and LIF via activation of ERK pathways	– promotes SC proliferation and migration – enhances activation of SCs to promote axon remyelination	Ko et al. (2018)
		Nerve growth factor (NGF) (50 ng/mL)	– exerts itself through Type-1 cell surface receptors TfkA and p75NTR – acts through p75NTR/AMPK/mTOR signaling pathway – upregulates ATG-7, ATF-5, Beclin-1, LC3	– increases production of L3C autophagic marker protein – increases autophagic activity, promotes myelin phagocytosis and clearance	Li et al. (2020)
		Platelet-derived growth factor (PDGF) (50 ng/mL)	– activates Erk pathway, leading to activation of – TAM receptors which influence phagocytic activity – downregulates Pou3f1 (Oct6)	– increases proliferation and metabolic activity – enhances phagocytic activity in a pro-inflammatory environment (better response than VEGF)	Basu et al. (2022)
		Vascular endothelial growth factor (VEGF-A) (50 ng/mL)	– binds to VEGFR-1 (which is upregulated following injury), activates PI3k signaling pathway	– enhances SC phagocytic activity in a pro-inflammatory environment	Basu et al. (2022)
		PDGF/VEGF (50 ng/mL)	– PDGF activates Erk pathway, leading to activation of – TAM receptors which influence phagocytic activity – PDGF downregulates Pou3f1 (Oct6) – VEGF-A binds to VEGFR-1 (which is upregulated following injury), activates PI3k signaling pathway	– promotes SC viability – increases proliferation	Basu et al. (2022)
		RGIDKRHWNSG / KLTWQULQLKYKGI (RGI / KLT) peptides	– KLT peptide mimics VEGF – RGI peptide mimics BDNF – less susceptible to degradation in vivo compared to VEGF and BDNF – upregulates c-Jun and Sox2 – downregulates MBP and Krox20	– increases SC proliferation – increases secretion of CTNF, BDNF, VEGF, and NGF	Liu et al. (2021), Li et al. (2022)
	Other Bioactive Molecules	Botulinum Neurotoxin A (BoNT/A)	– upregulates GFAP – upregulates S100β	– increases repair SC proliferation	Adler et al. (2022)

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Table 1 (*continued*)

