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The role of stem cells and biomaterials in peripheral nervous system regeneration

Periferik sinir sistemi yenilenmesinde kök hücre ve biyomateryallerin rolü

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ABSTRACT

Peripheral nerve injuries present significant challenges to patients and require intensive and costly treatments. The utilization of biomaterials is an effective treatment method. Personalized biomaterials are promising for the regeneration of damaged peripheral nerves. Stem cells have an important role in modern treatment methods because of their properties and promise to solve diseases requiring tissue regeneration, such as peripheral nerve damage. In this review, we aimed to investigate the relationship between stem cells and biomaterials, considering their different origins and potential compatibility in facilitating the regeneration of peripheral nerve injury.

Keywords: Peripheral Nervous System, Stem Cell, Biomaterials, Regeneration

ÖZ

Periferik sinir yaralanmaları hastalar için önemli zorluklar oluşturur ve yoğun ve maliyetli tedavi gerektirir. Biyomateryallerin kullanımı tedavide etkili bir yöntem sunmaktadır. Kişiselleştirilmiş biyomateryaller, hasar görmüş periferik sinirlerin yenilenmesi için umut vaat ediyor. Kök hücreler, sahip oldukları özellikler nedeniyle modern tedavi yöntemlerinde önemli bir yere sahip olup, periferik sinir hasarı gibi doku yenilenmesi gerektiren hastalıkların çözümünde umut vadediyor. Bu derlemede, kök hücreler ile biyomateryaller arasındaki ilişkiyi, bunların farklı kökenlerini ve periferik sinir hasarının yenilenmesini kolaylaştırmadaki potansiyel uyumluluğunu göz önünde bulundurarak araştırmayı amaçladık.

Anahtar Sözcükler: Periferik Sinir Sistemi, Kök Hücre, Biyomateryaller, Rejenerasyon

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INTRODUCTION

Peripheral nerve injuries can arise from accidents, trauma, or infections, and may lead to intense neuropathic pain, sensory impairment, and partial or complete loss of motor and autonomic functions depending on the type of injury. To reduce or eliminate these losses, researchers have conducted studies to enhance the quality of life of patients (1). Regeneration of the peripheral nervous system (PNS) has been a central research focus, yielding promising results. One of the defining characteristics of the peripheral nervous system (PNS) is its capacity for regeneration, which sets it apart from the central nervous system (CNS). Moreover, nerve regeneration occurs in target organs (2). Schwann cells (SC), which are associated with peripheral nerves, support repair in many tissues and contribute to regeneration through their migratory abilities (3).

The regeneration of fibers in the peripheral nervous system (PNS) allows for the repair of damaged nerves and restoration of their lost functions. This review discusses the structure of scientific research on the regeneration process and current treatment mechanisms involved. It examines the role of biomaterials and stem cells in the treatment of peripheral nerve injuries. It also considers potential future treatment methods for peripheral nerve regeneration.

Central and Peripheral Nervous System: Basic Differences

The human nervous system or neural network is a system consisting of two parts: the CNS and PNS. Glial cells support neurons. Each neuron connects to other neurons to process sensory information and respond to signals. The CNS consists of the brain and spinal cord, whereas the PNS is a cranial, spinal, and peripheral nerve network. Neurons and glia are cells found in CNS and PNS. Neurons generally consist of three main parts: perikaryons, also called cell body, dendrite extensions extending from the perikaryon and supported by microtubules, and axons (4,5,6). The neurons were classified according to the number of extensions that emerge from their bodies (Table-1).

Glial cells are cell types that can proliferate and provide mechanical support to neurons. They are also involved in nutrition, myelin sheath formation, and protection. There are different types of glia in the CNS and the PNS. Neuroglia in the CNS are called central neuroglia and glia in the PNS are called peripheral neuroglia and are classified as follows (7,8) (Table-2).

