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Umbilical cord mesenchymal stem cells and their secretome in peripheral nerve regeneration: a narrative review promising therapeutic strategy

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ABSTRACT

The injuries of peripheral nerves remain a substantial clinical challenge because of their limited regenerative capacity, the complexity of nerve repair, and limitations of current treatment strategies. Umbilical cord mesenchymal stem cells (UC-MSCs) and their secretome have shown promise as regenerative treatments due to their distinct biological characteristics. This review explores the possibility of UC-MSCs and their secretome in promoting peripheral nerve regeneration, by their action mechanisms, therapeutic applications, and current preclinical - clinical evidence. UC-MSCs have proven to be capable of support Wallerian degeneration, improving axonal growth, reducing inflammation, and improving functional recovery in both animal models and early clinical studies. Their secretome has been shown to promote neuroprotection and functional repair, avoiding the risks of receiving a direct stem cell transplant. Challenges remain in standardizing UC-MSC-based therapies, ensuring long-term safety, and enhancing delivery strategies. Further clinical trials are needed to determine the efficacy, safety, and scalability of UC-MSC therapies for widespread clinical use. UC-MSCs and their secretome provide a unique, cell-free and cell-based strategy to peripheral nerve regeneration. Future advancements in biomaterial integration, gene editing, and personalized medicine will be essential to implementing these treatments in clinical settings.

ABSTRAK

Cedera saraf perifer masih menjadi tantangan klinis yang substansial karena kapasitas regeneratifnya yang terbatas, kompleksitas perbaikan saraf, dan keterbatasan strategi pengobatan saat ini. Sel punca mesenkimal tali pusat (UC-MSC) dan sekretomnya telah menunjukkan potensi sebagai terapi regeneratif karena karakteristik biologisnya yang unik. Tinjauan ini mengeksplorasi kemungkinan UC-MSC dan sekretomnya dalam mendorong regenerasi saraf perifer, melalui mekanisme aksi, aplikasi terapeutik, dan bukti praklinis-klinis terkini. UC-MSC telah terbukti mampu mendukung degenerasi Wallerian, meningkatkan pertumbuhan akson, mengurangi peradangan, dan meningkatkan pemulihan fungsional baik pada model hewan maupun studi klinis awal. Sekretomnya telah terbukti meningkatkan neuroproteksi dan perbaikan fungsional, sehingga menghindari risiko transplantasi sel punca langsung. Tantangan yang masih ada adalah standarisasi terapi berbasis UC-MSC, memastikan keamanan jangka panjang, dan meningkatkan strategi pemberian. Uji klinis lebih lanjut diperlukan untuk menentukan efikasi, keamanan, dan skalabilitas terapi UC-MSC untuk penggunaan klinis yang luas. UC-MSC dan sekretomnya menyediakan strategi unik, bebas sel, dan berbasis sel untuk regenerasi saraf perifer. Kemajuan di masa depan dalam integrasi biomaterial, penyuntingan gen, dan pengobatan personalisasi akan sangat penting untuk menerapkan perawatan ini dalam pengaturan klinis.

Keywords:
Umbilical cord mesenchymal stem cells; secretome; peripheral nerve injury; peripheral nerve lesion

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INTRODUCTION

The injuries of peripheral nerves and lesions constitute a serious clinical problem, often resulting from trauma, surgical complications, or degenerative conditions. These injuries and lesions can lead to debilitating functional impairments, including sensory loss, motor dysfunction, and chronic pain, profoundly impacting the quality of life.[1] The prevalence of injuries to peripheral nerves varies according to the cause, with trauma (e.g., vehicular accidents, sports injuries) being the most common.[2] Surgical procedures, such as tumor resections or orthopedic surgeries, can also inadvertently damage peripheral nerves, while degenerative conditions, including diabetes or autoimmune diseases, can lead to progressive nerve deterioration.[3]

