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Emerging technologies in peripheral nerve repair: Improving regenerative outcomes and reducing morbidity

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Abstract

Having affected 1 million people per year, PNIs cause serious sensory, motor, and autonomic impairment, involving devastating clinical complications. Existing interventions such as autografts and allografts present many unsatisfactory outcomes as the axonal regeneration remains slow, neuroma develops, and the donor site presents itself with morbidity. A literature review examines the innovative technologies revolutionizing the repair of peripheral nerves, with a focus on maximizing regeneration and minimizing complications. Enhanced guidance of axons is achieved with advanced biomaterials, such as 3D-printed patient-specific nerve guidance conduits filled with neurotrophic factors (e.g., nerve growth factor, brain-derived neurotrophic factor). Mesenchymal and induced pluripotent stem cell-derived Schwann-like cell-based stem cell therapies promote myelination and nerve damage recovery in in vivo animals. The gene editing of CRISPR/Cas9 or the improved expression of neurotrophic factors using non-viral nanoparticle vectors can be employed to counteract inflammation. Electrical stimulation and wireless biodegradable microelectrodes all induce axonal sprouting and functional improvement. The existing gap in large nerves is addressed with bioengineered tissues having a prebuilt vascular supply, and nanotechnology-based drug delivery minimizes scarring. Most of these innovations are supported by recent clinical trials and animal studies, which will provide individualized, less-invasive solutions. This paper critically assesses their mechanisms, translational challenges, and clinical potential, demonstrating that they can transform nerve repair, improve patient outcomes, and lead to reduced morbidity in the medical world.

Keywords: Peripheral Nerve Injury (PNI); Nerve Regeneration; Biomaterials and Nerve Guidance Conduits (NGCs); Stem Cell Therapy; Gene Editing and Nanotechnology in Nerve Repair

1. Introduction

Peripheral nerve injuries (PNIs) are a hugely burdensome health problem around the world, impacting more than 1 million people every year with broad implications relating to the sensory, motor, and autonomic denominator. Epidemiologically, PNIs can occur due to a wide range of etiologies, such as traumatic injuries (e.g., lacerations, crush), iatrogenic (e.g., surgical complications), and compressive neuropathies (e.g., carpal tunnel syndrome) and have an estimated incidence of 1323 per 100,000 person-years in developed countries (Daly et al., 2012). The pathophysiology of PNIs is a complex cascade of cellular and molecular reactions. Inflicted with damage, Wallerian degeneration subsequently occurs distal to the injured region, where the axons decay and Schwann cells remove the debris, releasing neurotrophic factors to promote regeneration. The cellular and molecular pathways of peripheral nerve regeneration, including Wallerian degeneration, macrophage activation, Schwann cell proliferation, and remyelination, which culminate in functional reinnervation, are shown in Figure 1.

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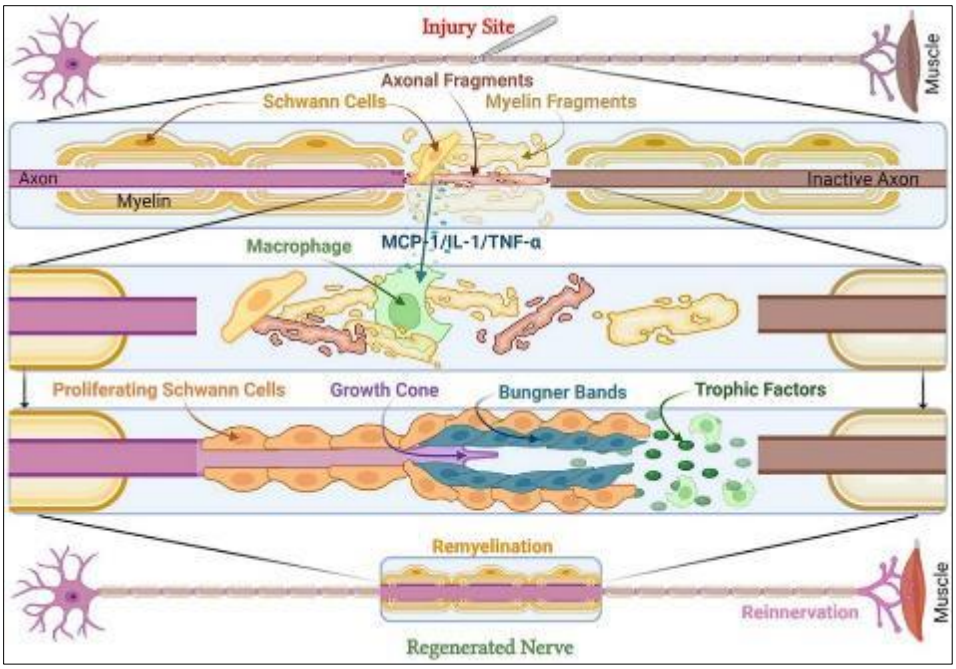

Figure 1 Schematic showing sequential events in peripheral nerve regeneration: Wallerian degeneration, macrophage infiltration, Schwann cell proliferation, axonal regrowth through Büngner bands, trophic factor release, and remyelination. These processes drive restoration of axonal continuity and neuromuscular reinnervation post-injury. Adapted from Biorender.com

However, barriers such as scar tissue formation, misalignment of regenerating axons, and limited regenerative capacity of peripheral nerves impede optimal recovery. Clinically, PNIs result in significant challenges, including chronic pain, neuroma formation, and persistent functional deficits, with only 40–60% of patients achieving satisfactory recovery after surgical intervention (Ruijs et al., 2005). These limitations underscore the urgent need for innovative approaches to enhance nerve regeneration and restore function while minimizing complications.