Table-1. Classification of Neurons According to the Extensions Protruding from Their Body (8)

TYPES OF NEURON	NUMBER OF AXON	NUMBER OF DENDRITE
Multipolar Neuron	It has a single axon.	It has two or more dendrites.
Bipolar Neuron	It has a single axon.	It has a single dendrite.
Pseudounipolar Neuron	They have a single extension extending from the perikaryon region, one end extends to the peripheral ending and the other to the CNS.	
Anaxonic Neuron	It does not have a true axon. It has multiple dendrites. They do not produce action potentials; they regulate the electrical impulses of their neighbouring neurons.	

Table-2. Classification of Neuroglia.

CENTRAL NEUROGLIA	PERIPHERAL NEUROGLIA
Astrocytes	Schwann cells
Oligodendrocytes	Satellite cells
Ependymal cells	Enteric Neuroglias
Microglia	Teloglias

Astrocytes in the CNS are the largest neuroglial cells and have star-like cytoplasmic extensions. They play a role in forming the blood-brain barrier, substance transport, and neurogenesis (8,9). Oligodendrocytes are involved in myelin sheath production in the CNS. It is also known that these neuroglial cells provide nutritional support for neurons (8,10). Ependymal cells are neuroglial cells involved in the production of cerebrospinal fluid (CSF) and they line the canalis centralis in the spinal cord. Ependymal cells, which are ciliated epithelial glia, are involved in brain homeostasis and metabolism (8,11). Microglia are the smallest glial cells and although they are structurally different, they resemble macrophages in their antigen presentation and phagocytosis functions; they are small neuroglia involved in neuroinflammation and defense (8,12).

SCs, similar to oligodendrocytes, which are responsible for myelin sheath formation in the CNS, these cells are also responsible for myelin sheath formation in the PNS. Glia is responsible for the protection and nutrition of axons (8,13). Satellite cells, as the name suggests, form a microenvironment surrounding neuronal perikaryons and provide electrical insulation. In the context of enteric neuroglia, it is known that these cells play a role in maintaining homeostasis and regulating digestive-related muscles associated with neurons in the ganglia of digestive organs within the autonomic nervous system (8,14,15). The teloglia is a neuroglial cell type that covers the nerve terminal at the end of the motor nerve fiber (8).

CNS and PNS are two parts of the vertebrate nervous system. There are differences between the cells of these systems and some of the tasks they fulfill. The CNS consists of the brain and spinal cord, while the PNS includes other nerves in the body - the nerves to the internal organs and the nerves to the limbs. The CNS is an information-processing mechanism that performs high-level neural activities such as memory and thinking. The peripheral neural network transmits signals and information generated by CNS activity to various parts of the body, as well as information generated by sensory activities such as touch and vision to the CNS. Both systems have glia with similar functions that provide support to neurons. With these similarities and differences, these two systems work interactively, providing neural control in the body and constituting the nervous system (16).

Peripheral Nerve Structure and Function

The peripheral nerve consists of a ventral and a dorsal root, each of which originates from the spinal cord. It contains both the motor and sensory neurons. The nerve fibers in the PNS come together in bundles and form nerves. This nerve organization includes axons and SC. The outer layers of these cells contain reticular fibers, fibroblasts, and capillaries. Together, these structures form the endoneurium, which is the innermost layer of the peripheral nerve. The perineurium layer surrounds the nerve fibers and regulates the microenvironment of the fibers. The outermost layer of the nerves is the epineurium, which protects the nerve fibers by holding them together. Myelinated and unmyelinated fibers are present between these nerve fibers. The myelin sheath is a structure consisting predominantly of lipids that enable faster transmission of impulses in the nervous system. The conduction velocity in unmyelinated fibers is very low compared to that in myelinated fibers. PNS is divided into two as autonomic and somatic nervous systems. The autonomic nervous system is also divided into two parts as sympathetic and parasympathetic and these systems work together to regulate the involuntary functions of the internal organs and provide homeostasis, while the somatic nervous system controls voluntary responses that regulate muscle movements as well as sensory perception (6,17,18).