Peripheral nerve repair is quite difficult. Spontaneous regeneration is limited and often insufficient for restoring function, particularly in cases of severe injury, where the gap between nerve stumps may be too large for natural regeneration.[4] Traditional surgical approaches, including nerve grafting or neurotization, are often associated with limited success, leading to suboptimal recovery.[5] Furthermore, development of scar tissue, loss of innervation, and inadequate vascularization complicate the regeneration process, highlighting the necessity of innovative therapeutic strategies to improve nerve repair.[6]

Mesenchymal stem cells (MSCs) have become a promising therapeutic option in the regenerative medicine sector. They are multipotent stem cells that can differentiate into several kinds of cells, such as osteoblasts, chondrocytes, adipocytes, and neuronal cells.[7] The following standards are used by the International Society for Cellular Therapy (ISCT) to specify MSCs: 1) are plastic-adherent when cultivated properly; 2) display CD73, CD90, and CD105 markers but not CD34, CD45, CD14, HLA-DR, CD11b, or CD19, and 3) have the capacity to develop into several lineages *in vitro*. The best interpretation and application of the most recent research to the clinical use of MSCs are made possible by the accurate usage of the term stem cells in accordance with the ISCT definition.[8]

Their regenerative potential stems not only from their ability to differentiate but also from their paracrine actions, which include the release of bioactive molecules that modulate the surrounding microenvironment.[9] Mesenchymal stem cells have been demonstrated to exert immunomodulatory, anti-inflammatory, angiogenic, and anti-apoptotic effects, all of which are critical for promoting tissue repair and regeneration.[10]

Umbilical cord-derived MSCs (UC-MSCs) offer unique benefits for therapeutic application among the several sources of MSCs, such as bone marrow and adipose tissue, especially in peripheral nerve regeneration.[11] Umbilical cord-derived MSCs are harvested from the umbilical cords Wharton's jelly, a non-invasive and ethically acceptable source.[12] Unlike bone marrow-derived MSCs (BM-MSCs), which require invasive procedures for collection, UC-MSCs are readily available following childbirth, eliminating ethical concerns.[13] Furthermore, UC-MSCs exhibit superior proliferative capacity and less immunogenicity than MSCs derived from other sources, making them highly suitable for allogeneic transplantation.[14]

Umbilical cord-derived MSCs are particularly well-suited for peripheral nerve repair due to several key characteristics. First, UC-MSCs are ethically sourced and collected without harm to the donor, addressing ethical concerns of stem cell treatments.[15] Additionally, their low immunogenicity lowers the possibility of immunological rejection in allogeneic applications, making them ideal for broad clinical use.[16]

Umbilical cord-derived MSCs also show a greater rate of proliferation compared to BM-MSCs, which is advantageous in regenerative therapies where large numbers of cells are required to support healing.[17]

The secretome of UC-MSCs, which is a rich mixture of bioactive chemicals that includes exosomes, cytokines, growth factors, and neurotrophic factors, is one of their most intriguing characteristics.[18] The UC-MSC secretome has been shown to exert powerful paracrine effects, promoting nerve regeneration through the modulation of inflammation, stimulation of angiogenesis, and support for survival of neurons and growth of axon.[19] This cell-free therapy offers distinct advantages over whole-cell transplantation, as it eliminates concerns related to cell survival, tumorigenesis, and immune rejection.[20] Thus, the UC-MSC secretome is a potentially effective, less invasive treatment method for enhancing peripheral nerve repair and regeneration.[21]

The objective of this review is to offer thorough analysis of the using MSCs specifically UC-MSCs with their secretome as a potential of regenerative medicine in treatment approaches for peripheral nerve injury and lesion. This paper highlighted the unique properties of UC-MSCs that give them suitable for regenerative therapy, challenges and limitations of UC-MSC therapies, and also future directions and innovations of UC-MSCs using with their secretome in the injuries of peripheral nerve and lesion.

MATERIAL AND METHODS

This article is a narrative literature review to compile the most recent evidence regarding the therapeutic potential of UC-MSCs and their secretome in the context of peripheral nerve injury (PNI) and lesion repair. The review was conducted following best practices for qualitative evidence synthesis and reporting. The following electronic databases were searched extensively for relevant literature: PubMed, Scopus, Web of Science, and Google Scholar.