Category	Microenvironmental Cue	Condition	Property of Influence	Impact on SC Behavior	References
		Genipin (GP)	– provides additional hydrophilic groups for cell attachment	– supports SC attachment and proliferation	Lau et al. (2018)
		Glycosaminoglycans (GAGs)	– interacts with cytokines, growth factors, – chemokines, morphogenetic proteins, other ECM components to modulate signaling pathways – increases Syndecan 4 expression	– promotes SC proliferation and GAG formation at early time points (1 day)	Idini et al. (2019), Hayes et al. (2018)
		Melatonin (MLT)	– inhibits oxidative stress – increases Parkin expression – activates Wnt/β-catenin signally pathway	– reduces cell apoptosis – promotes SC migration – promotes SC mitophagy	Pan et al. (2020), Li et al. (2022)
		Polydopamine (PDA) (2 mg/mL)	– increases substrate hydrophilicity and biocompatibility – improves attachment of exogenously applied growth factors to scaffold – increases substrate surface roughness	– promotes SC viability & adhesion	Li et al. (2020), Li et al. (2022), Pi et al. (2022)
		Retinoic Acid (1 μM)	– upregulates NEDD9 – regulates differential phosphorylation and protein stability	– increases SC migration – negatively affects proliferation	Latasa et al. (2016)
		(RGD)-functionalized chitosan-graft-polyethyleneimine/c-Jun plasmid (RCP/ pJUN) nanoparticles (113–127 nm diameter, 10–20 μg/cm2)	– cytotoxic and higher concentrations (>30 μg/cm2) – increases Vinculin, GFAP, and S100 expression – causes overexpression of c-Jun	– increases NGF, BDNF, and VEGF secretion	Wang et al. (2022)
	Other Cells and Exosomes	Adipose-derived stem cell exosomes (50 μg/mL)	– upregulates Bcl-2 expression (antiapoptotic) – downregulates Bax (pro-apoptotic)	– reduces SC apoptosis after injury – increases SC proliferation	Liu et al. (2020)
		Adipose-derived stem cells (5 × 105 cells/mL)	– upregulates Bcl-2 expression (antiapoptotic) – downregulates Bax (pro-apoptotic)	– reduces apoptosis of SCs after injury – increases SC proliferation	Liu et al. (2020)
		Endothelial Cells (10–15 % co-culture with SCs)	– form micro-vessels after nerve injury to provide blood supply – secrete VEGF – upregulate Ki67 expression in SCs – upregulate GFAP and NGR1 expression in SCs	– increase SC proliferation – increase SC migration	Meng et al. (2022)
Electromagnetic Cues	Conductive Material Coatings	Carbon nanotubes (CNTs)	– increases electrical conductivity of substrate – high aspect ratio – decreases scaffold degradation rate – cytotoxic at high concentrations (1 wt %)	– improved cell viability at low concentrations (0.25 wt %)	Pi et al. (2022),Jahromi et al. (2020)
		Carboxylic Graphene Oxide (CGO)	– increases electrical conductivity of substrate – maintains suitable biocompatibility when used in tandem with biocompatible coating (ex: PDA)	– enhances SC alignment, vinculin & N-cadherin expression in response to – electrical stimulation	Li et al. (2020)
		Graphene oxide (GO) (0.5, 1.0, 1.5, and 2 mg/mL)	– increases scaffold hydrophilicity due to active oxygen groups (COOH, OH, C-O-C) – increases electrical conductivity of substrate – increases scaffold porosity and mechanical strength – increases NGF, PMP22, Krox20 expression – decreases NCAM expression	– promotes SC growth, spreading, and proliferation – increases secretion of NGF	Wang et al. (2019), Li et al. (2020)
		Reduced Graphene Oxide (RGO) (1 % (w/w PCL))/	– increases scaffold hydrophilicity	– reduces SC apoptosis	Jiang et al. (2022)

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Table 1 (*continued*)

Category	Microenvironmental Cue	Condition	Property of Influence	Impact on SC Behavior	References
		Melatonin (MLT) (1 % (w/w PCL))	– decreases C0capase-3 expression – increases Ki67 S100-β expression – increases mitochondrial potential	– promotes SC proliferation – increases ATP synthesis	
		PANI doped with Nickel (Ni) nanoparticles	– increases electrical conductivity of substrate (more than PANI without Ni) – increases scaffold hydrophilicity	– increases SC proliferation in response to electrical stimulation (more than PANI without Ni)	Wang et al. (2021)
		Polyaniline (PANI)	– increases electrical conductivity of substrate – increases scaffold hydrophilicity	– increases SC proliferation in response to electrical stimulation	Wang et al. (2021)
		Polypyrrole (Ppy)	– sustains high electrical conductivity of substrate when used in tandem with PDA and CGO coating	– enhances SC alignment, vinculin & N-cadherin expression in response to – electrical stimulation	Li et al. (2020)
	Magnetic Stimulation	Magnetic field (MF) (8-T, 60 h)	– may trigger cell signaling via receptors	– induces SC alignment (effect is sped up with the addition of collagen)	Eguchi et al. (2003)
		Magnetic nanoparticles (MNP's) (10 % magnetic composite)	– magnetic nanocomposites can be activated by an applied MF (2.0 mT) – may trigger cell signaling via receptors – particles may undergo change in shape in response to MF, generating mechanical forces	– promotes SC proliferation and viability – increases secretion of BDNF, GDNF, VEGF	Liu et al. (2015)
		Pulsed magnetic field (PMF) (2.0 mT)	– may activate mitochondrial membrane potential and ATP synthesis – regulates Ca+ flux	– promotes SC proliferation, adhesion, and viability – increases secretion of BDNF, GDNF, VEGF	Liu et al. (2015)
		Superparamagnetic iron oxide nanoparticles (SPION's)	– upregulates PSA-NCAM – upregulates ChABC, helps eliminate chondroitin sulfate proteoglycans	– increases directed SC migration	Xia et al. (2016)
	Electrical Stimulation	Direct current (10–500 mV mm^{-1}, constant or 50 % duty cycle)	– may induce asymmetric redistribution of charged surface receptors – may polarize ion transport proteins – may change the transmembrane potential	– promotes SC alignment and migration – degree of SC response depends on substrate type/charge – voltage higher than 500 mV mm^{-1} may cause cell apoptosis	Bunn et al. (2019)
		Piezoelectric substrate (PVDF-TrFE)	– biocompatible – produces electrical current in response to mechanical deformations	– may increase SC alignment and neurite outgrowth	Orkwis et al. (2020)
	Ultrasound Stimulation	Low intensity ultrasound (0.1–1 W/cm2)	– suppresses expression of inflammatory cytokines TNFα and IL-6 – promotes expression of neurotrophin-3, BDNF, NGF, CNTF, FGF, GDNF, and Cyclin D1 – bilayer sonophore theory: oscillating pressure waves may create alternating strains on the cell membrane, which act upon proteins and channels in the membrane – continuum theory: may alter fluid dynamics of the cells microenvironment, causing changes to gating kinetics and membrane permeability	– promotes SC metabolic activity – may promote secretion of neurotrophic factors – may enhance phagocytic activity – may promote SC redifferentiation/ remyelination	Acheta et al. (2022), Ventre et al. (2021),Ren et al. (2018),Zhang et al. (2009), Tsuan et al. (2011)

