Treatment of Peripheral Nerve Injury using Mesenchymal Stem Cells

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Abstract

Due to the changing lifestyle in modern times, peripheral nerve injuries (PNI) are becoming more and more common and can arise from trauma, medical diseases, and even sports injuries. Healing these injuries is a prolongned and challenging process. Studies show different PNI rates; lifetime rates range from 2-3% to higher estimates of 13-23 cases per 100,000 people. Six million sciatic nerve injuries in children aged 2020 to 2022 were reported in Pakistan. Although surgery, physical therapy, nerve grafting, and amputation are among the present PNI therapies, these approaches are not always totally successful and may have side effects. Based on degree, PNI can be categorized as follows: nerve entrapment, axonotmesis, and neurotmesis. Recent developments point to mesenchymal stem cells (MSCs) being used in treatment because of their ability to regenerate nerves. Moreover, important for nerve regeneration are neurotrophic elements, which help axon development and microcirculation. Through regeneration and immunomodulation, MSCs show potential in treating PNI; yet, further study is required to fully understand their effects and uses in nerve injury recovery. This book chapter aims at summarizing peripheral nerve injury, its complexity, fuctional damage and the use of mesenchymal stem cells for treating periphaeral nerve injury.

Keywords: Neurotmesis, Nerve regeneration, Schwann cells, Wallerian degeneration, Neurotrophic factors

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Introduction

The fast pace of life in recent years has made peripheral nerve injury (PNI) a major issue. Trauma, accidents, medical disorders, heredity, or signs of other diseases can all be causes of peripheral nerve degeneration (Lopes et al., 2022). Structural problems, natural disasters, conflict, sports injuries, and electric shock can all cause peripheral nerve damage. Because they are complex and time-consuming, PNIs are complex and their healing is time-consuming and challenging. Important aspects of peripheral nerve regeneration are myelin regeneration, axon length, electrophysiological characteristics, Schwann cells, and nerve fibers (Chu et al., 2022). PNI is well-known for its sophisticated care environment targeted at helping patients and their families manage pain, disability, mental illness, life expectancy, hopelessness, and stress (Alvites et al., 2018).

Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic option for PNI due to their unique regenerative capabilities and low immunogenicity. MSCs can be sourced from various tissues, including bone marrow, adipose tissue, and umbilical cord, and possess the ability to differentiate into Schwann-like and neuronal-like cells as shown in figure 1, which are essential for nerve repair. These cells promote axonal regeneration and functional recovery through multiple mechanisms, such as secreting neurotrophic factors, extracellular matrix molecules, and pro-angiogenic factors that create a favorable microenvironment for neuronal survival and growth. Additionally, MSCs modulate immune responses by regulating cytokine expression and macrophage polarization, reducing inflammation at the injury site. Advanced strategies like genetically engineered MSCs, MSC-derived exosomes, and their integration into nerve conduits have further enhanced their therapeutic potential. Despite these advancements, challenges remain in standardizing MSC extraction, cultivation, and application methods to ensure consistent clinical outcomes

PNIs have a somewhat noteworthy frequency. Different research and approximations yield different PNI statistics and prognostic variables. According to earlier studies, PNI has a lifetime incidence between two and three percent (Martyn and Hughes, 1997). Other studies project 13–23 per 100,000 persons as the PNI prevalence (Hicks and Selvin, 2019). A study particular to Pakistan claims that in 2020–2022 there were 6 million cases of sciatic nerve injury in children (Dave et al., 2025). PNI affects 1–3% of trauma accident sufferers. The shifting PNI data emphasize the relevance of this disorder and the requirement of efficient therapy to guarantee recovery and return to life.

Common treatments for peripheral nerve injuries include surgery, physical therapy, nerve grafting, amputation, limb transplantation, prosthetic limbs, and nerve grafting. All of these treatments have various advantages and disadvantages, but none is 100% effective (Xu et al., 2024). Surgery and suturing lead to the formation of fibrous scar tissue, suture debris, and tissue damage material at the wound site. Other treatments have disadvantages such as organ loss, tissue rejection, organ rejection, toxicity, and immune rejection (Santosa et al., 2020). New strategies that provide enhanced nerve repair and regeneration, such as the use of allografts, mesenchymal stem cells, and biomaterials with minimal side effects, are urgently needed.