PNS establishes a connection between the CNS and the systems of the body. This communication occurs through the afferent and efferent fibers. While afferent fibers carry signals to the CNS, efferent fibers carry impulses from the CNS to the target organs. Depending on the direction of these impulses, sensory and autonomic ganglia function. The ganglia are oval structures that transmit signals to the nervous system. The PNS is a complex neural network system responsible for sensory transmission and motor function, control of reflexes, digestion of nutrients and regulation of respiration, control of smooth muscles, and regulation of homeostasis by working together with the CNS with all these structures (6,18,19) (Figure-1).

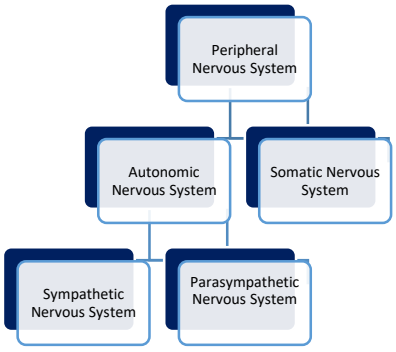

Figure-1. Peripheral Nervous System Subdivisions

Regeneration and Treatment of Peripheral Nervous System Injury

Peripheral Nerve Injury and Regeneration Process

Peripheral nerve injury is a common and life-threatening process that can occur as a result of traumatic situations and injuries such as traffic accidents, nerve compression, inflammation, and exposure to toxic chemicals such as alcohol and cigarettes. The incidence of peripheral nerve injuries in the community ranges from 13 to 23 per 100,000 people. A decline in the quality of life experienced by individuals with peripheral nerve damage has a detrimental impact on both the patient and their relatives, resulting in material and moral loss. In later periods, this nerve damage may result in loss of function (17,20,21).

Now, robust regeneration mechanisms of peripheral nerves have become operational. Zhang et al. delineated the peripheral nerve repair process into two phases: the remodeling of the organs by the CNS through the repaired peripheral nerve and the backward remodeling of the distal target organs by the CNS through the repair of the peripheral nerve. The regeneration process is initiated by phagocytosis of substances that cause nerve degradation by SC and macrophages. In the peripheral nerve, regeneration occurs from the proximal end to the distal end. Macrophages stimulate SCs for nerve growth by producing interleukin-1 (IL-1). SC are involved in axonal sprouting during regeneration. In this respect, SCs are an essential element in peripheral nerve regeneration (5,22).

During the process of peripheral nerve damage and repair, we encountered a condition called Wallerian degeneration. Wallerian degeneration refers to the degeneration of the distal part as a result of the destruction of axons and is defined as one of the basic reactions in the PNS. This degeneration process generates an inflammatory response associated with the upregulation of signaling molecules such as cytokines and chemokines during the regeneration process (23,24).

Growth factors (GFs) are some of the molecules commonly involved in peripheral nerve regeneration. GFs are involved in various biological activities, especially tissue repair by regulating cellular communication and are protein molecules that provide cell growth and division. GFs are directed to the damaged area through various nerve guide channels (NGCs), and axon regeneration in the degenerated area is triggered by the long-term, controlled release of GFs at adequate concentrations. Considering the wide variety of studies conducted, growth factors such as vascular endothelial growth factor (VEGF), nerve growth factor (NGF), and neurotrophic factors from bone morphogenetic proteins (BMPs) increase peripheral nerve regeneration capacity. In this process, various signaling pathways are effective in supporting the survival of neurons and the regeneration process. In some of these pathways, the PI3K/Akt signaling pathway comes first and plays a role in regulating cell proliferation, structural and morphological changes, migration, and apoptosis. The MAPK/ERK signaling pathway is involved in axon growth and myelination of regenerating axons, whereas the JNK/c-Jun signaling pathway can also be induced by growth factors and is involved in the plasticity of axons with remyelination (25).