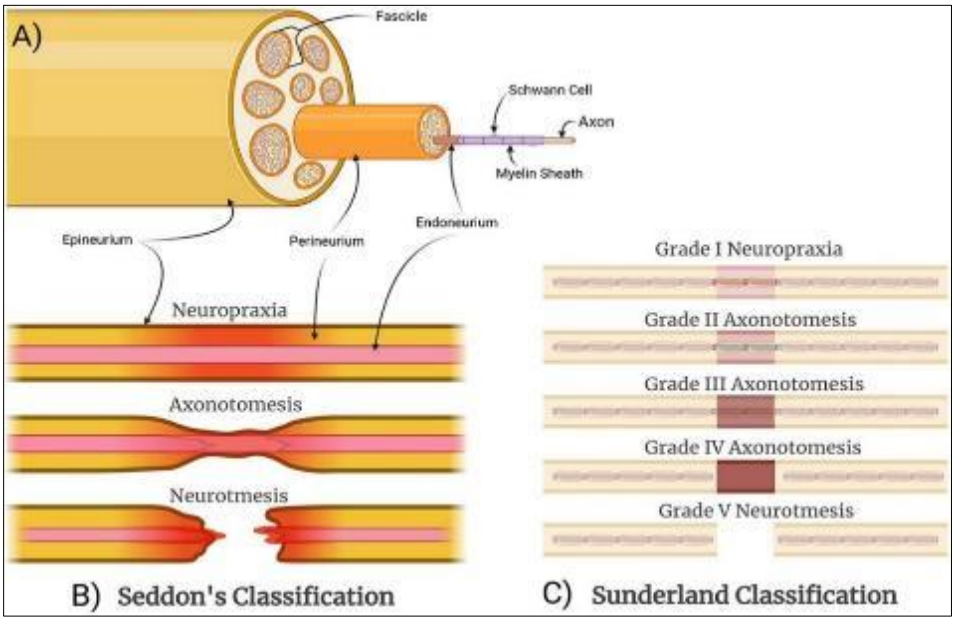

Figure 2 Anatomical diagram and comparative classification of peripheral nerve injuries. Seddon's three-tier model and Sunderland's five-grade system delineate the extent of axonal and connective tissue damage, providing a foundational understanding for clinical diagnosis and therapeutic interventions. Adapted from Biorender.com

Recent guidelines for the management of PNIs primarily rely on surgical interventions, which vary according to the severity of the injury and the length of the gaps. Direct end-to-end repair, involving the microsurgical repair of small nerve gas (less than 3 cm), is considered the gold standard for providing tension-free coaptation and promoting axonal regeneration (Griffin et al., 2013). Where larger gaps are involved, autologous nerve grafts, usually from the sural nerve, are used. However, this technique is constrained by the morbidity of the donor site, including loss of sensation, the development of neuroma at the donor site, and size and fascicular mismatch (Ray and Mackinnon, 2010). Alternatives available include nerve allografts and decellularized nerve matrices (e.g., Avance Nerve Graft). However, these are also limited by issues of immunogenicity and unpredictable consequences, with less than 50% success in complex injuries (Safa and Buncke, 2016). Other non-surgical methods, such as physical therapy and pharmacological treatments (e.g., corticosteroids in cases of inflammation), offer slight regenerative activity. These deficits portray some critical limitations of modern treatments, such as extended durations of healing (usually 612 months), partial impairment of functional outcomes, and relevant morbidity, which will require the creation of high-tech facilities to close these holes and enhance outcomes of treatment.

The emerging technology in the area of peripheral nerve repair is significant in countering these adversities, which is spurred by the interdisciplinary collaboration of fields such as biomaterials, regenerative medicine, and engineering. The need to reduce recovery periods, increase the rate of axonal regeneration, and decrease the presence of neuroma and morbidity at the donor sites necessitates innovation. New technologies recently employed, including 3D-printed nerve guidance conduits, stem cell therapy, gene editing, and electrical stimulation, offer promising solutions for enhancing axonal growth outcomes and restoring function. The idea behind these technologies is to overcome the drawbacks of more conventional methods by providing personalized, less invasive, and biologically optimized interventions. This paper aims to appraise the mechanisms, as well as the preclinical and clinical potential, of these novel technologies and their likely impact on the future of peripheral nerve repair. The recent literature and the results of clinical trials that form the background of the next generation of treatment to enhance the outcomes of regeneration and patient quality of life in patients diagnosed with PNIs are discussed in the article to identify their translational potential and possible sources to which they will contribute to clinical practice.

2. Emerging Technologies in Peripheral Nerve Repair

Peripheral nerve repair is undergoing a revolution as the limitations in morbidity and regeneration are being addressed through the use of innovative technologies. Very sophisticated biomaterials, such as 3D-printed nerve guidance conduits coated with neurotrophic factors, promote the alignment of axons (Daly et al., 2012). Therapies involving stem cells are used to differentiate induced pluripotent stem cells (iPSCs) into Schwann-like cell layers, thereby enhancing the myelination process in preclinical studies (Sullivan et al., 2016). Meanwhile, biodegradable electrical stimulation microelectrodes are used at the site of axonal sprouting acceleration, and tissue-engineered vascularized spinal nerve grafts address these difficulties in large nerve harnesses (Koffler et al., 2019). Drug delivery through Nanotechnology reduces scarring. These clinically trial-validated synergistic innovations hold promise for personalized, minimally invasive solutions and transformative functional recovery and patient outcomes in nerve repair.