Treatment and recovery are closely related to the type of injury, the degree of nerve damage, the extent of the injury, and the nature of the muscles and joints involved (Hussain et al., 2020). For example, in the case of high-energy traumatic injuries, recovery is negatively affected by the severity of the injury. Swelling, scar tissue formation, and adequate axonal and Schwann cell regeneration occur. Neurovascular expansion therapy for space-occupying wounds may have several limitations, including biological complexity, donor site morbidity, short graft distribution, and the need for multiple procedures (Gervois et al., 2016).

From a regenerative medicine perspective, mesenchymal stem cells are used to treat PNI because of their ability to differentiate into neural stem cells (Levorato et al., 2021). This therapeutic approach has the potential to improve treatment outcomes and improve quality of life. Sources of mesenchymal stem cells include adipose tissue, bone marrow, amnion, peripheral blood, cord blood, and muscle (Jiang et al., 2017). All mesenchymal stem cells require proper evaluation and classification before use. This chapter provides an overview of the basics of peripheral nerve injury by mesenchymal stem cells and their use and future efficacy and outcomes.

The main objectives of this book chapter covers a reviewing of PNIs and their treatment using mesenchymal stem cells, prognosis, functional outcomes and limitations.

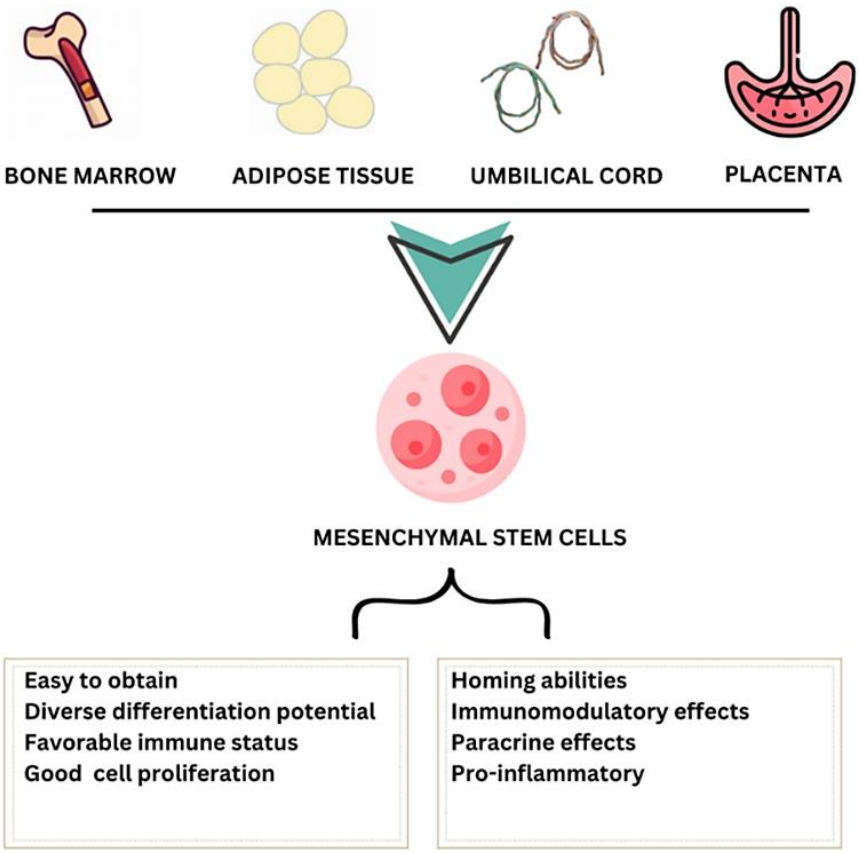

Fig. 1: Derivation and properties of MSCs

What is PNI?