Laminin and fibronectin, called neurite promoting factor (NPF), are glycoprotein molecules that have a positive effect on growth in the regeneration zone. NPF molecules are found in the basal lamina of the SC, as in laminin, and adhesion molecules such as neuron adhesion molecule (NCAM) and N-cadherin, found in the membrane of the SC, have positive effects on the regeneration process (5,25). Additionally, different transcription factors are expressed following peripheral nerve injury. Transcription factors are regulatory protein molecules that mediate the transcription of the genetic information of DNA into RNA by interacting with various proteins and enzymes. As stated by

Zhang et al., the transcription factors known to affect regeneration are as follows:

Klf4 and c-Myc, when examined in mouse retinal ganglion cells (RGC), it was reported that Klf4 deficiency induced regeneration of the damaged sciatic nerve and c-Myc expression in the damaged optic nerve accelerated axon growth. After sciatic nerve injury, the expression of the c-Jun transcription factor increased in motor and sensory neurons, suggesting that it plays a role in the recovery of motor functions and is also an inducing force in SC reprogramming. It has been reported that the Krox-20 transcription factor is involved in the myelination process of peripheral nerves and is an initiator of SC reprogramming (25).

Current Treatments Used in Peripheral Nervous System Injuries

PNS injuries are traumas with severe damage and high persistence and are very difficult to treat. The most important reason for the difficulty in the successful repair of PNS injury is the very slow healing rate (26). Research on the development of different treatment methods and tools has been focused on the fact that post-traumatic damage in the PNS is financially challenging and can relieve the person in terms of spirituality. For example, studies on GFs, microsurgery, autograft and allograft therapies, NGC, neural stem cells, and SC, and the use of one or a combination of the two are being conducted. In none of the studies conducted to date, a treatment method that is expected to be effective in a way that will not cause financial difficulties to the individual and in addition to this, will completely eliminate the damage that has not been developed (27).

Re-functionalization of the PNS damage depends on many distinct factors such as the localization and size of the damage, the patient's condition, damage to the nerve cells, and the recovery capacity of the nerves are important in the choice and process of treatment (28).

Currently, the most widely accepted method is microsurgery, but the disadvantage of this method is that it cannot prevent degeneration in neural conduction bundles because it cannot reduce the production of neurotrophic factors and does not guarantee functional recovery. Which approach is chosen among microsurgical applications is important and several factors determine this choice, such as the condition of the trauma, experience of the surgeon, patient-specific conditions (age, condition, etc.), and suitability of the trauma for treatment (27). If the gap in the nerve bundle is 1 cm or more, autologous or allogeneic nerve transplantation is performed to assist the microsurgical procedure; autologous nerve transplantation is more preferably used in PNS injury and is performed through SC and GF (29). Another procedure is to suture the two nerve endings from beginning to end, and this method attracts more attention from researchers owing to its more favorable clinical results. The most fundamental problem in allogeneic nerve transplantation is that the desired response cannot be obtained because of the rejection of the immune system. Although various immunomodulators have been used to eliminate immune system rejection, effective results have not been obtained (30).

The use of stem cells as another treatment method is common. It is generally aimed at supporting the nerve regeneration process in damaged areas by planting stem cells in appropriate polymers. Polymers are preferred owing to their high biocompatibility. Polypyrrole is the most preferred and widely studied polymer. Along with stem cells, neurotrophic factors and neural progenitor cells are also used because they have a positive effect on nerve regeneration owing to the improvement of action regeneration (26).

Some pharmacological treatment methods (4-aminopyridine (4-AP), erythropoietin and steroid hormones are some of the drugs mentioned) have been reported to improve myelination and nerve regeneration in peripheral nerve damage, but there are no clinically approved drugs (28).

The role of SC in nerve regeneration is to contribute to nerve regeneration resulting from peripheral damage by cooperating with stem cells and thus helping to repair peripheral nerve damage (31). SC is important for creating a suitable regeneration environment after peripheral damage by producing neurotrophic factors and for the regeneration of damaged axons (32). In addition, studies have shown that SC is a good option for the elimination of damages caused by surgical applications (31). Finally, the use of SC and various stem cells together in PNS damage is considered a promising approach in terms of bringing a different perspective to existing treatments or creating a new treatment process (33).

In conclusion, the most appropriate treatment for patients with peripheral nerve injury is the one that best suits the individual's condition. Although various treatment modalities are currently available, there is still no adequate and definite treatment modality that can obtain a definite result, because every treatment cannot be applied to every patient.