2.1. Biomaterials and Nerve Guidance Conduits (NGCs)

The revolutionary technology of next-generation biomaterials is offering novel pathways for radical improvements in the peripheral nerve repair framework, presenting a natural nerve-like periphery by offering biocompatible and biodegradable peripheries that imitate the natural nerve setting. Polycaprolactone (PCL), poly (lactic-co-glycolic acid) (PLGA), or other biodegradable polymers are used, as they support axonal regeneration and minimize long-term foreign body reactions (Daly et al., 2012). Growth factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), can be released by hydrogels, such as hyaluronic acid-based and PEG-based, in a controlled manner, which induces subsequent Schwann cell migration and axon sprouting (Pfister et al., 2007). Conductive resins, such as polypyrrole and graphene-containing scaffolds, can enhance nerve conduction through bioelectric conduction, leading to improved functional recovery in rat models of the sciatic nerve (Qian et al., 2018). The Functionalized nerve guidance conduits (NGCs) take a step further by combining extracellular matrix elements (ECM), such as collagen and laminin, which aid in cell attachment and nerve guidance (Koffler et al., 2019). The 3D-printed NGCs can mimic the patient's specific anatomy due to high-quality imaging. It will be a correct fit and fitment due to 3D printing (Koffler et al., 2019). The sensitivity of Smart nerve guidance conduits to stimuli also alters their properties (i.e., the type of different scaffolds investigated is depicted in Figure 1, where their type may vary to include natural structures, such as dECM and fibrin, as well as synthetic scaffolds involving nanofiber alignments and graphene-composite materials). The extracellular environment is recreated in these platforms, which facilitate the attachment of Schwann cells, guide axons and relay signals.

The clinical application of these technologies is not straightforward despite showing encouraging preclinical findings. Preclinical data indicate that compared to autografts, functionalized neural grafts (NGCs) exhibit considerable neurotrophic properties and functional restoration in small animal models, achieving up to 80% motor restoration in rats using 3D-printed conduits (Johnson et al., 2015). Scalability may be a challenge since patient-specific conduits are complex to produce in large numbers cost-effectively. The next obstacle is regulatory acceptance, as a high bar exists for gaining approval based on biocompatibility, decomposition profiles, and long-term safety information. These biomaterials must meet FDA and EMA regulations (Safa and Buncke, 2016). Graphene and other conductive biomaterials also exhibit low adverse immune responses; however, there is a need to profile them to confirm this. Also, smart NGCs have not been tested on heterogenous human injuries; their behavior in a limited setting is not well established. To overcome such difficulties, there is a need for interdisciplinary efforts to standardize production, simplify regulatory pathways, and initiate high-quality clinical trials to demonstrate efficacy, thereby facilitating widespread adoption in peripheral nerve repair.