The journals included in this review were published in 2020-2025, utilizing a mix keywords and Medical Subject Headings (MeSH) phrases, including: "Umbilical Cord Mesenchymal Stem Cells", "UC-MSCs", "Secretome", "Exosomes", "Peripheral Nerve Injury", "Peripheral Nerve Lesion", "Peripheral Nerve Regeneration", "Neuroregeneration", "Neurotrophic factors", "Schwann cells".

Peer-reviewed articles, *in vitro, in vivo* (animal), and clinical studies, articles published in English, and studies evaluating UC-MSCs or their secretome in the context of peripheral nerve injury/lesion were among the inclusion criteria. Studies that do not involve UC-MSCs or secretome, reviews, editorials, or conference abstracts without original data, studies that solely focus on central nervous system (CNS) injury were among the exclusion criteria. Data extracted included: Study design, animal / human model used, intervention type (UC-MSCs or secretome), outcomes assessed (e.g., axonal regeneration, functional recovery, histological analysis), and key findings.

RESULTS

Characteristics of UC-MSCs source and harvesting techniques

Umbilical cord-derived MSCs are derived from the Wharton's jelly of the umbilical cord (FIGURE 1), a gelatinous substance that surrounds the blood vessels in the cord.[9] This tissue is a rich, ethically acceptable source of MSCs, and its collection is non-invasive and performed without causing harm to the donor or recipient.[22] The umbilical cord is usually discarded after delivery, making it an abundant and readily

available source of MSCs for research and therapeutic use.[23] The use of UC-MSCs avoids the ethical concerns connected to embryonic stem cells, providing a favorable option for regenerative medicine.[24]

Umbilical cord-derived MSCs undergo isolation through enzymatic digestion or explant techniques after harvested, where the umbilical cord tissue is processed to release MSCs. These cells are then cultured in specialized media to allow for proliferation and expansion.[25] Umbilical cord-derived MSCs exhibit a high proliferation rate and able to expand the cell number *in vitro* to achieve the large cell numbers required for therapeutic applications. This ability to efficiently expand UC-MSCs makes them an attractive source for cell-based therapies.[26]