Stem Cells and Peripheral Nervous System

Stem Cell-Based Treatment Strategies

Stem cells possess the capacity to self-renew and differentiate into specialized cells. The primary rationale for utilizing stem cells in PNS injuries is to facilitate the generation of new cells to replace those that are dysfunctional or stimulate regeneration in the degenerated area. After repair, axonal regeneration at the distal end of the nerve requires a biochemically appropriate environment and the most suitable structure for this environment is the SC (34). The repair process progresses differently depending on the damage in the PNS. SC and mesenchymal stem cells are accepted as appropriate for treatment (17). It has been found that the increase or decrease in the proliferation of SC is effective in the repair of axons and it has been observed to be effective in the repair of large gaps in the distal nerve end denervation and proximal injuries in peripheral nerve damage (34). As a result of recent studies, the importance of SC in nerve autograft studies has been emphasized and alternative methods have been found (29).

Stem cells are used in tissue and bioengineering-based applications and are one of the most frequently preferred treatment methods for various diseases and PNS injuries, which are also the focus of this review. Utilizing the properties of stem cells, repair and regeneration of nerve damage and migration of new stem cells to the damaged area or target area are the main methods for the treatments used and current therapies are shaped around these abilities.

Stem Cell Types and Applications to Peripheral Nervous System

Stem cell types to be used in treatment methods can be obtained from different tissues and organs and are suitable for specific use. The source of the stem cells used in these applications varies due to the use of patient-specific treatment methods, considering the damage that each patient has and the size and location of the damage. When transplanting stem cells to patients, they can be used with different biomaterials with high biocompatibility.

This review examines the various types of stem cells employed in the treatment of PNS injuries, their respective applications, and the relationship between stem cells and SCs.

Neural Stem Cells

Neural stem cells, which are the primitive cells of the nervous system and can differentiate into neurons and neuroglial cells, are stem cells that should be used in PNS injury. These are the most important sources of nerve regeneration (35). The subventricular and subgranular regions in the brain are the primary sites of neural stem cells (34). Various studies have shown that the implantation of neural stem cells into PNS damage has favorable effects (34). It has been observed that neural stem cells transplanted into damaged areas of the peripheral nervous system can differentiate into nervous system cells, including neurons and SC-like cells (35). They promote angiogenesis by synthesizing the trophic and growth factors required for nerve regeneration. They also repair and support nerve growth and myelination (35).

Stimulated/Induced Pluripotent Stem Cells (iPSC)

Although iPSCs are very similar to embryonic stem cells, they have some differences (34): they can differentiate into different cell lines, whereas undifferentiated iPSCs can differentiate into many different cell types, including myelinated SC and neural crest stem cells. The addition of iPSC to NGC enhances the recovery of the nerve gap and axonal growth (35).

One of the disadvantages of iPSC is that they may cause malignancy; since they originate from somatic cells, they may have epigenetic memories of these cells, which may make them more malignant (34,35).

Mesenchymal Stem Cells (MSCs)

The therapeutic use of MSCs for nerve regeneration is intensive. MSCs are multipotent stem cells derived from various tissues. The tissues from which they are obtained include the umbilical cord, bone marrow, dental pulp, and Wharton's jelly (36). Allogeneic transplantation is

possible in PNS damage because of their characteristics such as easy isolation and lack of differentiation (31). The repair capability of MSCs not only in PNS injury but also in cardiovascular disorders, neurological diseases, bone repair, etc. is preferred in terms of providing support to the treatment process (30). Simultaneously, because of their ability to synthesize neurotrophic factors, self-renewal, differentiation into cells such as SC, and migration, MSCs are one of the factors supporting regeneration in tissue damage, which causes them to play an important role in peripheral nerve damage (31).

In addition, mesenchymal stem cells can adhere to plastic and because of this ability, they are frequently used in studies using NGC made of polymers. These studies were usually performed by damaging the sciatic nerve in rats. Stem cells combined with appropriate GF were added to the surface of the NGC and placed in the damaged area to support the regeneration of the two ends of the cut nerve by stem cells.

