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CURRENT TOPIC

Stem Cell-Based Therapies Combined With Nano-Biomaterials for Nerve Regeneration and Repair

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Abstract

Nerve injuries, often resulting from trauma or degenerative diseases, pose significant challenges due to limited regenerative capacity of nervous system. Conventional treatments, including surgical nerve grafts, exhibit limitations such as donor site morbidity and limited functional recovery. Emerging regenerative strategies combining stem cell-based therapies with nano-biomaterials offer promising solutions for enhancing nerve regeneration and functional restoration. A comprehensive review of recent advancements in stem cell sources and induced pluripotent stem cells (iPSCs) was discussed. Also design, properties and applications of nano-biomaterials such as nanoparticles, nanofibers and hydrogels in nerve repair were analysed. Preclinical and clinical studies demonstrating effectiveness of these combined strategies were evaluated. The integration of stem cells with nano-biomaterials has demonstrated improved nerve regeneration outcomes, including enhanced neuronal differentiation, reduced inflammation and accelerated axonal growth. Studies indicate that biomaterial scaffolds provide structural support and biochemical cues, facilitating stem cell survival and integration into damaged neural tissues. Stem cell-based therapies combined with nano-biomaterials represent a promising approach for nerve regeneration. This combinatorial strategy offers enhanced neuroprotection, functional recovery and long-term stability in neural repair. Future research should focus on optimising scaffold properties, improving cell survival rates and translating preclinical findings into clinical applications.

Key words: Nerve regeneration; Stem cells; Nanostructures; Nanotechnology; Biomedical engineering, scaffolds; Growth, axonal; Neuroprotection.

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Introduction

A prevalent cause of disability worldwide, peripheral nerve damage (PNI) can lead to severe sensory impairment and persistent neurogenic pain.[1] A conduction block is defined as a physiological impairment of nerve conduction along axon at site of damage. It is normal for self-healing to occur in these circumstances. Axonal disruption, Wallerian degeneration and an intact endoneurium are characteristics of the second grade. Nerve self-healing is observed to proceed at a pace of 1 mm/d in these circumstances.[2] Injuries occur in 3rd, 4th and 5th grades, respectively, to endoneural tubes, perineurium and epineurium.[3] Consequently, surgery may eventually be required.

Patients who have grades four and five PNI are unlikely to recover on their own and surgery is often necessary. Many surgical advancements in the management of PNI have been made throughout the past ten years. However, as patients still suffer from somatosensory problems, rehabilitation success has not significantly improved.[4]

PNI is a common neurological condition that can cause problems in motor function and sensory perception in addition to neuropathic pain.[5] Target organs may potentially be affected by prolonged denervation. Because of this, the pathogenic mechanisms are complex and necessitate a holistic viewpoint. Target-end organs cannot be properly reinnervated by regenerated axons. Many PNI patients consequently never fully recover their normal function.[6-8]

Treatment options for PNI range from conservative methods to surgery.[9] Neurotrophic drugs that are commonly used include methylcobalamin, exogenous neurotrophic agents and B vitamins. However, because local drug concentrations in peripheral circulation are usually small, pharmacological interventions often fail to elicit long-lasting therapeutic effects.[10, 11]

Emerging role of stem cell therapy and nano-biomaterials

Using either autologous (the body's own cells) or allogeneic (donor) cells, stem cell treatment is a cutting-edge medical procedure that can regenerate and repair damaged tissues.[12] Stem cell therapy, also referred to as stem cell treatment, is therapeutic application of stem cells to cure or manage a variety of medical conditions. Muscle, bone and nerve cells are among the body cell types that can develop from undifferentiated cells known as stem cells.[13]

Using stem cells' capacity for regeneration and repair to treat or manage a variety of illnesses is main objective of stem cell therapy. Specifically, treatment aims to:

Promote tissue regeneration: Muscle, bone and nerve cells are among the injured tissues that stem cells can help heal and regenerate by differentiating into new cell types.[14, 15]

Reduce inflammation: The symptoms of chronic inflammatory illnesses can be alleviated by anti-inflammatory compounds released by stem cells, which can reduce systemic and localised inflammation.[16]

Improve quality of life: Stem cell therapy seeks to improve patients' overall quality of life by addressing underlying causes of degenerative diseases and injuries.[17] The following points encapsulate benefits of using biomaterials to treat neurological illnesses.[18]

Stem cell-based therapies for nerve regeneration

Types of stem cells in neural repair

Mesenchymal stem cells (MSCs): Mostly found in connective tissues, mesenchymal stromal cells (MSCs) are pluripotent stem cells. A range of human tissues, such as muscle, skin, adipose tissue, peripheral blood, placenta and amniotic fluid, can be isolated from it.[19] Clinical uses for MSCs in peripheral nerve healing are still being developed and the cellular processes via which they produce their biological effects are not fully known.[20] MSCs have therefore been given a lot of thought for both *in vitro* and *in vivo* research to see how well they assist nerve regrowth. In addition to replacing damaged tissue cells under certain circumstances, mesenchymal stem cells can also enhance intrinsic regenerative potential of damaged tissue by generating growth factors and cytokines and by regulating the immune system following nerve damage.[21-23]