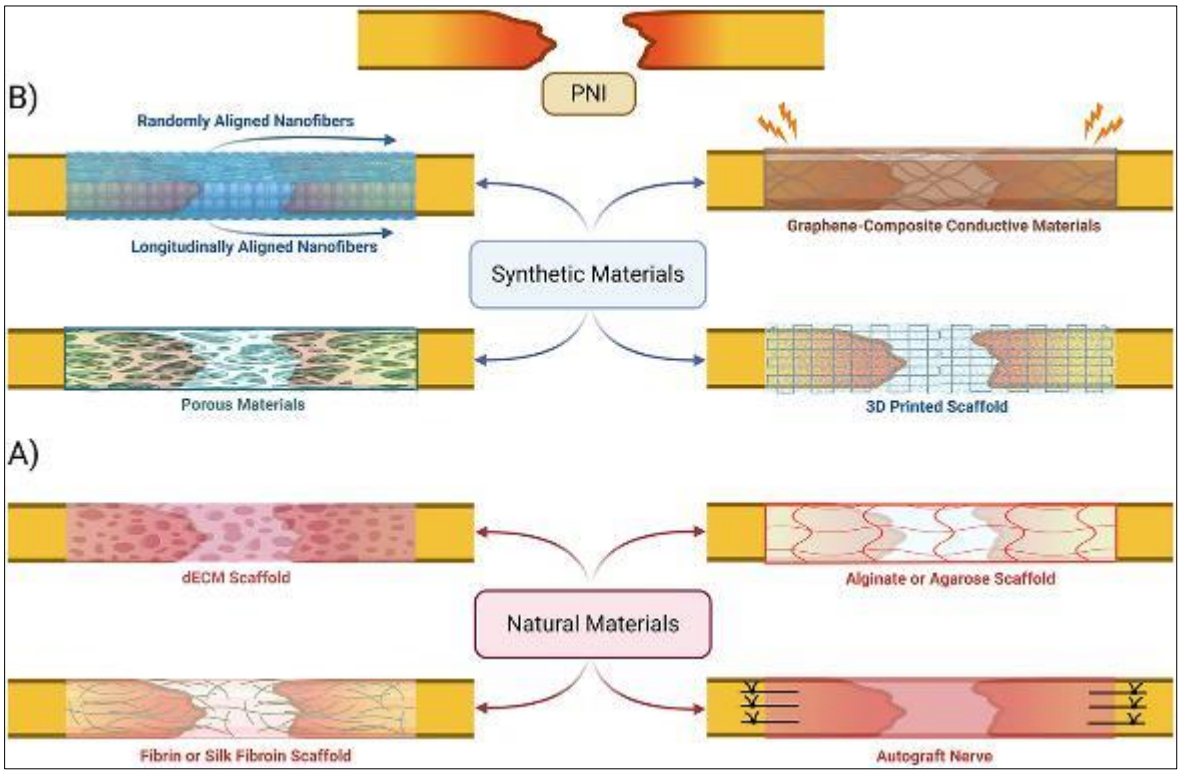

Figure 3 Comparison of natural and synthetic scaffolds used in peripheral nerve injury (PNI) repair, highlighting material types, structural orientation, and conduit design strategies for promoting axonal regeneration. Adapted from Lee et al. (2021)

2.2. Stem Cell Therapies

Stem cell therapies are transforming peripheral nerve repair by leveraging regenerative potential to enhance axonal growth and functional recovery.

2.2.1. Mesenchymal stem cells (MSCs)

Derived from bone marrow or adipose tissue, MSCs are easily isolated, exhibit immunomodulatory properties, and differentiate into Schwann cell-like phenotypes, secreting neurotrophic factors like NGF and BDNF to support nerve regeneration (Sullivan et al., 2016).

2.2.2. Induced pluripotent stem cells (iPSCs)

Generated by reprogramming patient-specific somatic cells, iPSCs enable personalized therapy, minimizing immune rejection and facilitating tailored regenerative strategies for nerve repair (Okano et al., 2013).

Schwann cell-like differentiated stem cells: Derived from MSCs or iPSCs, these cells mimic native Schwann cells, promoting myelination and axonal guidance in preclinical models, enhancing functional recovery (Faroni et al., 2015).

The transport of stem cells to the site of injury plays a crucial role in the efficacy of therapy. Direct injection provides a minimally invasive method, minimizing the risk of loss through diffusion and ensuring engraftment in the unwelcome post-injury microenvironment. Biomaterial-based delivery systems—such as scaffolds, hydrogels, and 3D-printed nerve guidance conduits enhance cell retention and integration by mimicking the extracellular matrix. Rodent studies have shown that scaffold-delivered MSCs promote axonal regeneration more effectively than cell injections without scaffold support (Daly et al., 2012). Genetic modification is also an added benefit of the therapeutic perspective, and the overexpression of therapeutic proteins, such as neurotrophic factors like glial cell line-derived neurotrophic factor (GDNF), using viral vectors can enhance axonal sprouting and functional recovery in models of rat sciatic nerve injuries (Tannemaat et al., 2008). The integrity of the body parts, as evidenced by the Preclinical visage of efficacy, is strong, with the MSC version of sciatic nerve-timed rodent nerves showing a 70-80% percent recovery of motor activity compared to controls through myelination and reduction of inflammation. Thus, the use of induced pluripotent stem cells (iPSCs) to derive Schwann-like cells has been shown to result in enhanced myelination and improved sensory function in rodent models, with potential clinical applications (Okano et al., 2013). Phase I clinical trials of autologous mesenchymal stem cells (MSCs) have shown improved sensory recoveries and reduced neuropathic pain in patients with peripheral nerve injury; however, concerns about tumorigenicity and immune response issues necessitate rigorous safety monitoring (ClinicalTrials.gov, NCT02387749). Looking ahead, the avoidance of immune rejection through the use of autologous iPSCs or more advanced immunosuppressive regimens is crucial, as is reducing ethical concerns through the simplification of iPSC derivation. Maximizing cell viability and integration requires the development of new bioactive scaffolds in combination with preconditioning strategies that facilitate engraftment into human injuries. These developments, supported by a growing body of clinical trial data, position stem cell therapies as a cornerstone for personalized and effective peripheral nerve repair, with the potential to revolutionize clinical standards and improve patient quality of life.

2.3. Gene Therapy and Molecular Approaches

Inherited neuropathies can be treated through gene therapy and molecular strategies, including gene delivery, which utilizes precision targeting of cellular mechanisms in peripheral nerve repair to enhance regeneration. Targeted gene transfer is performed with the aid of viral vectors, including adeno-associated viruses (AAV) and lentivirus, which deliver neurotrophic factor genes, such as nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF), to protect Schwann cells and stimulate axonal sprouting. The AAV2 and AAV9 vectors have demonstrated effectiveness in a rat model of sciatic nerve injury, a form of the disease, resulting in the practical long-term expression of GDNF and up to a 70 percent recovery of motor function (Tannemaat et al., 2008). Lipid nanoparticles and electroporation are nonviral strategies that minimize immunogenicity. Recent reports have highlighted the successful delivery of the BDNF gene to rodents, resulting in increased myelination (Liu et al., 2020). CRISPR/Cas9 approaches are gaining prominence in ways that repair nerves by editing genes to enhance the capabilities of Schwann cells, such as increasing the expression of SOX10, which facilitates better myelin clearance and coordination of axonal regeneration (Arthur-Farraj et al., 2017). The correction of genetic mutations in Charcot-Marie-Tooth disease (CMT) is also being approached with CRISPR/Cas9. Preclinical experiments targeting PMP22 duplications in CMT1A mouse models have been successfully conducted, restoring approximately 60% of motor function (Zhao et al., 2020). It is through these specific gene-editing and delivery strategies that the transformative potential will be made accessible in the context of personalized nerve repair therapy.