Orofacial Stem Cells

The origins of orofacial stem cells vary; dental pulp, deciduous teeth, and gingiva are some of them and they are isolated from these tissues. Orofacial mesenchymal stem cells (MSCs) are multipotent stem cells that exert immunomodulatory effects. Orofacial stem cells share a common embryonic neural crest origin and form orofacial tissues by preserving certain features of neural cells. Some mesenchymal stem cells are a source of orofacial stem cells (29).

The relationship between orofacial stem cells and PNS damage is that orofacial mesenchymal stem cells express neurotrophic factors such as brain derived neurotrophic factor (BDNF) and nestin at higher rates that other MSCs and it is easier to differentiate into nerve cell types because they originate from neural cells. In this case, it shows us that orofacial MSCs are more suitable for use in regeneration-based treatment methods than other MSCs for PNS damage (29).

Mesenchymal Stem Cells Derived from Bone Marrow

Mesenchymal stem cells obtained from bone marrow can differentiate from all three embryonic layers - ectoderm, mesoderm, endoderm - and synthesize neurotrophic factors, myelin basic protein, and GF differentiate into SC-like cells and participate in nerve regeneration for repair. One disadvantage of this method is that it is painful. In studies performed in combination with bone marrow stem cells, repair was faster because of the presence of bone marrow stem cells (37). At the same time, when compared with other stem cell sources, proliferation and differentiation ability is less, and stem cell potential is low (34).

Olfactory Mesenchymal Stem Cells

Olfactory mesenchymal stem cells are a type of mesenchymal stem cell that originates from the ectodermal germ layer and the neural crest, moreover they are easily collected due to their location in the nasal cavity (38). The biggest difficulty in the use of MSCs is collecting them from the anatomical niches where they are located, but this is not the case for olfactory mesenchymal stem cells due to their anatomical location. Olfactory mesenchymal stem cells are capable of immune modulation and can stimulate and modulate trophic factors required in damaged tissues (39).

Although there are a limited number of studies on olfactory mesenchymal stem cells *in vivo*, these stem cells have been shown to have therapeutic potential in neurodegenerative diseases and the treatment of spinal cord injury (38).

Mesenchymal Stem Cells Obtained from Umbilical Cord and Cord Blood (UC-MSCs)

Stem cell harvesting from the umbilical cord (UC) raises ethical questions because it is difficult to use and access. However, UC-MSCs have greater proliferation and differentiation capacity than MSCs, and studies using UC-MSCs have shown increased axon regeneration after PNS injury (30).

Cui et al., collagen nerve conduit and UC-MSCs were combined and used to stimulate regeneration in the damaged area of artificially induced sciatic nerve injury in dogs and as a result of the experiment, it was observed that the damage to the sciatic nerve positively affected regeneration (30).

Mesenchymal Stem Cells Derived from Gingiva and Dental Pulp

They can be isolated from various tooth tissues (dental pulp, gingiva, papilla, deciduous teeth,

etc.). Dental pulp stem cells (DPSC) obtained from molars do not cause some ethical controversies as in the harvesting of some stem cells (27), and they have higher immunomodulation and self-renewal abilities than other types of stem cells; therefore, they are used as an alternative source in studies in the field of regenerative medicine (36). They are multipotent stem cells originating from the neural crest, which demonstrate their capacity to undergo neurological differentiation when exposed to environments different from normal (27).

Recent studies have found that human DPSCs can differentiate into neural progenitor cells, which in turn can differentiate into SC-like cells. DPMSCs have also been found to support regeneration and repair in conditions such as spinal cord injury and nerve damage (36).

Adipose Stem Cells

Adipose stem cells have generally been found to have similar characteristics to bone marrow stem cells (40). They represent another source of multipotent stem cells capable of differentiating into all three germ layers (37). Since they are derived from the stroma of adipose tissue, their accessibility is high, they can be collected at higher rates compared to bone marrow stem cells, and their differentiation and proliferation abilities are considerably higher compared to other MSC types (17). Neurons and SC-like cells are produced from differentiated adipose stem cells and some studies have found that adipose stem cells may be as effective as autologous SC (34).