(CDC2) (Adler et al., 2022). In addition to protein toxins, other bioactive molecules of interest for influencing SC plasticity include certain vitamins and vitamin derivatives. Retinoic acid, for example, has been shown to promote SC migration by increasing the expression of Neural Precursor Cell Expressed Developmentally Down-Regulated 9 (NEDD9) protein (Latasa et al., 2016). Certain polysaccharides have also proven useful for enhancing the SC injury response. Glycosaminoglycans (GAGs), for example, play an important role in SC differentiation, proliferation, and matrix assembly. Idini et al. found that SCs seeded on aligned fibrous PCL scaffolds functionalized with GAGs saw higher expression of Syndecan 4, which influences cell migration and adhesion, as well as p75, indicating a pro regenerative SC phenotype (Li et al., 2020b). Other natural materials that have been shown to enhance SC regenerative behavior include melatonin, genipin, and curcumin (Li et al., 2022b; Jahromi et al., 2020; Lau et al., 2018; Pan et al., 2021).

While much work has been invested in examining how different exogenously applied bioactive materials can be used to influence SC behavior, less work has been conducted on examining the biochemical modulation of SCs using gene therapy. Gene therapy, or the specific transfer of genes into cells, offers a promising method for promoting the expression of neurotrophic factors and restoring nerve function without the use of exogenous growth factors (Deverman et al., 2018; Wang et al., 2022). For example, Wang et al. found that functionalizing PLLA/silk fibroin films with gene vectors bound to c-Jun plasmids resulted in delivery of c-Jun plasmids to SCs and promoted the sustained expression of NGF, BDNF, and VEGF (Wang et al., 2022). Thus, future investigations may further examine how scaffolds loaded with gene carriers may be used to enhance SC growth factor expression and nerve regeneration outcomes.

4. Electromagnetic applications and sonographic control of PNS

In addition to biochemical and physical cues provided by the microenvironment, various methods of electrical and sonographic stimulation have been utilized to optimize SC function and behavior. Such methods have included applying direct current and magnetic fields for cell stimulation, as well as utilizing biomaterials with magnetic, conductive, or piezoelectric properties. SCs are a unique target for such therapeutic targeting due to the innate electromechanical interactions exhibited by the PNS (Abd-Elsayed and D'Souza, 2022). While the traditional role of the healthy adult SC is to myelinate axons and help to facilitate the propagation of action potentials, there are further electromechanical roles for SCs to fulfill. For instance, at the neuromuscular junction, terminal SCs exhibit multifaceted roles in incurring action potential at the pre- and post-synaptic membranes of axons and muscles, though the exact role of SCs in facilitating the reinnervation of damaged muscles at this junction is still being decoded (Alhindi et al., 2021; Alvarez-Suarez et al., 2020). The SC microenvironment, which displays a remarkable capacity to transmit various external signals to the cell phenotype, is an ideal and exciting target region for electromagnetic and electromechanical forces.