Neural stem cells (NSCs): The names, morphologies and differentiation traits of NSCs probably change during ontogenic development. Early in development, neuroepithelial stem cells (NSCs), often referred to as matrix cells, divide symmetrically in the embryonic neural tube.[24] These results suggest potential therapeutic strategies for employing NSCs to repair injured central nervous system (CNS) tissue, given their existence in adult central nervous system. The lack of foetal tissues, difficulties in confirming grafted cells, moral quandaries and potential adverse effects like graft-induced dyskinesia remain some potential problems, despite their research demonstrating the therapeutic benefits of cell transplantation for Parkinson's disease.[25, 26]

Induced pluripotent stem cells (iPSCs): ESCs and iPSCs are not the same, despite their many

similarities.[27] An important turning point in study of stem cells and regeneration has been reached with the effective induction of somatic cells into iPSCs. From creating illness models to performing patient-specific therapeutic transplants, iPSCs have a wide range of potential applications. Better disease models are already being developed thanks to availability of iPSCs from patients with a specific neurological condition. The pathophysiology of retinal degenerative illnesses has been studied using iPSC derivatives and a model for neurodegenerative diseases like Alzheimer's disease has developed using iPSCs.[28]

Mechanisms of action in nerve regeneration

In injured peripheral nerves, transplanted neural stem cells can develop into neurons and Schwann-like cells. They are also capable of secreting several important neurotrophic factors.[29] They can also promote myelin development, neuron growth and angiogenesis. It is possible to grow neural stem cells and embed them in a hyaluronic acid–collagen conduit that is composited with neurotrophin-3. The voltage amplitude of electromyography is increased and facial nerve repair is encouraged when a neural stem cell-based nerve conduit is transplanted into a transected rabbit facial nerve.

Nano-biomaterials for nerve repair

Many inert, stabilisable biomaterials, both natural and synthetic, have been found as promising therapies for neurological disorders.[30] These features facilitate accurate biomaterial characterisation for a variety of applications. Without requiring invasive procedures, biomaterials provide a physical scaffold that prevents therapies from deteriorating after delivery and enables ongoing drug release. They also increase cell survival rates and stimulate stem cells.[31]

Types of nano-biomaterials

Nanoparticles

Simple, economical and biocompatible procedures are made possible by nanotechnology. Because nanomaterials have the potential to close greater nerve gaps after severe injury, they have been used specifically in PNS.[32] Nanoparticles imitate extracellular matrix's (ECM) structure and architecture to facilitate cellular adhesion and nutrient transfer.

Nanofibers

It has been shown in recent years that nanofibers and both organic and inorganic nanoparticles work well in PNR. The random or aligned nanofibers created from nanoparticles using the electrospinning approach have been shown to be advantageous for PNR. Inorganic nanoparticles include: silica (SiO_2), gold (Au), silver (Ag) and magnetic (most notably Fe_3O_4) nanoparticles. Organic chitosan nanoparticles can be made from chitosan, a well-known biopolymer.[33]

Hydrogels

Hydrogel is a hydrated, flexible matrix composed of water-insoluble polymers and have a strong, porous, three-dimensional structure that protects against internal CNS injury and they feel good to the touch.[34] Similarly, highly biocompatible but non-biodegradable materials like polyacrylamide and polyethylene glycol can be used to create it synthetically. Both natural and manmade materials are frequently used to create hydrogels. Additionally, they are divided into self-assembled hydrogels and polymeric covalently cross-linked hydrogels according to internal bonding and cross-linking structures. While the later preparations are injectable and self-assemble into hydrogels as a result of modifications in internal physicochemical characteristics, the previous hydrogels are rigid and need to be surgically implanted.[35, 36]

Biocompatibility and biodegradability

Things to think about: both natural and synthetic materials make up the nanoscaffolds; carbon nanotube (CNT) fibres and electrospun silk fibroin nanofibers are examples of natural biomaterials, whereas carbon nanomaterials most notably, CNTs with graphene sheets are greatest examples of synthetic biomaterials.[37]

Synergistic role of stem cells and nano-biomaterials

The joint role of stem cells and nano-biomaterials long-term therapies usually target symptoms of secondary damage.[38] Treating SCI and enhancing functional recovery are extremely difficult tasks because of difficulty of drug-targeted delivery across blood-spinal cord barrier. By providing exogenous neural stem cells to stimulate nerve

regeneration and prevent further neuron loss, respectively, pathophysiology of the current treatments is predicated on preservation of neurons and the development of nerve regeneration. Biological approaches, physical and pharmacological therapies and surgical techniques are the four basic categories into which the many therapy modalities can be separated.[39]