Stem Cells Derived from Skin and Hair Follicle

Skin-derived stem cells are found in the dermis and are multipotent, whereas stem cells derived from hair follicles are easily accessible pluripotent stem cells. Skin stem cells are very similar to neural crest cells and express significantly with SC when cultured with neuregulin, which is known to promote the proliferation and differentiation of SC (34).

Hair follicle stem cells originate from the neural crest and the follicle contains nestin, which stimulates the production of neural progenitor cells that can differentiate into neurons and neuroglial cells. In very few studies, undifferentiated hair follicle stem cells were used in sciatic nerve injury, and it was observed that they differentiated into SC-like cells and participated in myelination (34).

Clinical Studies

Current (Experimental) Clinical Research and Findings on Biomaterials and Stem Cells in PNS Damage

Due to the decrease in the quality of life of patients with peripheral nerve damage and the occurrence of great material and moral losses, researchers have intensified studies on the repair and regeneration of peripheral nerve damage in recent years. The development of new materials and methods with advancements in science has increased the belief that promising treatments can be realized.

In a study conducted by Berrocal et al. in 2013 on the repair of peripheral nerve defects in rats, a collagen tube with the SC was used to successfully close long segmental gaps in the PNS. When we examined the findings of the study, it was found that in the group with collagen tubes, axons grew and extended to distal nerves. Thus, they stated that directing the SC to the nerve defect through a collagen channel realized nerve repair and that the repairable distance increased, and that they took the first steps in the use of the SC in peripheral nerve repair (41).

A clinical study conducted by Bozkurt et al. in 2014 evaluated the use of nerve guides in the proximal medial sural nerve biopsy model. In this study, a micro structured nerve guide (Neuromaix) was used. It was reported that regenerating axon clusters were formed in all 11 patients included in the study, and this model was proposed as a valid technique for reproducible peripheral nerve-guide evaluation in humans (42).

In 2018, Saeki et al. conducted a clinical trial to test the efficacy of new collagen channels filled with collagen filaments in patients with peripheral nerve injuries. Of the patients included in the study, 49 underwent artificial nerve tract grafting and 7 underwent autologous nerve grafting. Postoperative improvement in sensory function was found in 21 patients in the artificial nerve tract graft group and in 4 patients in the autologous nerve graft group. Collagen plays an important role in nerve regeneration by forming epineural and perineural sheaths, suggesting that an artificial nerve pathway graft is a suitable

alternative to autologous nerve grafts for peripheral nerve injury (43).

In 2018, Neubrech et al. investigated the role of chitosan nerve tubes in the healing of sensory nerve lesions in the hands. These studies concluded that the additional use of chitosan nerve tubes for primary nerve repair in digital nerve lesions enhances nerve healing and is effective in increasing sensory peripheral nerve regeneration ability as a result of tactile gnosis and sensitivity tests (44).

In a 2022 study by Dastagir et al., the effectiveness of nerve guides in healing the sural nerve was investigated. The results showed that patients with vascular grafts had better lateral foot sensitivity regeneration compared to those without, leading to the conclusion that distal sural nerve biopsy can serve as a model for evaluating peripheral nerve regeneration (45).

Comparative Analysis of Treatment Approaches

Here the provided table explains a comparative analysis of various treatment approaches, highlighting key data on the effectiveness and side effects of each method. This information enhances our understanding of the differences between treatment options (Table-3).

Table-3. Various Biomaterials Used in Peripheral Nerve Injury.