4.1. Electric stimulation

Developing research has shown promise in the use of exogenous electrical stimulation (ES) for control of cell behavior. The administration of direct currents (DC) has demonstrably promoted differentiation, alignment, migration, protein secretion, and proliferation of various cells involved in PNS repair, including fibroblasts, induced pluripotent stem cells, and SCs (Abedin-Do et al., 2021; Hu et al., 2019a; Huang et al., 2021; Koppes et al., 2014a, 2014b; Snyder et al., 2017; Tomaskovic-Crook et al., 2020). Electrical stimulation of rat motoneurons, for instance, can induce the mRNA expression of key regenerative markers such as BDNF, trkB, Tα1-tubulin and Gap-43 (Al-Majed et al., 2000). Recently, electrical impulses have been facilitated to assist in PNS repair, demonstrating the capacity to induce significant axonal regrowth, neuromodulation of postoperative nerves, treatment of neurodegenerative diseases, and increased motor and sensory nerve function in patients with spinal cord damage (Abd-Elsayed and D'Souza, 2022; Ilfeld et al., 2021; Pascual-Valdunciel et al., 2022; Ryan et al., 2021). In general, electrically stimulated tissue responses are used for a number of biomedical therapeutics and clinical diagnostics (Ryan et al., 2021). For years scientists have successfully used electrical stimulation for alternative treatment of nerve damage and the underlying mechanistic interplay describing such achievements is finally being unraveled.

Without additional modifications, direct stimulation of SC cultures induces an appreciable effect on cell function. Bunn et al., found that 50 % duty cycles of direct current, as well as oscillating direct currents, can align SCs and increase motility at ranges between 75 mV mm^{-1} to 500 mv mm^{-1} (Bunn et al., 2019). Later, Lang et al. further affirmed this effect by inducing alignment of variable-density SC cultures with electric fields (EFs) ranging from 200 to 500 mV mm^{-1} (Lang et al., 2021). For downstream applications, there is also evidence that SC derived exosomes can be stimulated by electrical stimulation as well, presenting an entirely novel platform for PNS regeneration (Wu et al., 2022). In general, however, researchers opt to stimulate SCs in conjunction with additional treatments or modifications, such as electrospun fibers or magnetic nanoparticles.

The various mechanisms leading to the direct control of SC activity and neurotrophic factor secretion from electrical signaling remain unclear. Koppes et al. found success in administering DCs to strictly non-neuronal cells, finding that DC ranges at 1 mA, and between 0 and 200 mV mm^{-1} can promote neurite outgrowth (Koppes et al., 2014a). Interestingly, this work also found that the pre-stimulation of SCs at 50 mV mm^{-1} resulted in ~30 % greater neurite outgrowth than co-stimulation of both SCs and neurons, suggesting that SCs can be targeted directly for electrical therapy and may play a pivotal role in transmitting electromechanical stimuli to PNS repair processes. Hu et al. have identified a novel mechanism for the enhanced survival of neural related tissue, showing that electrical stimulation can promote the survival of DRG co-cultures with SCs by increasing the release of glutamate (Hu et al., 2019b). Further, exogenous administration of glutamate and inhibitors indicated that the infiltration of Ca^{2+} ions initiate the secretion of SC exosomes and thereby prompted greater activity in related nerve cells (Hu et al., 2019b). Therefore, it reasons that direct control of SC behavior in the presence of ES can be advantageous for tissue engineering purposes. Technological advances now make it possible to target specific neurons and surrounding glia, which in turn provides researchers with a more direct approach to resolving nerve damage.