PNI can be defined as any damage to a peripheral nerve that impairs its ability to function. Distal limb atrophy is due to decreased PNI because connections between damaged nerve fibers and organs are negatively affected and sometimes completely lost (Yousefi et al., 2019). Major injuries almost always involve PNI in 1%-3% of patients. The condition has been identified in children who have fallen, as a side effect of treatments such as radiation, chemotherapy, and surgery, and sometimes as a contributing factor to chronic diseases such as cancer and diabetes. PNI can also arise as an iatrogenic injury. Three primary types of conditions lead to PNI: transection, tension, and compression (Brull et al., 2015). Transection is commonly caused by penetrating trauma, tension occurs when the nerve is excessively stretched, and compression can be resolved if the underlying cause of the injury is addressed within eight hours.

Anatomy and Classification of Peripheral Nerve Injury

Neurologists and physicians classify spinal injuries, especially severe ones, into different categories, or schools, to aid in diagnosis and treatment. In 1943, Sir Herbert Seddon developed a classification system based on injury severity, recovery time, and extent of injury, which described three types of injury: nerve entrapment, axonotmesis, and neurotmesis (Warwick et al., 2010).

Neuropraxia (type I) is a rare type of nerve damage that usually results from nerve injury or ischemia. In this case, nerve fibers are blocked at the site of injury, resulting in loss of movement and sensation, while all morphological components of the nerve (including the endoneurium, perineurium, and epineurium) are affected (Fehlings et al., 2016). Since the axon remains connected to the cell body, Wallerian contraction does not occur. Recovery of neurologic function and function is usually rapid, although the time frame may vary from hours and days to weeks or months.

Axonotmesis (Type II) represents a severe injury to a peripheral nerve, usually caused by compression, stretching, or compression (Grant, 2023). In this case, the epineurium remains intact, whereas the perineurium and endoneurium may be damaged. The axon is separated from the cell body, resulting in damage to the axon and its myelin sheath, and Wallerian degeneration of the distal axon stump occurs within 24-36 hours after injury. Visual and motor impairments were observed, and nerves were unable to reach the site of injury (Fox et al., 2017). The surrounding matrix helps the axons remain continuous with the underlying tissue and allows for repair if the damaged nerve stump remains attached to the tissue. The diagnosis of axotomy is greatly influenced by the proximity of the tumor to the target organ. However, self-renewal is rare and requires appropriate treatment.

Neurotmesis (stage III) is caused by nerve entrapment or neurotoxins and is the most severe type of nerve injury. In a neurotome, the entire nerve trunk, including the endoneurium, perineurium, and epineurium, is completely severed. This damage can lead to the destruction of axons, myelin, and connective tissue and can significantly affect cognition. In 1951, Sunderland expanded Seddon's classification (particularly axonal loss) to five levels (Sheaths, 2021). Sunderland grade 1 injuries represent the mildest type of nerve injury, similar to the Seddon nerve. Sunderland diseases 2, 3, and 4 are similar to Seddon axonotmesis. In Sunderland grade 2 injuries, the endoneurium, perineurium, and epineurium are intact despite damage to the axons. Sunderland grade III injuries involve axotomy at the site of injury with loss of continuity of the endoneurium and perineurium. In a Sunderland type IV injury, only the epineurium is intact, whereas the axon, endoneurium, and perineurium are damaged. Sunderland's type V injury met Seddon's definition of neurotmesis, a severe traumatic injury characterized by complete loss of neurological function resulting in complete transection (Radic et al., 2018). Large nerve root injuries with wide gaps require nerve grafting rather than nerve resection to avoid severe compression.

Changes at the Molecular and Cellular Level

Several changes occur at the cellular and molecular level following PNI. In severe transection injuries due to penetrating trauma, pathological changes occur in the damaged proximal and distal nerve trunks. Damaged axons undergo "Wallerian degeneration" at the distal stump, transforming into granular debris that is eventually cleared by macrophages. While activated Schwann cells switch to a regenerative phenotype and proliferate in the distal stump to form longitudinal columns known as "Büngner bands" that are important for guiding growing axons, the proximal stump also first returns to the nodes of Ranvier before attempting to reach the distal stump by releasing the growing axon (Wang et al., 2019). The slow rate of axonal regeneration, which varies by region but is usually expressed as 1 mm/day, almost always defeats this process and results in a lack of active SC force, abnormal axons, and target organ attenuation due to long-term axonal loss. - the term axonal loss remains within. However, the above events and the secretion of neurotrophic factors by SCs create an ideal environment for axonal sprouting.