Living Organisms Used in the Study	Material	Method	Conclusion
Fischer Rat	A collagen tube filled with SC	Through an incision made on the right iliac crest, the nerve part was resected to create a gap, and the NeuroGen tube was added.	Increase of the repairable distance between the two ends of the damaged nerve (41).
Human	Neuromaix, a nerve guide prepared for peripheral nerve defects	Nerve biopsy and placement of Neuromaix between nerve endings	A reproducible model has been suggested with the formation of regenerating axon clusters in patients (42).
Human	New collagen channels filled with collagen filament	Artificial nerve graft was applied to the patients and compared with patients who had autologous nerve grafts.	It has been stated that collagen offers an alternative treatment for peripheral nerve regeneration with its ability to repair peripheral nerve sheaths (43).
Human	Chitosan nerve tube	The efficiency of using a chitosan nerve tube in the sensory nerve lesion healing process was investigated with sensitivity and tactile gnosis.	It has been observed that the additional use of chitosan nerve tubes increases nerve healing (44).
Human	Vascular graft	A sural nerve biopsy was performed, and sensory tests were performed by placing the proximal and distal nerve endings into a vascular graft.	According to sensory test results, it has been reported that there is an increase in lateral foot sensitivity and better regeneration in patients in whom vascular grafts were used (45).
Human	Hyaloglide, a cross-linked and biocompatible hyaluronan gel	A microsurgical procedure was performed on the peripheral nerves in the hand and the gel was applied intraoperatively along the damaged nerve.	The application of hyaloglide supported the regeneration of nerve tissue and enabled the healing of lesions by creating a favorable microenvironment (46).

Limitations

Challenges in Research and Practice: Limitations of Current Treatment Methods

Every study brings along ethical and economic debates regarding its results. In studies of stem cells, the methods of obtaining stem cells are the most frequently discussed ethical issues. It is thought that expanding the field of study by considering the rights of individuals in ethical issues will bring discoveries and treatment methods. This situation obliges scientists who do not want to experience ethical conflicts to look for alternative ways and sometimes these alternative ways may force the research group economically. By increasing the budget allocated to scientific experiments, new scientific studies can be added to the literature by expanding the working areas of research groups and facilitating their access to materials. In addition to all these, another limitation is to ensure biocompatibility in biomaterial-based studies. Researchers expect that biomaterials produced from the polymers used in their studies, such as NGC, can become fully biodegradable in the living body after completing their function. However, no definitive solution has been found in current studies.

Conclusion and Expectations

Overview of Innovative Treatment Approaches

Peripheral nerve damage has severe and difficult consequences and affects the health of a living person physically and mentally. Many scientists have conducted various studies to reverse this situation. Scientists are working on current treatment methods such as stem cell therapy, biomaterials, and the combined use of stem cells and biomaterials. As we have frequently stated in the review, different perspectives should be added to current treatments with combinations that consider the patient's condition and damage. The diversity of treatment methods is important in terms of not having the same needs and damage for each patient.

Future of the Field and Possible Developments

Significant advances will be made in the field of peripheral nerve repair shortly. Furthermore, the increasing utilization of *in silico* studies, such as molecular docking, will facilitate the development of novel approaches to repair and regeneration, which will not only complement surgical interventions but also enhance the efficacy of existing pharmacological agents. Consequently, treatment of peripheral nerve injury may be a more straightforward endeavor. However, it is postulated that the efficacy of these treatments will be optimized if they are tailored and specific.

ADDITIONAL SECTION

Firstly, literature databases such as PubMed and WoS (Web of Science) were searched for the last 10 years (2014-2024) by typing '*peripheral nerve injury, current treatments', 'stem cells and peripheral nerve injury treatment', '(name of the relevant stem cell) and peripheral nerve injury'* and the appropriate articles were taken as reference.

Abbreviations Used in the Review:

PNS: Peripheral Nervous System

CNS: Central Nervous System

SC: Schwann Cell

CSF: Cerebrospinal fluid

GF: Growth factor

NGC: Nerve Guide Channel

VEGF: Vascular endothelial growth factor

NGF: Nerve growth factor

BMP: Bone morphogenetic protein

NPF: Neurite promoting factor

NCAM: Neuron adhesion molecule

RGC: Retinal ganglion cell

PPy: Polypyrrole

iPSC: Induced Pluripotent Stem Cells

MSC: Mesenchymal Stem Cells

BDNF: Brain Derived Neurotrophic Factor

UC: Umbilical cord

UC-MSCs: Mesenchymal stem cells obtained from umbilical cord and cord blood

DPSC: Dental Pulp Stem Cells

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Ethical Approval

This article does not contain any studies on human or animal subjects.

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Availability of Data and Materials

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