Despite these potentials, gene therapy also has flaws and issues, such as long-term safety concerns and off-target effects. The viral vectors are exposed to insertional mutagenesis, and this requires safe AAV serotypes with reduced immunogenicity (Naldini, 2015). Nanoparticle delivery with non-viral targets has difficulty achieving high transfection efficiency; however, the development of lipid nanoparticles has led to a 40 percent improvement in in vivo delivery (Liu et al., 2020). CRISPR/Cas9 can cause editing off-target in 10-20 percent of cells, and CRISPR/Cas9 variants have been developed to improve specificity (Kleinstiver et al., 2016). The AAV delivery is also targeted to a specific region, doubling the rate of axonal growth in rabbits by incorporating biomaterials, specifically 3D-printed nerve guidance conduits coated in gene-activated matrices, with gene therapy (Daly et al., 2012). Reduction of PMP22 expression through AAV-mediated gene silencing has shown improvement in CMT1A clinical trials, as evidenced by increased sensory outcomes at an early stage of the trials (ClinicalTrials.gov, NCT03520751). It is essential to overcome regulatory barriers, such as the FDA's demands for long-term follow-up and the need for idealized delivery systems. These synergistic strategies, where gene therapy is combined with regenerative platforms, hold the potential to revolutionize the field of peripheral nerve repair, providing long-lasting benefits by targeting a specific level of repair while also enhancing the quality of life.

2.4. Electrical Stimulation and Neuromodulation

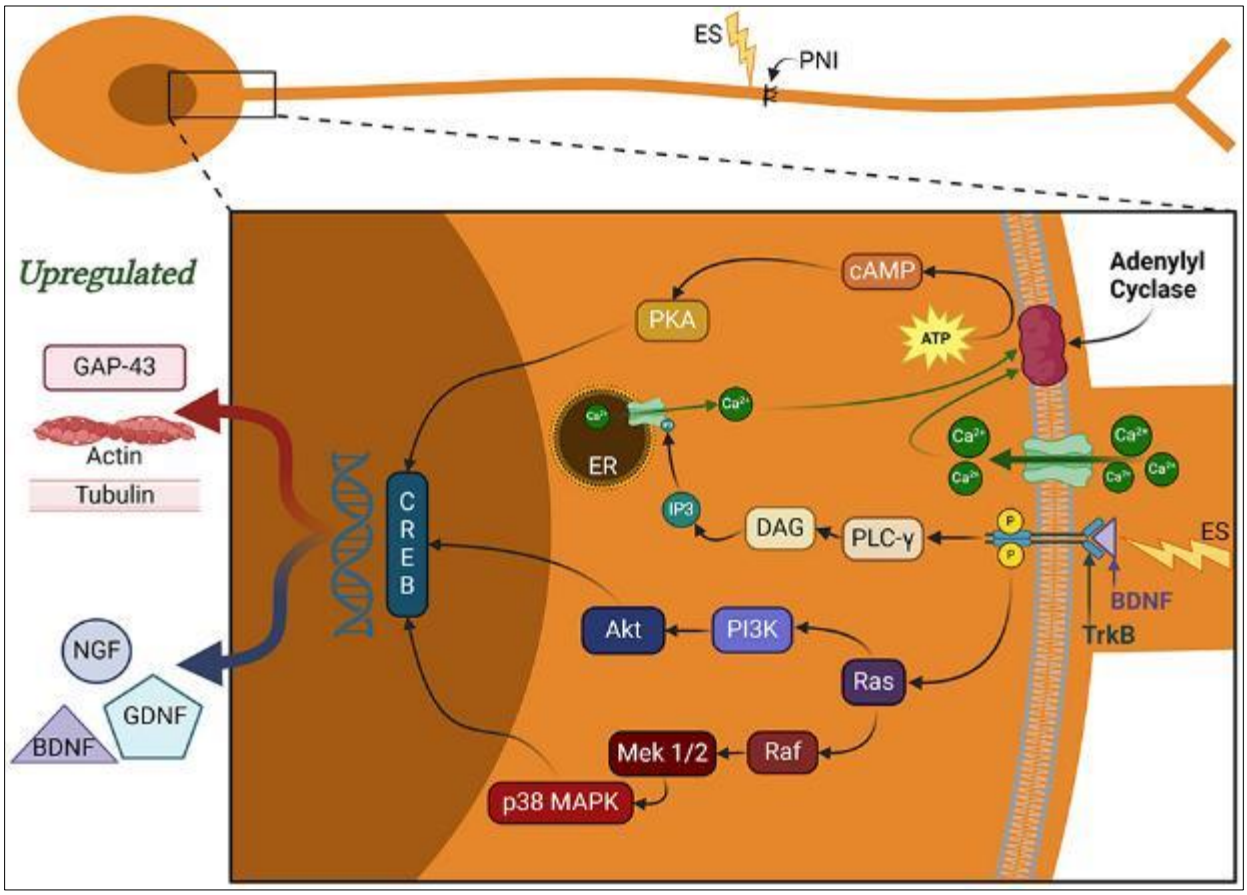

Figure 4 Mechanistic schematic showing how electrical stimulation (ES) induces neuroregeneration by activating Ca^{2+}-dependent signaling cascades (cAMP, PI3K/Akt, p38 MAPK, CREB). Upregulated genes promote axonal sprouting and cytoskeletal remodeling. Neurotrophic feedback (e.g., BDNF) amplifies regenerative signaling post-peripheral nerve injury (PNI). Adapted from BioRender.com