Treatment Methods

The gold standard approach to treating transection injuries involves surgical fusion of the proximal and distal nerve stumps. However, a nerve graft or nerve conduit is required to bridge the gap if the gap is too large to repair without nerve fiber extension. Cell transplantation has been proposed in recent years as a way to enhance peripheral nerve regeneration (Lam and Leung, 2024). As mentioned earlier, SCs activated in response to nerve injury are critical for Wallerian degeneration and the development of Büngner bands. These properties make SCs the best choice of cells for transplantation; however, other important characteristics of SCs include their high immunogenicity, poor culture growth, and difficulty in harvesting.

Biomaterials and Surgical Techniques

Because the sural nerve is the most common sensory and vascular donor used for autotransplantation, it is not a suitable choice for repairing a nerve with combined motor and sensory or motor components. Given the problems with nerve expansion, researchers have focused on finding alternatives that can fill large gaps without damaging the nerves. Canals have been made from various absorbable biomaterials, with authors worldwide reporting varying results. Canals can be synthetic or natural. Early studies demonstrated the effectiveness of scaffolds engineered nerve conduits, which avoided issues like mechanical incompatibility and nutrient exchange limitations by relying on fibroblast monolayers and neural stem cells to promote axonal growth and functional recovery. Later, nanofiber-based conduits, such as self-assembling peptide nanofiber scaffolds (SAPNS), were shown to enhance motoneuron protection, axonal regeneration, and remyelination in sciatic nerve defects, achieving promising functional outcomes. Regardless of the positive results, autologous drainage, like venous drainage, may include plasma components containing muscle or platelets. These channels require a donor area for collection. Despite great advances in surgical techniques and equipment, further research is needed in this area to establish the best combination of root canal-compatible cells and neurotrophic factors to improve clinical outcomes.

Neurotrophic Factors in PNI

Although activated SCs must localize rapidly to maintain their functional state, axon sprouts grow very slowly and, in the worst case, take a long time to reach the distal stump. Neurotrophic therapies and growth factors that can accelerate this process have therefore attracted attention (Wan et al., 2024). After nerve injury, brain-derived neurotrophic factor (BDNF) is critical and has been shown to promote axonal growth. In addition to increasing SC motility, nerve growth factor (NGF) also has a positive effect on the elongation of growing sensory axons. SCs are chemically attracted to glial-derived neurotrophic factor (GDNF). One important transcription factor that is

increased in response to PNI is Sox11. Myelin levels, nerve length, and BDNF levels can be affected by its expression. It can also help neuronal survival through the production of TNF receptor-associated activators (TANKs) associated with NF-κB. Vascular endothelial growth factor (VEGF) can improve nerve regeneration outcomes by improving microcirculation. Insulin-like growth factor (IGF) has been shown to stimulate axonal elongation and SC mitosis (Chernov and Shubayev, 2021). Although there are potential benefits from the shared use of channels and neurotrophins, it remains important to maintain SCs in a functional state, as they rapidly lose their ability. To facilitate the healing process, scientists have developed methods to obtain cell types that can develop into SCs or SC-like cells or to transplant newly activated SCs into the wound site.

