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Three Dimenionsal Schwann Cell Culture Models In Peripheral Nerve Regenration: Advances And Future Perspctives

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Abstract

EXECUTIVE SUMMARY:

Significant impairment results from peripheral nerve injuries (PNIs), although endogenous recovery is frequently insufficient and sluggish (1). Schwann cells (SCs), the myelinating glia of the peripheral nervous system, are essential for nerve healing because they direct axon regeneration, remove debris, and remyelinate regenerating axons (2)(3). Conventional two-dimensional (2D) SC preparations frequently result in altered shape and decreased neurotrophic factor synthesis because they lack the intricate spatial cues and cell–matrix interactions of in vivo nerve tissue (5). Spheroids, hydrogels, scaffolds, and bioprinted structures are examples of three-dimensional (3D) SC culture models that maintain SC phenotypic and function while more closely mimicking the in vivo milieu. This narrative summary examines the biology of SCs and their roles in regeneration (Section 2), the emergence of 3D SC systems (Section 4) and their variations (Section 5), and the drawbacks of 2D culture (Section 3). We compare biomaterials (natural, synthetic, and hybrid; Table 2), model techniques (Table 1), and important studies (Table 3). Co-culture methods, stem cell-derived SCs, and advanced biomaterials (such conductive polymers and decellularized matrices) enhance 3D models even further. Applications include in vitro drug screening, disease modeling platforms, and nerve tissue engineering (grafts and conduits) (7) (8). Replicating the full brain architecture and transferring it to the clinic remains difficult despite advancements. Future potential include more biomimetic bioinks, stem cells derived from induced pluripotent stem cells (iPSCs), and standardized techniques to connect the lab and bedside. All things considered, 3D SC cultures have the potential to improve peripheral nerve regeneration studies and therapies (10).

Introduction

Although peripheral nerves can regenerate more readily than the central nervous system, they frequently do not fully heal from injuries. While similar spinal cord injuries show limited recovery, crushed sciatic nerves can regenerate most axons and regain function in a few weeks in mouse models (11). However, even PNS injuries can induce chronic deficits due to target atrophy during denervation and slow axonal regrowth (~1 mm/day) (1). Conventional methods such as auto grafts and end-to-end suturing are ineffective for wide gaps and endanger healthy nerves (13). New tactics therefore seek to improve regeneration.

Following axon injury, Schwann cells (SCs) dedifferentiate into a "repair" phenotype that upregulates trophic factors, clears myelin debris, and forms Büngner bands to guide regenerating axons (2). Exogenous SC transplantation into damaged nerves can accelerate regeneration, but cell supply and survival are still concerns. SC in vitro culture models are critical for biological research and the development of cell-based treatments (14). In contrast, traditional flat (2D) plastic cultures lack the 3D structure, mechanical signals, and cell-matrix interactions present in brain tissue(4). Cells grown in 2D are intentionally distributed and polarized, altering gene expression and inhibiting neurotrophic factor release. In contrast, 3D culture techniques allow SCs to adopt in vivo-like morphologies and interactions, resulting in increased proliferation, migration, differentiation, and secretory profiles (5). Several 3D SC models have been developed over the last decade (Table 1), utilizing spheroid aggregation, hydrogel embedding, fibrous scaffolds, and 3D bioprinting. These models are used to create nerve tissue (e.g., cell-laden nerve conduits), as well as in vitro platforms for drug testing and disease modeling. This review discusses SC biology (Section 2), 2D culture limitations (3), and 3D SC culture advances, including reasoning (4.1), 2D versus 3D differences (4.2), model types (5.1-5.4), biomaterials (6), applications (7), and current difficulties (8). Advanced biomaterials, stem cell technologies, and clinical translation are all potential future prospects (9). To give a comprehensive, evidence-based narrative, we refer to both recent primary studies and high-quality reviews (2015-2025).

BIOLOGY AND FUNCTIONS OF SCHWANN CELL IN PERIPHERAL NERVE REGENRATION:

Origin and Types:

Schwann cells (SCs) are produced from the embryonic neural crest, a migratory cell population that generates many peripheral lineages (18). Schwann cell precursors (SCPs) on developing peripheral axons differentiate into two types of SCs: myelinating SCs, which wrap large-diameter axons in insulating myelin sheaths, allowing for rapid saltatory conduction, and non-myelinating (Remak) SCs, which ensheath smaller axons (17). Myelinating SCs have unique markers including P0 protein and myelin-associated glycoprotein (MAG), which are controlled by axonal Neuregulin-1 signaling (20). Non-myelinating SCs express markers that promote unmyelinated fibers, such as L1 cell adhesion molecule and p75^NTR. In response to injury, both SC types decrease myelin gene expression, including P0, and adopt an immature, repair-promoting phenotype (14). Unlike CNS oligodendrocytes, mature SCs can function independently and form autocrine loops to compensate for axon loss (22).