Enhancing stem cell survival and differentiation

Nerve cells injured by diseases or trauma must be replaced or repaired for the nervous system to regenerate.[40] While lower organisms have enormous potential for brain regeneration, higher animals, such as humans, have limited capacity to repair nerve cells. The inability of nerve cells to transmit neural impulses to specific regions of nervous system is a common consequence of neurological damage, irrespective of the underlying cause. To restore function, one of the three forms of nervous system healing is needed. While rest of neuron, including cell body, remains unaffected, damaged neuronal axons can recover. Other strategies include replacing lost neurons with new ones and mending damaged nerve cells. Although these three methods of nervous system repair have the ability to fix any kind of damage or degeneration, they often only work on certain nervous system components.[41] In order to influence the electrical characteristics, differentiation and proliferation of neurons, nanomaterials mimic these processes.[42]

Bioengineered scaffolds for neuronal support

Their niche, or microenvironment, governs stem cells. Stem cells in their niche are influenced and guided by a combination of chemical and physical stimuli, which gives them the ability to decide or uphold their fate.[43]

Controlled drug and growth factor release

The goal of nanomedical drug delivery methods is to create nanoscale molecules or particles that will guarantee a medicine's stability and bioavailability. Drug bioavailability and stability are influenced by a number of mechanisms, including opsonisation by plasma proteins, fast drug leakage into blood capillaries that leads to drug uptake by fixed macrophages that are embedded in the reticuloendothelial system, including the liver and spleen.[44]

Preclinical and clinical studies

Biomaterial neural scaffolds have been studied for half a century. Only three compounds have progressed to the point of therapeutic use: polyglycolic acid, collagen and polycaprolactone.[45] Before being employed in clinical settings, nerve scaffolds must undergo testing in pre-clinical animal models. Due to the complete absence of systemic elements such vascularisation, oxygen and nutrition delivery, waste removal and immune system or foreign body response, *in vitro* assays are unable to determine tissue responses to materials. Animal models are therefore crucial for assessing the mechanical function, tissue reaction and biocompatibility of any nerve conduit before it is used in clinical settings. The evaluation of material in biological conditions that are clinically relevant and over extended periods of time is made possible by *in vivo* experiments conducted in a variety of animal species.[46]

Animal models for nerve regeneration

More research is needed because knowledge of nerve regeneration and physiology is necessary to improve functional recovery after peripheral nerve loss.[47] The use of experimental animals in research has been around for a while and the information gathered has undoubtedly improved the standard and effectiveness of healthcare and medicine. Apes, small ruminants, pigs, lagomorphs, carnivores and rodents are animals most commonly used in neuroscience. An ideal translational animal model must match the exact mechanisms behind peripheral nerve damage in humans.[48]

For pre-clinical research on peripheral nerve regeneration, choice of experimental animal model is essential. When testing a new approach *in vivo*, a researcher should choose an animal model according to the study's objectives. Naturally, one must also carefully consider the benefits and drawbacks of each option. A number of criteria are typically used to choose the best experimental nerve injury model.[49]

Key findings from preclinical research

Numerous transgenic animals can be used to study biology of peripheral nerve regeneration. Mice make up the majority of transgenic animals available on the market and they are a useful tool for using inducible systems to investigate effects of gene mutation, over-expression, or depletion in a specific cell type.[50]

Biocompatibility and immune response

Specific immunological response the preexisting IgG and IgM in naïve WT mice bind to specific epitopes in myelin debris and target them for rapid clearance. During PNR, inflammation and the immune system are crucial. An inflammatory process is always involved in PNI, regardless of the underlying reason.[51] Chemotactic gradients are created throughout the BNB and along the injury site in part by matrix metalloproteinase. The first immune cells to enter are neutrophils. Within eight hours of the damage, they begin to amass in the distal stump, but their existence is brief. To guarantee complete WD, these hematogenous macrophages become main leukocyte population. T-lymphocytes and other inflammatory cells also infiltrate the injury site within hours of the injury by penetrating the damaged BNB.[52]

Scalability and standardisation in clinical applications

Our understanding of brain systems in animal models and human brain is currently lacking.[53] However, neurotechnologies are making it increasingly possible to do research on the human brain. Progress will surely depend on our capacity to scale data collection and analysis at the same time, given the size and complexity of human brain. Thus far, stretchable, high-density, biocompatible electrode grids have been used to capture local field potentials (LFPs) and spikes at surface of the human brain. Using high-density interfaces to scale up data collecting could further improve spatiotemporal resolution of human brain mechanisms.[54]