Stem Cells in PNI

Stem cells are undifferentiated cells capable of developing into various cell types and producing multiple cell types. The two primary sources of stem cells are embryos, from which embryonic stem cells can be extracted during the embryonic stage, and adult tissues, which contain adult stem cells present in every tissue of the body (Prochazkova et al., 2015). Stem cells are classified based on their ability to differentiate into different cell types. For instance, muscle stem cells and other immature cells can only differentiate into their respective cell types. Myeloid stem cells are a distinct category of oligopotent stem cells. Multipotent stem cells can differentiate into closely related cell types, such as blood stem cells, which can develop into platelets, white blood cells, and red blood cells. Pluripotent stem cells, including embryonic stem cells and those from the ectodermal, mesodermal, and endodermal layers, can develop into nearly any cell type (Kolios and Moodley, 2012). Totipotent stem cells, which include early cells formed during the division of a zygote and the fertilized zygote itself, are unique in their ability to differentiate into all cell types. Mesenchymal stem cells (MSCs) are highly potent stem cells derived from sources such as adipose tissue, bone marrow, umbilical cord, amniotic fluid, and teeth (Costella et al., 2022) as explained in table 1. Morphologically, these cells are characterized by small cell nuclei with large nucleoli and round clear nucleoli. Their cytoplasm contains a Golgi apparatus, mitochondria, rough endoplasmic reticulum, ribosomes, and several elongated cell processes, and they are widely distributed within an extracellular matrix containing small reticular fibers.

Table 1: Summary of Mesenchymal Stem Cells and their use in Peripheral Nerve Injury(PNI

Type of Mesenchymal Stem Cells (MSCs)	Source	Differentiation Potential	Mechanism of Action	Clinical Applications	Key Factors Associated	Challenges	References
Adipose-derived stem cells (ADSCs)	Adipose Tissue	Neuronal, Schwann-like	- Promote axonal growth - Immunomodulation - Paracrine signaling - Anti-inflammatory effects	Peripheral nerve injury repair - Diabetic neuropathy	- VEGF - BDNF - NGF - IL-10	Limited availability in older patients - Variability in yield and quality	Zack-Williams et al., 2015
Bone Marrow Mesenchymal Stem Cells (BMSCs)	Bone Marrow	Neuronal, Osteogenic	- Differentiation into Schwann-like cells - Secretion of neurotrophic factors - Modulation of immune response	Treatment of nerve injuries in various models	- Neurotrophic factors - Cytokines (e.g., IL-6) - Growth factors	Invasive extraction procedure - Limited expansion potential in vitro	Fermandes et al., 2018
Wharton's-Jelly derived Stem cells (WJ-MSCs)	Umbilical Cord	Neuronal, Chondrogenic	- Immunomodulatory effects - Enhanced angiogenesis and neuronal survival - Secretion of exosomes	Use in acellular nerve grafts - Regenerative medicine applications	- BDNF - NGF - VEGF - HGF	Ethical considerations in sourcing - Limited understanding of long-term effects	Guo et al., 2015
Dental Pulp Stem Cells (DPSCs)	Dental Pulp	Neuronal, Odontogenic	- Neuroprotective effects - Ability to differentiate into neuronal-like cells - Secretion of growth factors	Potential for nerve regeneration in dental procedures	- Growth factors (e.g., FGF, EGF) - Anti-inflammatory cytokines	Limited availability post-extraction - Variability in differentiation capacity	Xing et al., 2023
Mesenchymal Stem cells derived exosomes	Various Sources (e.g., ADSC)	N/A	- Paracrine signaling effects similar to MSCs - Promote nerve regeneration through extracellular vesicles	Innovative therapeutic strategies for nerve repair	- miRNAs (e.g., miR-21) - Proteins involved in regeneration	Stability and delivery challenges - Regulatory hurdles for therapeutic use	Fan et al., 2020

Bone Marrow Mesenchymal Stem Cells

The differentiation of bone marrow mesenchymal stem cells (BMSCs) into mesodermal, ectodermal, and endodermal lineages can be induced. By releasing neurotrophic and growth factors such as BDNF, GDNF, and myelin basic protein and regulating SC behavior, they are known to differentiate into SC-like cells, facilitating nerve regeneration (Hopf et al., 2020). Due to certain challenges associated with BMSC

procurement, including the need for invasive and painful procedures that can lead to low cell yields, BMSCs have some limitations in clinical research. BMSCs exert their beneficial effects in a dose-dependent manner.