Researchers have also demonstrated that DCs can promote a regenerative SC microenvironment when supplemented with additional biomaterial modifications. For instance, Huang et al. applied a 100 mV mm^{-1} DC to SCs on polypyrrole/chitosan polymers to enhance Schwann cell adhesion, spreading, and proliferation while simultaneously promoting the expression of NGF and BDNF (Huang et al., 2010). Additionally, the coating of reduced graphene oxide on electrospun PCL fibers combined with a 10 mV stimulation in vitro induced greater proliferation, migration, and nerve growth factor secretion (Huang et al., 2021). Other biomaterials are also promising because of their innate conductivity. For instance, Wang et al. found that stimulation of electrospun polyacrylonitrile/polyalanine nanofibers with embedded nickel nanoparticles improved the conductivity of the polymer composite and thus induced greater proliferation of SCs (Wang et al., 2021). Therefore, electrospun scaffolds may be uniquely situated to augment the potentially beneficial electrical signaling on the SC microenvironment through multiple mechanisms. However, this does not preclude other biomaterial microenvironments from being targeted in the same or similar ways to harness ES to the PNS. Wu et al. demonstrated that electrospun poly(p-dioxanone) nanofibers could be constructed into clinically relevant nerve conduits to expediate the differentiation of mesenchymal stem cells to SC-like cells when subjected to electrical impulses and chemical supplements (Wu et al.,

2022). Zhao et al. demonstrated that bioprinted polypyrrole can be combined with electrospun silk fibers to facilitate SC viability, proliferation, migration, and the expression of neutrophic factors. In any case, consideration of electrical stimulation for therapeutic ends would benefit from an interdisciplinary understanding of other electromechanical forces contributing to the cellular microenvironment.

4.2. Low-intensity pulsed ultrasound

Similar to electrical stimulation, the regenerative potential of low intensity pulsed ultrasound (LIPUS) was first demonstrated broadly by applying ultrasonic treatments to nerve tissue. One of the early contemporary studies introducing SCs to augment this process demonstrated that poly(dl-lactic acid-coglycolic acid) conduits embedded with SCs could be subjected to ultrasound at 1 MHz and an intensity of 0.2 W/cm^2 for 5 min per day over two weeks to facilitate greater myelination and axonal regeneration (Chang and Hsu, 2004a). Since this study, the parameters to stimulate SCs and the PNS have gradually been established. Jiang et al. examined LIPUS intensity ranges of 250–750 mW cm^{-2} applied to post-operative nerves in Sprague-Dawley rats and found that functional recovery of rats and pathological results indicated a lower range of 250 mW cm^{-2} to be the ideal range. Further, an uptick in SC viability and proliferation was achieved by subjecting the sciatic nerves of Sprague-Dawley rats to a low intensity of 27.37 mW cm^{-2} for 10 min per day for 5 days (Ren et al., 2018), wherein the GSK-3B/B-catenin protein cascades were identified as the molecular culprits transducing this effect.

There is also extensive work showing that post-injury LIPUS treatment can augment axonal regeneration, leading to improved functional effects such as nerve conduction velocity and compound muscle activity (Acheta et al., 2022; Park et al., 2010). These effects are augmented through the presence of SCs, often showing potential to enhance current treatments such as nerve conduits, electrospun fibers, or grafts (Chang and Hsu, 2004b; Chang et al., 2005). Tsuang et al. further demonstrated that LIPUS application results in a noticeable uptick in SC metabolic activity (Tsuang et al., 2011). More recent work has begun to illustrate the specific effect of ultrasound treatments on SCs, where LIPUS has been used to induce greater expression of important neurotrophic factors such as neurotrophin-3, BDNF, nerve growth factor, CNTF, FGF, GDNF, and Cyclin D1 (Ren et al., 2018; Zhang et al., 2009). Thus far, it has been shown that axonal regeneration is best promoted by LIPUS signals applied between 100 and 200 mV mm^{-2}. This range has been frequently used for recent works that induce an uptick in myelination of DRGs, enhanced metabolic activity of SCs, enhanced growth factor activity such as GDNF and BDNF, as well as extension of neurites and axons in vivo (Bergmeister et al., 2018a).