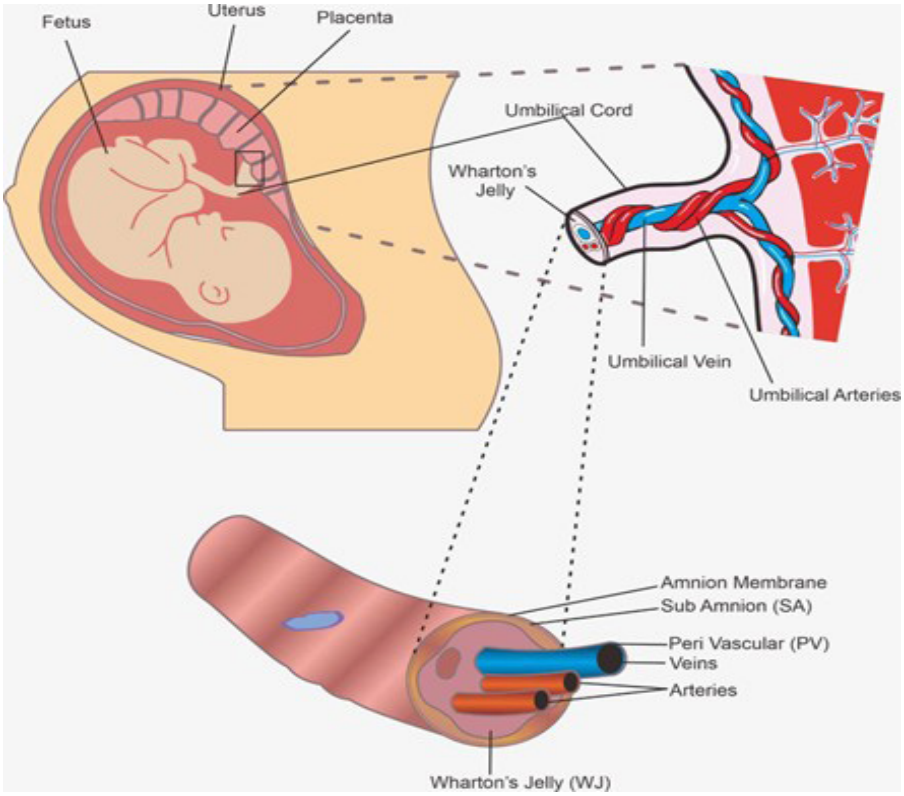

FIGURE 1. This illustration summarizes the umbilical cord anatomy, highlighting Wharton's Jelly. On the left, a cross-section of the pregnant uterus shows the fetus connected to the placenta via the umbilical cord, which enables nutrient, gas, and waste exchange. Zooming in, the cord contains three vessels: one umbilical vein carrying oxygenated blood from the placenta, and two umbilical arteries returning deoxygenated blood. These are embedded in Wharton's Jelly, a gelatinous connective tissue that cushions the vessels and ensures blood flow. The magnified view shows internal layers: the amnion (outer membrane), sub-amnion, and perivascular region rich in mesenchymal stem cells. Wharton's Jelly is biologically significant as it harbors MSCs with regenerative and immunomodulatory potential, making it valuable for regenerative medicine

Biological properties of UC-MSCs

Umbilical cord-derived MSCs possess potent immunomodulatory properties, meaning they are able to regulate the immune system's activity, suppressing excessive immune responses and promoting a balanced, healing environment.[27] They release a range of cytokines and factors that exhibit anti-inflammatory effects, reducing inflammation at injury sites, which is crucial for minimizing secondary damage in peripheral nerve injuries.[28] Additionally, UC-MSCs demonstrate anti-apoptotic properties, preventing cell death in damaged tissues, which further aids in the preservation and regeneration of neural structures.[29]

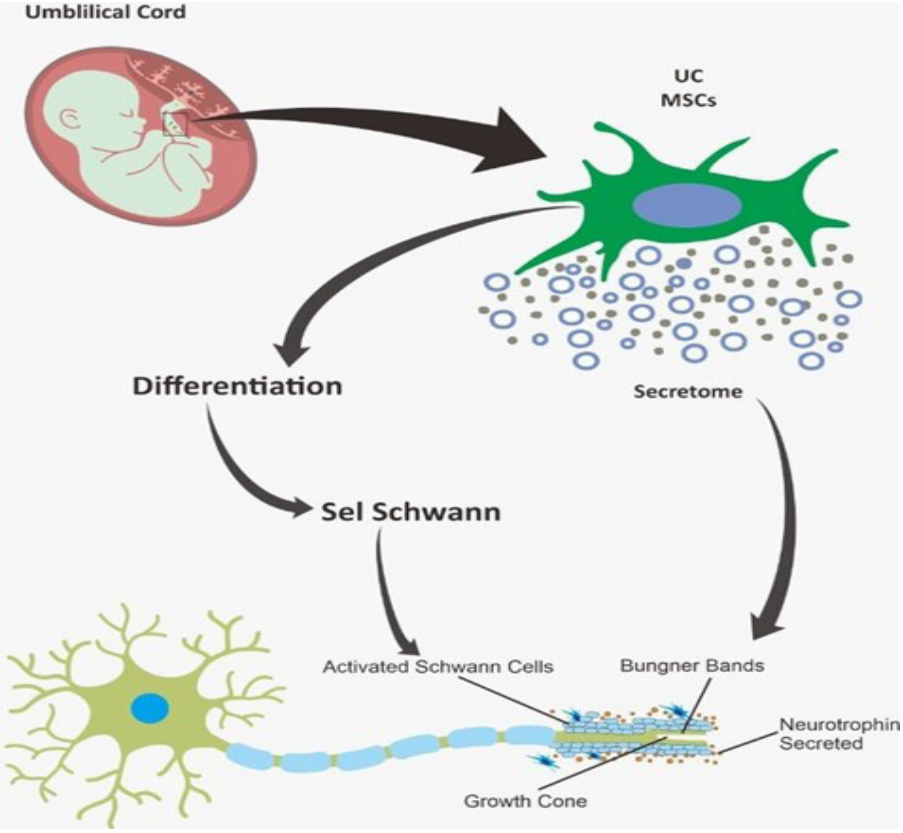

FIGURE 2. This schematic illustrates how UC-MSCs aid peripheral nerve repair through two mechanisms: (1) Differentiation into Schwann-like cells that support axonal regrowth, remyelination, and repair; and (2) Paracrine action via secretome release, including neurotrophic factors, cytokines, and extracellular vesicles. These secretome components activate resident Schwann cells, promote Büngner band formation, enhance growth cone activity, and support neuronal survival and axonal elongation