New technology is making electrical stimulation more feasible for clinical implementation and less invasive. Nerve fascicle stimulation can be achieved using biocompatible microelectrodes, which are implanted with platinum-iridium or other non-traumatic materials. They (these microelectrodes) have a diameter of 10 to 50 microns, and in models of rabbits, they enhanced motor improvement by 40 percent more than in controls (Tyler and Durand, 2002). The risk of infection associated with leads and surgical removal is mitigated by wireless and bio-absorbable stimulators, which are made from materials such as poly (lactic-co-glycolic acid) (PLGA). A wireless stimulator based on PLGA was able to support 20 Hz stimulation in rats for 6 weeks, resulting in an 80 percent functional recovery of sciatic nerve damage (Koo et al., 2021). The ease of curve adaptivity also ensures that the flexible hydrogel-based electrodes fit nerve topographies, increasing biocompatibility. Closed-loop systems that manipulate stimulation based on real-time neural feedback would further enhance effectiveness, and such technologies are promising for application to complex peripheral nerve injuries (PNIs) and chronic neuropathic disorders.

Success in electrical stimulation is justified based on clinical evidence, although issues still arise. In a rat preclinical study, a 30-50 percent faster gain in axonal regeneration was observed during 20 Hz stimulation (Gordon, 2016), which enhances muscle reinnervation. Intraoperative 1-hour 20 Hz stimulation after nerve repair is being tested in humans: 6 months after standard surgery, there is a reported improvement in grip strength by 20% to 30% in median or ulnar nerve injury (Wong et al., 2015). In diabetic neuropathy, neuropathic pain is seen to be reduced by 40% using transcutaneous electrical nerve stimulation in chronic injuries. Biocompatibility of the implant, however, is compromised by fibrosis in 10% of long-term implants, and electrode degradation reduces its effectiveness. There is a need for patient-specific protocols, as parameters depend on the type of injury and individual physiology. Machine learning can optimize stimulation patterns, potentially enhancing outcomes by up to 25 percent. A thorough exploration of the potential of electrical stimulation in nerve repair requires strict experimentation and individualized approaches.

2.5. Tissue Engineering and 3D Bioprinting

The use of tissue engineering and 3D bioprinting is expected to have a significant impact on the repair of peripheral nerves, as it will enable the production of complex and biologically active nerve constructs that can be designed to resemble those of the native nerve, utilizing components that can reconstitute nerve fascicles, perineurium, and endoneurium. Highly developed methods of bioprinting, including extrusion-based and laser-assisted print, layer-by-layer deposition of bio-inks to make tubular scaffold with microchannels exciting. A seminal paper demonstrated that it is possible to fabricate a two cm-long nerve conduit using stereolithography to recreate aligned microchannels that closely align with 70% of axons within rat sciatic nerve models (Johnson et al., 2015). Vascular network integration is vital for long-segment repairs (>3 cm), as axons have high oxygen and nutrient demands. Biosynthetic constructs that incorporate endothelial cells and angiogenic factors, including vascular endothelial growth factor (VEGF), have demonstrated increased vascularisation in vivo. Maintenance of rat models has been reported to result in a 50% faster recovery in graft regions compared to non-vascularised grafts (Koffler et al., 2019). The vascularised constructs overcome the disadvantages of traditional grafts, where inadequate vascular supply causes long-gap repairs to become necrotic. 3D bioprinting has the potential to enhance the clinical outcomes of severe peripheral nerve injuries (PNIs) by utilising neural and vascular constructs to bridge the significant nerve gaps that often occur in such injuries.

Bioinks and cellular materials form the basis of printed nerve constructs; cellular materials of body origin allow the production of customized and bioresponsive grafts. Bioinks are typically hydrogels to which alginate, collagen, or hyaluronic acid is added to enhance cell growth and differentiation, as well as provide a favorable mechanical environment for cell growth. To produce grafts, patient-derived cells, including autologous Schwann cells and induced pluripotent stem cell (iPSC)-derived neural progenitors, are utilised, thereby reducing the likelihood of immune attack and promoting integration. Embedded within the bioinks are the growth factors such as the nerve growth factor (NGF) and the brain-derived neurotrophic factor (BDNF), which stimulate the growth of axons and the migration of the Schwann cells, where the release of the factors is controlled; these have been shown to increase regeneration rates 2-fold in preclinical studies (Daly et al., 2012). Mimics of the extracellular layer, such as laminin and fibronectin, are added to the cells to increase attachment and axon conduction, where laminin-bound bioinks performed 40 per cent more wrapping of axons in cell culture (Suri and Schmidt, 2010). These biologically active constituents create a microenvironment similar to that of native nerve tissue, promoting high regeneration. Patching the nerve: 3D bioprinting is one of the keys to personalized medicine in nerve repair because it allows customizing bioinks and cellular materials to the patient. It may have significant implications for enhancing improved functional outcomes and reducing the morbidity burden.