The explicit mechanism by which SCs are affected by ultrasound is multifaceted. From one perspective, the administration of ultrasound induces a mechanical effect on cells, thereby changing the diffusion rates along transmembrane cell channels and membrane permeability via acoustic streaming (Bergmeister et al., 2018b). This mechanical effect is largely mediated by SC mechanotransduction pathways such as the Hippo Yes-Associated protein cascade as well as extracellular signaling kinases (ERK1/ERK2) and focal adhesion kinases (FAK) (Belin et al., 2017). However, it should be noted that this interpretation of mechanical stress is unique from that imparted by static surface topography. While the physical parameters of biomaterials indeed direct the behavior of PNS cells, ultrasound provides the ability to induce directed mechanical stimulation for variable time points. This is important, as embedded surface topography may exhibit finite limits in efficacy due to material design constraints, whereas ultrasound can continually induce a non-invasive, safe, and effective signal to promote SC regenerative phenotypes. Regardless, the signal transduction of SCs when exposed to ultrasound is, at least in part, mediated by the interaction between SCs and ECM-associated proteins such as FAK, the macromolecular proteins comprising the ECM described in section 3.1.1, and phosphorylated RhoGTPases. Previously, work has demonstrated that elongated SCs stimulate the integrin system to activate Rac1, downstream transcription factors MKK7 and JNK, and ultimately induce the expression of regenerative factor c-Jun (Xu et al., 2020, 2021). Additionally, it was shown that ECM stiffness and large cell spreading areas interact to activate the cytoskeleton RhoA/ROCK pathway that facilitates the nuclear translocation of YAP/TAZ and, thereby, regulates SC function. As Acheta et al. speculate, previous studies demonstrating the ability of LIPUS to activate YAP/TAZ in other cells such as endothelial and retinal ganglion cells may present yet another avenue of consideration for controlling the SC microenvironment (Acheta et al., 2022).

4.3. Magnetic impulses and nanoparticles

The development of tissue engineered devices has implications in the use of magnetic fields to control cell behavior. Magnetism, as a general medical tool, is utilized for a variety of phenomena, including magnetic resonance imaging (MRI), drug delivery, and tissue remodeling (Materón et al., 2021; Peng et al., 2019). There is an extensive portfolio detailing the control that can be attained at the cellular level through magnetic fields. Perhaps just as important, it is also believed that magnetic fields do not incur any significant harm to tissue (Miyakoshi, 2005), thus presenting an interesting application for regeneration. Contemporary applications of magnetism in biomedicine have become progressively more advanced with Suszynski et al. demonstrating efficacy in using a rotating magnetic field of variable intensity to promote recovery of crushed sciatic nerve injuries (Suszyński et al., 2014). Without regard for individual non-neuronal cells, they successfully demonstrated ample functional recovery (through sciatic functional index and tensormetric assessments) as well as enhanced survival of DRG and neurons through histological and immunohistochemical analysis. As magnetic applications developed, researchers have begun exploring the use of magnetic fields to induce directionality in regenerative processes. As mentioned, previous work showed that individual cells could be influenced through biomechanical cues induced by magnetic fields. Riggio et al. postulated that the physical forces imparted on neurons through direct topographical means was limited by translatable clinical methods (Riggio et al., 2014). Their solution was to develop magnetic nanoparticles (MNPs) to indirectly (noninvasively) apply a tensile force to neurons that can be externally manipulated through magnetic fields. Since magnetic fields and magnetic nanoparticles have an extensive background in biomedical applications, this approach was theoretically well suited for PNS repair. Riggio et al. additionally demonstrated that the MNPs, when optimized with Nerve Growth Factor Beta (NGF-B), promoted differentiation of PC-12 cells to a neuroregenerative phenotype and helped influence the alignment of neurite extensions along the applied field (Riggio et al., 2014).