Future outlook

As regenerative medicine progresses, combining stem cell biology with nanotechnology is expected to pave the way for highly personalised therapies. Emerging techniques such as CRISPR/Cas9-mediated gene editing, bioelectronics interfaces and 4D bioprinting could further enhance the regenerative potential of stem cells while ensuring precise control over their differenti-

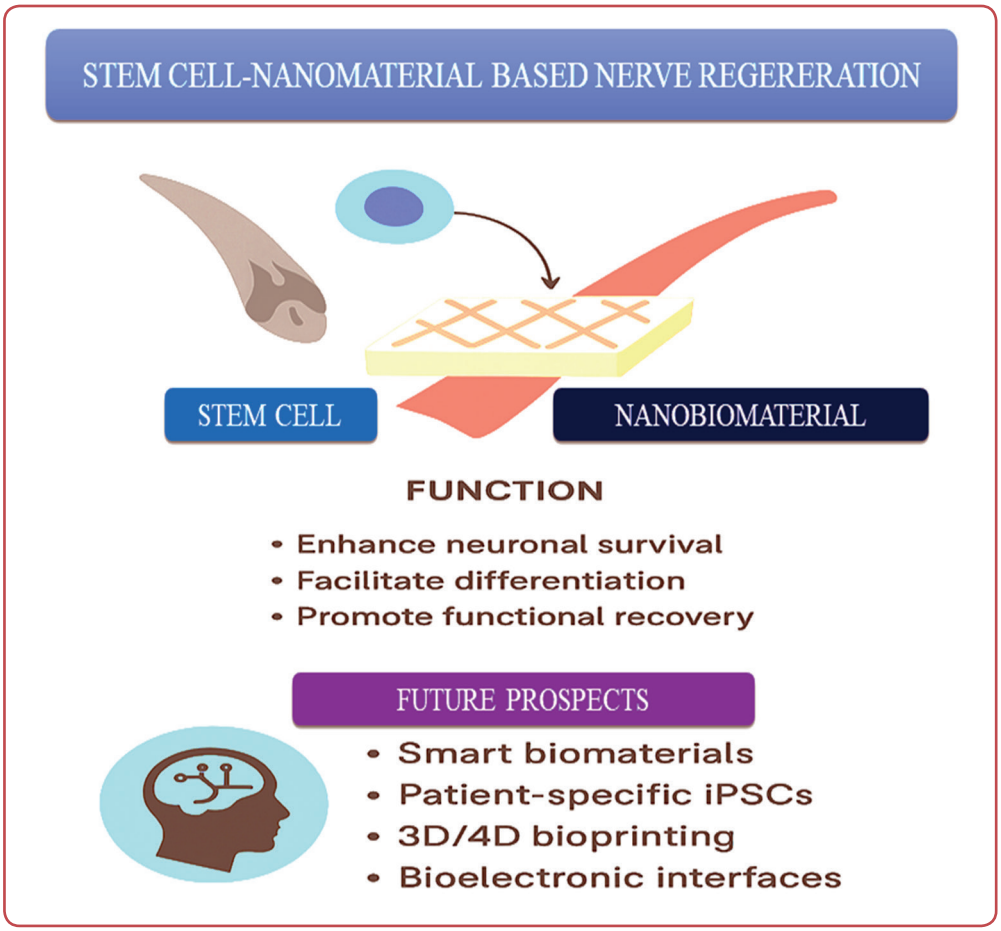

Figure 1: Stem cell–nanomaterial-based nerve regeneration: functions and future prospect

iPSCs: induced pluripotent stem cells;

ation. Moreover, integrating biomaterials with biosensors may allow real-time monitoring of transplanted cells, providing feedback-guided therapeutic adjustments. Such advancements could not only overcome current translational hurdles but also expand applications to CNS injuries, chronic neurodegenerative disorders and age-related neuronal decline, thereby broadening the clinical relevance of these innovative therapies (Figure 1).

Conclusion

Stem cell-based therapies combined with nano-biomaterials have emerged as a transformative strategy for nerve regeneration and repair. By leveraging the regenerative capacity of stem cells and the supportive, bioactive environment offered by nanoengineered scaffolds, significant improvements have been achieved in axonal growth, neuronal differentiation and functional recovery. Preclinical studies highlight the synergistic benefits of this approach, including enhanced neuroprotection, reduced inflammation and long-term structural stability. However, clinical translation remains limited due to challenges in cell survival, immune compatibility, ethical concerns and standardisation of scaffold properties. Looking ahead, future research should prioritise the design of next-generation biomaterials that can closely mimic the native neural microenvironment, while enabling controlled delivery of bioactive molecules and electrical/biomechanical cues. Advances in patient-specific iPSCs, 3D bioprinting and smart nanomaterials offer immense potential to improve therapeutic precision and reduce risks such as tumorigenicity or graft rejection.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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