Role in Axonal Regenration:

SCs coordinate critical regenerative events after an injury. Distal to a nerve lesion, denervated SCs (formerly myelinating or Remak) convert into "repair Schwann cells" or Büngner cells, which release neurotrophic factors (e.g., NGF, BDNF, GDNF) and cytokines and actively phagocytose myelin debris (with macrophage help) (23). Repair SCs multiply and extend long cellular processes, resulting in Büngner bands

that guide regrowing axons back to their destinations (2). SCs activate macrophages and eliminate inhibitory myelin debris through cytokine signaling (24). When axons renew, SCs remyelinate them or form non-myelinating ensheathments to reestablish conduction (1). SCs are essential for nerve regeneration in vivo, as grafts from devitalized nerves without them only partially guide axons (3). As a result, SCs act as both biophysical guides and biochemical support cells, making them important participants in peripheral nerve repair.

Schwann cell axon interaction:

Schwann cells and axons exchange messages in both directions. NRG1 isoforms, particularly type III, play an important role in SC development and myelination. High NRG1 levels on axons promote SC myelination (thicker myelin sheaths), whereas low NRG1 causes thinner or non-myelinating ensheathment (20). In contrast, SCs provide contact-dependent cues by expressing adhesion molecules and growth regulators, which impact axon activity. SCs express the L2/HNK-1 carbohydrate epitope on glycoproteins, which is prevalent in motor-nerve-associated SCs and promotes motor neuron regeneration (27). SCs express polysialic acid (PSA) on NCAM, which inhibits cell adhesion and promotes flexibility during regeneration. They also use inhibitory molecules like MAG at the nodes to prevent aberrant sprouting (28). The coordinated form of SCs in nerve cables directs axon growth along optimal pathways (29). The SC-axon unit works as a system, with regenerating axons relying on SC guidance and trophic support, and SCs requiring axonal signals (e.g., NRG1) to survive (41-2). Any 3D culture model of nerve regeneration should include these strong SC-axon connections.

Limitations of traditional 2DSchwann Cell Culture Models :

Conventional SC cultures grown on flat plastic are useful for basic research, but they have severe limitations in simulating regeneration. In two dimensions, cells flatten and polarize abnormally, exposing only one face of the substrate. This geometry affects cell shape and gene expression profiles in respect to in vivo circumstances (4). Most importantly, 2D systems lack the 3D matrix and cell-to-cell interactions present in native SCs in nerves. As a result, numerous SC activities are reduced, including poorer neurotrophic factor production in 2D compared to 3D (5). Cells in two dimensions cannot develop aligned structures or multilayered "bands" to guide axons. Furthermore, stiffness in 2D cultures is usually orders of magnitude higher (plastic dishes vs. soft tissue), which may influence SC differentiation and mechanosensitive signaling (30).

SCs in 3D hydrogels or scaffolds exhibited increased proliferation, migration, differentiation, and expression of repair-associated genes relative to 2D cultures (31). Two-dimensional models also fail to capture growth hormone concentration gradients and spatial signals required for axonal guidance. According to [12], traditional two-dimensional culturing techniques are insufficient to recreate the distinct microenvironment of brain tissue. In conclusion, 2D cultures create artificial conditions that limit SC functionality. These constraints have prompted the development of 3D culture techniques that better replicate in vivo architecture and biology.

DEVELOPMENT OF 3D SCHWNN CELLS CULTURE SYSTEM

Rationale for 3D Culture:

The goal of 3D SC culture is to better imitate the neural microenvironment. Embedding SCs in 3D matrices or aggregating them into spheroids enables cell-cell and cell-matrix interactions that are not present in 2D. This often leads to more physically realistic behavior. Like the one below: "3D cell conglomerates often serve

as more reliable experimental models than monolayer cultures" (30) . SCs grown in 3D hydrogel networks or scaffolds with physiologic stiffness enhance injury models and drug screening by imitating the biochemical and mechanical signals found in normal nerve tissue (32). Early study showed that SCs delivered in 3D structures (such as injectable gels or cell-loaded conduits) could survive and integrate better into host tissue (34).