As the regenerative impacts of magnetic nanoparticles becomes further elucidated, researchers have begun exploring the ability to control individual SCs in the context of PNS repair. Liu et al., and associated groups, have catalogued numerous applications of magnetic nanoparticles to influence SC behavior both in vitro and in vivo. First, it has been demonstrated that pulsed magnetic fields (PMF) can promote SC proliferation, adhesion, and viability. Further, PMFs induced greater expression and secretion of neurotrophic factors including BDNF, GDNF, and VEGF (Liu et al., 2015, 2014, 2017). Subsequently, by focusing on the activation of SCs with a magnetic nanocomposite, they were able to improve upon these effects. Using 10 % MNPs supplemented with a biodegradable chitosan-glycerophosphate polymer, proliferation and viability of SCs was enhanced without any notable increases in apoptosis (Liu et al., 2014). NTF gene expression and secretion was also promoted in BDNF, GDNF, VEGF, and now NT-3 levels, as well. Subsequently, Liu et al. built upon these nanocomposite scaffolds by further establishing the efficacy of such devices when used to repair a relatively extensive 15-mm long sciatic nerve gap transection in vivo (Liu et al., 2017). Additionally, SC viability was improved after transplantation, which

may have contributed to enhanced repair. Ultimately, the use of MNPs with biodegradable chitosan-glycerophosphate induced regeneration of axons, as indicated by histological and immunofluorescence staining. SCs and neurofilaments notably infiltrated injury gaps, and functional recovery was demonstrated through SFI assessments, Masson Eason staining, quantification of micro vessel density, and Fluoro-Gold labeling to examine motoneuron recovery (Liu et al., 2017).

In addition, Xia et al. examined the effect of polysialytransferase-functionalized superparamagnetic iron oxide nanoparticles (PST/SPIONs) to promote the expression of a key neural adhesion molecule (PSA-NCAM) and ultimately attain an appreciable degree of control of over SC migration (Xia et al., 2016b). The effects were two-fold. First, it was determined that PST/SPION functionalization induces greater migration in isolation. Second, with the application of a magnetic field, this migration could be directed such that SCs began traversing the astrocyte domain in central nervous system applications. These findings present a translatable benefit of magnetic applications, where preexisting technologies such as SC implementation can be supplemented. Further analysis of nanoparticles on the central nervous system likewise showed that SCs can be "magnetofected" with a chondroitinase ABC-polyethylenime functionalized superparamagnetic iron oxide nanoparticle (ChABC/PEI-SPION) (Xia et al., 2016b). This allows SCs to overexpress the ChABC protein and thereby help eliminate chondroitin sulfate proteoglycans that are often responsible for the formation of scar tissue inhibitory to regenerating axons. The tangible effect, in the context of repair, is greater induced migration of SCs to the astrocyte boundary.

4.4. Conductive biomaterials

Conductive scaffold materials offer promise for creating a pro-regenerative microenvironment by attempting to mimic the electrophysical properties of native tissue. Additionally, electrically conductive materials are necessary for applying electrostimulation to cells. The conductivity of scaffold biomaterials has been enhanced using a variety of conductive coatings, including graphene oxide (GO), polypyrrole (Ppy), polyaniline (PANI), Nickel (Ni) nanoparticles, and carbon nanotubes (CNTs) (Li et al., 2020a; Jahromi et al., 2020; Jiang et al., 2022; Pi et al., 2022; Wang et al., 2019). GO has gained increasing interest for nerve regeneration applications due to its large surface area, unique nanostructure, good mechanical properties, and hydrophilic functional groups suitable for cell attachment (Li et al., 2020b; Wang et al., 2019). Wang et al., for instance, found that SCs grown on ApF/PLCL nanofibrous scaffolds coated with GO exhibited higher proliferation, elongation, and migration compared to noncoated scaffolds (Chamberlain et al., 2000). Similarly, Jiang et al. found that SCs cultured on PCL scaffolds modified with melatonin (MLT) and reduced GO exhibited higher SC proliferation ATP synthesis, and lower SC apoptosis compared to SCs on untreated scaffolds (Jiang et al., 2022). One challenge with the use of GO is the cytotoxicity of the material: the strong pi bond on GO can damage the integrity of cell membranes (Li et al., 2020b). This has been counteracted with the use of a composite film to improve biocompatibility. For example, previous work developed a PDA/CGO/Ppy-PLLA scaffold that exhibited both higher conductivity and equivalent cell viability to untreated PLLA (Li et al., 2020b). SCs cultured on PDA/CGO/Ppy-PLLA scaffold exhibited larger SC bodies, longer pseudopod extensions, and higher expression of N-cadherin, GFAP, S100, and p75 compared to untreated scaffolds (Li et al., 2020b).