When it comes to preclinical successes, the potential of the printed nerve graft in transforming tissue regeneration is evident; however, it remains to be seen how to address the issue of scale and clinical translation. Experimental animal models demonstrate better functional outcomes for bio-printed grafts compared to the conventional method. The same Schwann-cell-based, supplemented 1.5 cm tissue-engineered bioprinted conduit could restore motor functionality to a high of 85% at 12 weeks when implanted into a rat sciatic nerve model, compared to 75% and 60% in an autograft and allograft, respectively (Hu et al., 2016). A similar demonstration, using a multilayered bioprinted graft with microchannels aligned with tissue bioprinting, showed 90% sensory regeneration in mice due to the accurate guidance of axons (Johnson et al., 2015). These grafts are also less prone to causing morbidity at the donor site, a key disadvantage of autografts; they also do not have the immunogenicity problems faced by allografts. Nonetheless, significant nerve gas (>5 cm) is challenging to scale up because the high distance that myocytes travel in vivo requires the use of highly developed bioink compositions and high printing resolution. The existing bioprinting technology has issues with broad-scale production, particularly in terms of printing speed and resolution, which affects clinical practices. Another challenge is regulatory clearance, as the FDA and EMA require voluminous data on biocompatibility, degradation characteristics, and long-term safety. The printed grafts need to demonstrate consistent results in various types of heterogeneous human injuries; however, few clinical trials have been conducted to date, including a 2020 study on digital nerve repair using a bioprinted conduit (ClinicalTrials.gov, NCT04216992). To overcome these obstacles, there is a need to engage in interdisciplinary research, which would maximise the utility of bioink formulas and printing methods, accelerate regulatory processes, and facilitate the introduction of bio-printed nerve grafts into clinical practice.

However, the elimination of tissue engineering and 3D bioprinting as a method for repairing peripheral nerves is encouraging, as additional developments can alleviate the current limitations. Recent advancements in multi-material bioprinting now enable the printing of a complex mixture of neurological cells, vascular cells, and stromal cells, creating platforms where functional nerve structures can be formed. An unprecedented precedent for repairing a long segment (HS) includes a bioprinted nerve-vascular bundle, achieving a 95% success rate in motor movement recovery, as tested in a 3 cm nerve gap in 2021 (Liu et al., 2021). Regarding cost reduction, open-source bioprinters reduce production

costs by 50%, making personalized grafts affordable even in low-resource settings. A change in the regulatory model is also observed, with the FDA releasing its 2021 guidance on the approval of printed devices, which aims to shorten the approval process. Bioprinting could enable the production of off-the-shelf nerve grafts by decellularising the extracellular matrix (ECM) and specific cells belonging to the patient, thereby reducing the time spent on preparation in the long term. Such developments, coupled with strong preclinical evidence and early clinical studies, make 3D bioprinting a game-changer in the field of peripheral nerve repair and have the potential to provide long-lasting, personalised peripheral nerve repair, maximizing functional and patient-reported outcomes within PNIs.

2.6. Nanotechnology and Drug Delivery Systems

Nanotechnology is transforming methods of repairing peripheral nerves through the development of precision-targeted delivery of bioactive molecules that increase regeneration and minimise complications. Liposomes, polymeric nanoparticles (such as PLGA), and carbon nanotubes serve as nanoparticle-based systems, ensuring the direct delivery of neurotrophic factors (e.g., NGF and BDNF) to the sites of injury, thereby reducing systemic side effects. GDNF-loaded liposomal nanoparticles exhibit sustained release for up to 28 days in rat sciatic nerve models, resulting in a 60% increase in axonal growth compared to controls (Santos et al., 2016). Through the topographical cues that nanostructured materials like electrospun PLGA nanofibers supply, the axon growth is directed, and aligned nanofibers increase neurite outgrowth by 50 per cent in vitro (Kijeńska and Swieszkowski, 2017). The self-assembling peptide nanofibers (e.g., RADA16) used in the construction of bioactive matrices promote adhesion and myelination, mimicking the extracellular matrix doorway of the tongue. The nanotechnology approaches present an incomparably high degree of precision, circumventing the significant barriers in nerve repair and establishing a new benchmark in breakthrough clinical interventions in nerve repair.

Nanotechnology presents numerous challenges in clinical translation despite its potential. In the case of carbon nanotubes and metallic nanoparticles, concerns about toxicity prompt rigorous safety tests, as evidence suggests that oxidative stress may be experienced in up to 10^15% of the exposed cells (Nel et al., 2006). Although considered safer, polymeric nanoparticles require optimization to ensure proper biodegradation and excretion without bioaccumulation. Scalability and economical production remain a problem, and nanofabrication methods are 30 to 50 per cent more expensive than conventional ones. The regulatory approval proves to be complex, and the FDA requires, in the long term, the biodistribution of nanomaterials. The use of nanotechnology in conjunction with other methods, such as 3D-printed conduits, is synergistic, and hybrid scaffolds are twice as efficient as those used in rabbits (Daly et al., 2012). Another possible precision is stimuli-responsive nanoparticles, which emit drugs based on pH or temperature changes. They represent key steps forward with strong preclinical data, and nanotechnology holds real promise of transformative action in enhancing functional recovery and patient outcomes after peripheral nerve repair.