2D VS 3D: CONTRAST IN SCHWANN CELL BEHAVIOR:

Comparative studies have proven the effect of 3D culture on SCs. In vitro, SCs in hydrogels or scaffolds proliferate and migrate more than in 2D monolayers (5). Tokunaga et al. discovered that 3D spheroids of adipose-derived SC-like cells outperformed 2D cultures for differentiation efficiency and neurotrophic factor secretion (34). Entezari et al. observed that SCs on aligned conductive scaffolds expressed higher levels of SC markers (e.g. S100β) and produced more neurotrophic factors than on flat surfaces (35). Podder et al. discovered that functionalizing PCL nanofibers with Neuregulin-1 stimulated SC formation by boosting myelin protein expression, despite somewhat lower proliferation than 2D cultures (36). In 3D cultures, repair-associated genes such c-Jun and BDNF, as well as extracellular matrix proteins, are increased, resembling nerve injury (9, 5). Aggregation into 3D SC. Spheroids produced a repair phenotype by upregulating c-Jun and downregulating myelin proteins, which corresponded to the in vivo damage response. 3D cultures improve on 2D by restoring cell polarity, allowing for cell-matrix interactions, and creating nutrition and signal gradients (38).

TYPES OF 3D MODELS:

Model type	Description	Materials used	Key advantages
Spheroids	3D cultures improve on 2D by restoring cell polarity, allowing for cell-matrix interactions, and creating nutrition and signal gradients (38).	None (often methylcellulose or low-adhesion plates for formation)	High cell–cell contact; preserve SC phenotype; mimic cell clusters; concentrated factor secretion
Hydrogel-based	SCs embedded in natural/synthetic hydrogels (e.g. collagen, fibrin, alginate, PEG) (32)	Natural ECM proteins (collagen, fibrin, Matrigel, laminin), synthetic polymers (PEG, PEGDA, GelMA)	Provides 3D matrix; tunable stiffness; supports uniform cell distribution; can be injected
Scaffold based	SCs seeded into 3D porous scaffolds or fibers (electrospun, freeze-dried)(37)(38)	Polymer fibers (PCL, PLLA), composite matrices (collagen-chitosan, graphene)	Structural guidance for alignment; high surface area; mechanical support; can form aligned channels (Bands of Büngner mimic)
3d bio printed	SCs (sometimes	Printable hydrogels	Precise spatial

	with other cells) are printed within bio-inks to construct specified architectures (39)(7).	(fibrin, GelMA, alginate blends, decellularized ECM bioink)	patterning; heterogeneous constructs; integrate multiple cell types and cues; scalable fabrication

SPHEROIDS:

Spheroids are multicellular, scaffold-free aggregates made from hanging-drop, low-adhesion plates or micro-molds (34). Spheroids are usually made from primary Schwann cells or SC-like cells derived from stem cells, such as differentiated adipose MSCs. Spheroids create extensive cell-to-cell contacts and deposit their own matrix, promoting survival and trophic factor secretion. Lin et al. used methylcellulose to create spheroids of umbilical cord MSC-derived Schwann-like cells; these 3D spheroids contained more neurotropic and angiogenic factors than dissociated cells and, when transplanted into injured sciatic nerves, significantly improved axon regeneration and functional recovery(6).

HYDROGEN BASED MODELS:

Hydrogels are water-swollen polymer networks that look like the hydrated extracellular matrix. 3D SC cultures have been carried out using both natural hydrogels (collagen, fibrin, gelatin, Matrigel, alginate, chitosan, hyaluronic acid) and synthetic hydrogels (PEG, polyisocyanides (PIC), GelMA, polyacrylamide) (37). Natural hydrogels typically contain cell-binding motifs and growth factors to aid in attachment and signaling. Collagen and fibrin gels are commonly employed as luminal fillers in nerve conduits and SC substrates (32). Collagen matrices can be constructed into aligned channels that mirror Büngner's bands, guiding SCs and axons; aligned collagen scaffolds connected in conduits stimulated robust axon development in rat sciatic nerve grafts(42). (13). Fibrin, a blood clotting protein, is injectable and encourages cell migration. Bio printing studies often use fibrin blends: Wiklund et al. found that 3D-printed fibrin conduits (9 mg/mL fibrinogen) with SCs (and half-strength MSC co-culture) supported high viability and neurite outgrowth (41)(7)

SCAFFOLD BASED MODELS:

3D scaffolds are solid matrices with interconnected pores or fibers that help cells grow. Natural materials include collagen-chitosan composites, silk, and decellularized nerves, whereas synthetic materials include electrospun PCL, PLA, PLGA, polyurethane, and conductive polymers such as polypyrrole. Electrospinning, freeze-drying, 3D printing, and other techniques can be used to create scaffolds with the appropriate architecture (44). One notable advantage is structural guidance: matching fibers or channels replicate Büngner's Bands, which physically guide SCs and axons. In rat nerve healing models, fused oriented electrospun PCL fibers (typically coated with ECM) have been demonstrated to induce SC elongation and alignment, hence aligning regenerating axons(45).