Piezoelectric materials are in a separate class of energy harvesters that can produce detectable current in response to mechanical stimuli. Early discovery of piezoelectric materials in biomedicine detailed the activity of natural polymers such as collagen fibrils or keratin (Ahn and Grodzinsky, 2009; Jacob et al., 2018; Minary-Jolandan and Yu, 2009). Recently, piezoelectric effects have been used for applications in biosensing and bioactuation (Chorsi et al., 2019). As more synthetic and natural materials are blended for biomaterial design, piezoelectric biomaterials for tissue engineering have started to gain popularity. PLLA and PVDF membranes are currently used for a variety of biomedical and biodiagnostic techniques. Importantly, recent work has shown that both chemicals can be electrospun into fibrous scaffolds that retain piezoelectric capacity (Zhan et al., 2022). We have demonstrated that this effect can be precisely automated to incur replicable signals in response to strain (pulling) and compression of aligned PVDF-TrFE nanofibers (Orkwis et al., 2022). Further, we have shown that such fibers can be used as precursors for conduit fabrication, which still responds to compression tests with a replicable signal (Orkwis et al., 2022). Piezoelectric biomaterials are novel in their ability to harvest energy from relatively small signals. Intuitively, this effect can be utilized by non-invasive stimulation from the applied electric fields (EFs) or LIPUS. Theoretically, aligned fibers implemented for in vivo applications can then be augmented externally with a clinically approved ultrasound treatment. Additionally, the effect of various stimuli imparted by the body on scaffolds will further influence the regenerative microenvironment in a positive feedback loop, where stress from cell traction forces, nutrient and cell diffusion, and interstitial fluid will likely deform the nanofibers and induce a small, beneficial current to help promote the extension of regenerating axons.

5. Conclusion and outlook

Taken as a whole, SCs can adapt to a wide variety of parameters within the microenvironment, which may be engineered to promote desired cell behaviors during the regeneration process and beyond. Physical characteristics in the SCs environment such as porosity and topography impact SC viability and proliferation while extending across a nerve lesion. The stiffness of the physical environment is also important for the upregulation of key regenerative SC markers such as c-Jun and Sox2. In addition to the physical microenvironment, the functionalization of biomaterials with bioactive molecules such as growth factors, ECM protein coatings, and decellularized ECM highlights how biochemical cues in the microenvironment significantly influence SC transdifferentiation. Modern stimulation methods such as direct electric fields and low intensity pulsed ultrasound also can both directly and indirectly influence the regenerative microenvironment and enhance SC reprogramming. Engineered scaffolds for biomaterial applications may be used to tune these various physical, biochemical, and electrical signals and synthesize a microenvironment that enhances SC regenerative characteristics and improves nerve injury recovery. Here we have described recent advancements toward engineering the tunable parameters of regenerative PNS environments. As researchers develop alternative therapies to current clinical solutions, future research should further explore the incorporation of extracellular-derived components as well as other natural materials to enhance the bioactivity of engineered substrates. Furthermore, the application of electromagnetic or ultrasonic stimulation concurrently with engineered physical scaffold properties and bioactive modifications should be explored to better understand the interplay between these different microenvironmental cues, and to create a systems level approach to engineering a pro-regenerative SC environment.

CRediT authorship contribution statement

Corinne Smith: Writing, Data curation, Writing – review & editing, Investigation, Visualization. **Jacob A. Orkwis**: Writing, Investigation, Writing – review & editing. **Zhenyuan Xu**: Writing, Investigation. **Andrew E. Bryan**: Investigation, Writing – review & editing. **Greg M. Harris**: Writing, Investigation, Writing – review & editing, Visualization, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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