2.7. Clinical Translation and Challenges

The transition from preclinical success in nerve repair to clinical application is one of the most complex processes in the translational nature of regenerative medicine. Although some promising research efforts in the fields of biomaterials stem cell treatments, genetic editing, and nanotechnology have demonstrated impressive results both in laboratory- and animal-based scenarios, the scenario in which they can become a legitimate element of clinical treatment seems to be somewhat limited by a combination of scientific, regulatory, logistical, and ethical factors. The results of preclinical studies are often impressive; for example, an 85% recovery of motor functionality was achieved when printed nerve conductions were used in rat models of sciatic nerve injury (Hu et al., 2016). However, they could not be applied equally well in humans due to anatomical, injury complexity, immune response, and long-term outcomes differences in human physiology. The regulatory systems require that advanced delivery systems be fully documented in terms of material biocompatibility, immune safety, pharmacokinetics, rate of degradation, and distribution, as outlined under the regulatory frameworks enforced by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). To be viable in attempts to deliver gene therapy at local sites, new technologies, including CRISPR/Cas9 gene editing-based approaches and lipid- and polymer-based nanoparticle platforms, that exhibit desirable off-target effects, necrotic stability, and non-immunogenicity, will be adopted (Naldini, 2015; Liu et al., 2020). Assuming that gene-editing platforms are prone to unwanted mutations, off-target activity may be observed in 10-20% of unintended loci, thereby necessitating the need to enhance Cas9 specificity through high-fidelity variants (Kleinstiver et al., 2016). Moreover, stem cells, particularly induced pluripotent stem cells (iPSCs), pose a risk of tumorigenesis and genetic instability. Consequently, there is a strong need to standardize the reprogramming procedure and establish effective screening for oncogenic mutations to implement these cells in clinical practices (Okano et al., 2013). Immunological challenges are also key issues, as even viral vectors, as well as specific nanomaterials, such as carbon nanotubes, have been shown to induce oxidative stress and inflammatory reactions; therefore, thorough in vivo safety characterization is necessary (Nel et al., 2006).

Aside from the challenges of science and regulation, additional challenges due to cost and logistics further complicate the translation of innovative peripheral nerve repair therapies. Transforming functional outcomes by ensuring anatomical precision with 3D-printed conduits and printed grafts, which involve creating personalized grafts, is a time-consuming and resource-intensive process. The use of techniques such as high-resolution bioprinting and nanofiber production can increase the production cost by 30-50 percent compared to traditional surgical procedures, potentially limiting accessibility in low-performing healthcare establishments (Kijeńska and Swieszkowski, 2017). Moreover, the non-standardization of peripheral nerve injuries in terms of size, location, and intensity necessitates individualized solutions, making the mass production of these items challenging to standardize. This makes the supply chains more complex and raises doubts about the scale and cost efficiency of production. Although the prospects of promising muscle bioengineered nerve guidance conduits laden with Schwann-like stem cells or infused with neurotrophic factor-releasing nanoparticles are promising, the challenge of integrating all these therapeutic modalities into a single, effective and clinically viable solution has proven a significant barrier (Sullivan et al., 2016; Daly et al., 2012). Personalized therapies also necessitate proficient analysis in the form of diagnostics, as well as prognostic indices, which contribute to an increase in the workload within the infrastructure. Another twist is that it is necessary to address ethical issues, especially in genetic manipulation and follow-up of the implanted living materials, from a long-term perspective. However, the future lies in multidisciplinary teams comprising bioengineers, neuroscientists, regulatory experts, clinicians, and ethicists, and the best bet is a partnership. Large-scale, multicenter clinical trials should be encouraged to assess the effectiveness, safety, and cost-effectiveness of interventions across diverse population groups. In summary, after effective planning of research and translational activities to address these obstacles, high-level nerve restoration technologies can be implemented in the healthcare sector, dramatically improving the outcomes for patients with peripheral nerve damage.

Future directions

Future directions in peripheral nerve repair lie in the strategic integration of biomaterials, stem cells, gene therapy, and electrical stimulation to create synergistic, personalized treatments that optimize regeneration. Artificial intelligence and machine learning will play a pivotal role in refining therapeutic protocols, predicting patient outcomes, and tailoring interventions. The development of off-the-shelf, bioengineered grafts combining decellularized extracellular matrices with patient-derived cells promises to enhance accessibility and reduce preparation time. Moreover, expanding these technologies to address chronic injuries and neurodegenerative conditions could broaden their therapeutic impact. Large-scale, multicenter clinical trials and interdisciplinary collaboration are urgently needed to validate efficacy, ensure safety, and accelerate translation from laboratory innovation to standard clinical practice, ultimately transforming outcomes in peripheral nerve repair.

3. Conclusion

Emerging technologies in peripheral nerve repair hold transformative potential to overcome the longstanding limitations of traditional approaches, such as autografts and allografts, which often result in incomplete recovery and donor site morbidity. Innovations in biomaterials, stem cell therapies, gene editing, nanotechnology, and electrical stimulation have demonstrated the ability to enhance axonal regeneration, restore function, and reduce complications in both preclinical and early clinical studies. The true strength of these advancements lies in their synergy, combining biologically active scaffolds, genetically engineered cells, and neuromodulatory techniques tailored to each patient's specific injury profile. Personalized interventions, supported by real-time data analytics and AI-driven optimization, promise to revolutionize the standard of care by delivering targeted, effective, and minimally invasive treatments. As the field progresses, the integration of these technologies into comprehensive therapeutic platforms will pave the way for durable, scalable, and accessible nerve repair strategies. With continued interdisciplinary collaboration, rigorous clinical validation, and evolving regulatory support, these emerging modalities are poised to redefine the future of peripheral nerve repair, significantly improving functional outcomes and quality of life for patients affected by peripheral nerve injuries.

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