3D BIO PRINTED CONSTRUCTS:

Bioprinting involves layering cells and biomaterials to create accurate 3D structures (30). In peripheral nerve research, bioprinting allows for the creation of personalized nerve conduits or tissue models with spatial control over cell placement. For example, fibrin- or GelMA-based bioinks containing SCs (sometimes in conjunction with MSCs or neurons) have been printed into conduit or grid patterns. Wiklund et al. (2023) found that 3D printing fibrin hydrogels containing SCs and MSCs resulted in

stable conduits with high cell survival (>90%) and neurite outgrowth (41). Importantly, they discovered that even after 50% reduction in SC numbers (and replacement with MSCs), neurite growth remained well regulated.
Liu et al. bioprinted a conduit of PCL and an alginate-gelatin-fibrin bioink containing SCs and endothelial cells, resulting in aligned SCs and neural growth in vitro (39). Bioprinting can also incorporate gradients of growth agents or heterogeneity. Zhu et al. employed coaxial printing to insert SCs into a conduit, resulting in enhanced neurite outgrowth compared to controls (39).

BIOMATERIALS USED:
Biomaterial selection is critical in 3D SC models. Materials are classed as natural, synthetic, or hybrid composites (37). Natural biomaterials like collagen, fibrin, laminin, silk, and Matrigel are bioactive and imitate the extracellular matrix (10). The most often utilized collagen is type I, which forms gels and fibrous scaffolds, has RGD patterns for SC adherence, and can be molded into aligned channels (42). Fibrin, a blood clotting protein, is injectable and promotes fast cell invasion. Laminin-rich Matrigel (basement membrane extract) and decellularized neuronal ECM (dECM) offer complex cues, although they are obtained from animals with batch variability (45). Hyaluronic acid (HA), gelatin, and alginate are also employed; however, HA must be treated for proper cell adherence. Synthetic biomaterials (including PEG, polyacrylamide, PIC, PCL, PLA, PLGA, polyurethanes, and poly-L-lactic acid) provide tunable mechanics and chemistry (320). PEG-based hydrogels are bioinert unless functionalized with peptides, allowing for precise control of stiffness and disintegration. Polyisocyanide (PIC) is a thermoresponsive polymer capable of producing injectable gels. Xu et al. demonstrated that PIC can support long-term SC spheroids (43). Electrospun PCL and PLA fibers are effective guides for SC alignment, but they lack natural cell attachment sites (which are normally coated in collagen) (37). Conductive polymers (polypyrrole, polyaniline) are being studied to mimic neuron electrophysiology; they have been demonstrated to promote SC differentiation and factor release (19).

CATEGORY	EXAMPLES	PROPERTIES
NATURAL	Collagen,fibrin,gelatin	Bioactive (cell adhesion ligands); enzymatically degradable; mimics the ECM. SC attachment and migration are supported by collagen and fibrin (35) while HA and alginate often require RGD. Matrigel also includes growth factors. The dECM nerve preserves native proteins and can direct cell phenotypes (31).
SYNTHETIC	PEG (and PEGDA), Polyacrylamide, Polyisocyanide (PIC), Poly(ε-caprolactone) (PCL), PLA, PLGA, Polypyrrole (PPy)	Highly adjustable stiffness and deterioration; repeatable; bespoke chemical. PEG and polyacrylamide gels are bioinert until changed (32). PCL/PLA offers durable

		scaffolding for conduits (44). Conductive polymers (PPy) improve electrical cues (35).
HYBRID	Collagen–Chitosan, GelMA (gelatin-GMA), Fibrin–Gelatin, PCL–Gelatin, Graphene/Carbon composites	Combine bioactivity with mechanical strength. For example, PCL fibers can be coated with ECM proteins to aid in cell binding. GelMA imparts crosslinkable stiffness to gelatin. Silk/collagen composites provide long-lasting, cell-friendly scaffolds (33) and dECM polymers resemble nerve-specific microenvironments (29)

APPLICATIONS:

NERVE TISSUE ENGINEERING:

One common application is to create nerve grafts or conduits for nerve repair. Cell-laden 3D structures can close nerve gaps by providing a biological substrate for axon growth. SC-seeded tubular scaffolds, such as collagen or synthetic conduits, have been implanted over nerve lesions to guide axon regeneration (18). Bioprinting techniques produce cell-laden conduits with specific lumens and cell distributions. In animal studies, conduits including SC spheroids have showed increased regeneration compared to acellular conduits. Chuang et al. implanted SC spheroids in rat sciatic nerve gaps and reported improved nerve structure and motor function recovery(9)(21). Researchers have also developed "living nerve grafts": aligned fibrous scaffolds seeded with SCs and extracellular matrix that may be prepared in vitro and then transplanted. Aligned collagen-PCL scaffolds seeded with SCs improved axon ingrowth across gaps, resulting in higher nerve fiber counts distant to the injury (39). Tissue-engineered nerve grafts can be optimized using growth factor gradients or directed channels, and microfluidic "organ-on-chip" devices allow for graft pre-conditioning. In summary, 3D SC cultures are employed to create implantable structures that actively stimulate nerve healing in vivo.

NERVE GRAFTS AND CONDUICT:

Nerve guidance conduits (NGCs) are hollow, biodegradable tubes that bridge nerve transections. Traditional conduits (silicone or collagen tubes) are suitable for small gaps (~1 cm) but lack SC content (44). Modern conduits are designed to include SCs or SC-like cells to resemble autografts. Conduits can be pre-seeded with SCs (generated from nerve or stem cells) or have SC spheroids put in the lumen(7). Bioprinted conduits with embedded SCs are a next-generation NGC. Another strategy is to use decellularized nerve allografts, which give native basal lamina tubes and can be recellularized with SCs (or SC precursors) to increase their regeneration capacity. Cell-based conduits can be enhanced by slow-release growth agents.

DRUG SCREENING AND DISEASE MODELING:

Beyond implantation, 3D SC cultures are useful in vitro platforms for testing treatments and simulating illnesses. Biomimetic nerve-on-chip technologies mimic certain features of nerve physiology. Sharma et al. created a "human nerve-on-a-chip" using iPSC-derived neurons and primary human SCs in a microfluidic device, resulting in around 5 mm neurite extension and detectable conduction velocity (8). This all-human in vitro nerve enabled for drug testing on electrophysiology and histology, which is not possible with typical 2D. Park et al. created a 3D model of motor neurons and SCs in collagen gel. They found that adding ascorbic acid increased myelin gene expression whereas neuregulin-1 therapy decreased it (10). These models can be used to replicate neuropathic states or injuries in order to investigate demyelinating disorders and potential treatments.

CURRENT CHALLENGES AND LIMITATIONS:

Despite progress, 3D Schwann cell models have challenges. It is tough to establish uniform cell distribution and viability in large constructions because nutrient diffusion limits thickness, necessitating the use of perfusion bioreactors or microfluidic flow. Hydrogels can lose mechanical strength over time, necessitating the use of composite scaffolds for implantable grafts (36). Optimizing SC alignment and forming organized Büngner Bands in vitro is difficult; while aligned fibers and microchannels can help, accurate replication of natural neural architecture remains elusive. Immune responses to implanted biomaterials and cells can be problematic; even decellularized scaffolds can produce inflammation if not properly handled (33). Scalability and standardization are another barrier. Generating consistent, functioning SCs in large quantities is difficult: primary SCs must be carefully grown, and stem cell-derived SC differentiation techniques varies between laboratories. Many published 3D models use small rat SCs, while human SC models are less common and more varied. Adoption of functional readouts, such as nerve conduction velocity, is limited due to the need for specific instruments and expertise (12).

CONCLUSION:

Schwann cells play an important role in peripheral nerve regeneration, and 3D culture models provide effective platforms for harnessing and studying their capacities. Compared to 2D cultures, 3D settings sustain SC shape and function, resulting in physiologically appropriate behavior (15). Spheroids, hydrogels, scaffolds, and bioprinted constructions all have distinct advantages (Table 1) and can be customized with various biomaterials (Table 2) to enhance SC viability and alignment. Advances in biomaterials and stem cell technologies will further refine these models, making them important for building nerve grafts as well as in vitro disease or medication testing platforms (16). While challenges with fabrication, scalability, and translation remain, the field is continually evolving. Finally, adding 3D SC systems into preclinical research and therapy development opens up the possibility of more effective treatments for peripheral nerve injury and neuropathies. Future study should focus on standardizing techniques, comparing models to clinical outcomes, and demonstrating long-term safety. The large recent literature demonstrates that 3D Schwann cell models are capable of bridging the gap between experimental nerve regeneration research and clinical application.

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