Adipose-derived Mesenchymal Stem Cells

Adipose-derived mesenchymal stem cells (ADSCs) are an alternative source of multipotent stem cells capable of differentiating into all three germ layers (Berry et al., 2015). In addition, they have been shown to produce a large number of cells compared to other adult tissues. This is achieved using minimally invasive surgical techniques and simple isolation protocols involving irrigation; and enzymatic agents to facilitate reproduction; centrifugation; and destruction of red blood cells (RBCs). This technique produces cell fragments consisting of several cell types. Among these, ADSCs are of particular interest because they adhere to the plastic surface of culture dishes and exhibit rapid proliferation, allowing for direct identification and isolation from other cell populations. Studies have shown that ADSCs can be induced to express glial cell markers such as S100B, GFAP, and the neurotrophin receptor P75 in vitro (Konno et al., 2013). However, it was found that differentiation of ADSCs into Schwann cells in vitro did not lead to significant improvement, likely due to the innate ability of ADSCs to differentiate into SCs in vivo. Furthermore, the researchers reported that ADSCs did not undergo differentiation into SCs in vivo, despite successful differentiation in vitro. Although undifferentiated ADSCs have been shown to produce neurotrophins, this occurs at low levels. Polycaprolactone conduits seeded with mesenchymal stem cells (MSCs) showed improved permeability and function compared to empty conduits (Yarak and Okamoto, 2010). Another research team used collagen conduits filled with collagen gel containing ADSCs, and their results showed that the improvements observed were comparable to nerve transplantation.

Umbilical Cord Mesenchymal Stem Cells

Despite ethical considerations regarding the use of umbilical cord stem cells (UC-MSCs) and limitations associated with their access, there is evidence to suggest their advantages over other adult cells of various origins: First, the stem cells can be harvested in large quantities. Quantities that are not harmful to the donor, as they are obtained from tissue discarded after birth; second, because they are obtained during pregnancy, the risk of genetic damage is significantly reduced (Bongso and Fong, 2013); Third, they have a smaller biological profile than other adult stem cells, allowing them to undergo more mitotic divisions and be cultured to a greater extent; Fourth, although they do not express HLA-II, their immune properties are less pronounced compared to other mature cells. Furthermore, tubular cells that arise from UC-MSC differentiation have been shown to facilitate axonal regeneration (Mebarki et al., 2021).

Immunomodulatory Effects of MSCs in PNI

PNI triggers a series of inflammatory responses in host cells, leading to alterations in cell morphology and immune-related factors. Current immune signaling factors include interleukin-1 (IL-1α, IL-1β), IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-17, tumor-induced cytokines (TNF-α), HGF, nitric oxide (NO), human leukocyte antigen G5 (HLA-G5), and prostaglandin E2 (PGE2) (Li et al. , 2022). Mesenchymal stem cells can produce a range of immune factors that affect responses to both autologous and allogeneic tissues, in addition to innate immune cells such as natural killer (NK) cells, neutrophils, macrophages, mast cells, dendritic cells (DCs), and immune cells derived from T and B cells. MSCs mediate their immune response through two primary mechanisms: paracrine secretion of cytokines, including IDO (in humans) or NO (in mice), PGE2, IL-4, IL-10, IL-12, IFN-γ, and TNF-α, as well as cell adhesion (Ge et al., 2019). The function of human MSCs (hMSCs) following injury is attributed to their secretion of bioactive molecules such as cytokines, chemokines, and growth factors, rather than their differentiation capability. Numerous studies indicate that many beneficial effects of stem cell therapy may stem from paracrine mechanisms. However, the immunomodulatory effects of MSCs in the context of PNI are still not well understood (Rufino et al., 2023).

Conclusions

To enhance nerve regeneration and improve sensory and motor recovery, the application of stem cells, particularly MSCs, is beneficial. These cells possess the capability to differentiate into Schwann cells in vitro and can also convert directly into SCs at the injury site. Additionally, manipulating stem cells can modulate the function of native SCs, alter inhibitory and excitatory states, promote myelination and cell survival, and enhance neurotrophic functions. In conclusion, MSCs, with their favorable characteristics such as ease of collection (especially adipose-derived stem cells) and low risk of immunogenic reactions, hold significant potential for improving the regenerative process. Consequently, further research may yield crucial advancements in MSCs' role in promoting nerve regeneration.

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