One of the key attributes of UC-MSCs is their ability to differentiate into different cell types, including those of neuronal and glial lineages (FIGURE 2). This makes UC-MSCs particularly valuable for nerve repair, as they can potentially replace damaged neurons and supporting glial cells in the peripheral nervous system.[30] The ability of UC-MSCs to encourage axonal growth, myelination, and in general nerve regeneration enhances their effectiveness in treating peripheral nerve injuries and lesions.[31]

Advantages of UC-MSCs for nerve repair

Umbilical cord-derived MSCs exhibit reduced immunogenicity, which means that an immunological reaction is less likely to be triggered when introduced into a patient's body, even in allogeneic (non-self) transplantations. This property significantly reduces the possibility of immune rejection, which is a common concern in stem cell therapies.[32] The reduced immunogenicity of UC-MSCs is largely because of their reduced expression of major histocompatibility complex (MHC) molecules, which makes them less identifiable by the immune system. This allows for wider clinical applications without the need for strict donor-recipient matching.[33]

Umbilical cord-derived MSCs are recognized to secrete a wide range of growth factors, cytokines, and neurotrophic factors that play a crucial role in tissue repair and regeneration.[34] These consist of vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-**β**), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF), among others.[35]

The higher secretion of these bioactive molecules, in contrast to other MSC sources like bone marrow or adipose tissue, enhances UC-MSCs' ability to promote nerve regeneration. These factors contribute to angiogenesis, neuroprotection, and axonal outgrowth, which are essential for successful peripheral nerve repair.[36]

Mechanisms of UC-MSCs in injury of peripheral nerve repair

UC-MSCs and Wallerian degeneration

Wallerian degeneration is a critical process that occurs following peripheral nerve injury, defined by the distal segment's disintegration of the nerve after axonal injury. It is necessary for clearing the debris and creating an environment favorable to nerve regeneration.[37] Umbilical cord-derived MSCs have demonstrated the ability to play a supportive role in modulating Wallerian degeneration by promoting phagocytosis of myelin debris and enhancing the clearance of apoptotic cells through their secretion of bioactive molecules.[38] This not only facilitates a more efficient degeneration process but also accelerates the transition to the regenerative phase, enabling a quicker initiation of nerve repair.[39]

Umbilical cord-derived MSCs release neurotrophic factors (TABLE 1), like NGF and BDNF, that are critical in protecting remaining axons and promoting Schwann cell activation, an essential player in Wallerian degeneration.[40] Schwann cells help remyelinate regenerating axons and construct a supportive environment for nerve regeneration. By modulating Schwann cell activity, UC-MSCs contribute to an enhanced regenerative environment post-Wallerian degeneration.[36]

Promotion of axonal regeneration

Umbilical cord-derived MSCs promote peripheral nerve repair through their ability to support axonal regeneration[31]. They secrete a rich variety of growth factors and extracellular vesicles (EVs), like exosomes, which contain proteins, lipids, and RNAs that stimulate axonal outgrowth; these factors generate a favorable microenvironment that encourages the regeneration of severed axons, aiding in their guidance towards the target tissue.[36]

TABLE 1. Neurotrophic factors secreted by UC-MSCs and their roles

Neurotrophic factor	Full name	Function in nerve repair
BDNF	Brain-derived neurotrophic factor	Encourages survival and growth of neurons; enhances synaptic plasticity and neurogenesis.
NGF	Nerve growth factor	Aids in maintenance and survival of sensory and sympathetic neurons; aids axonal regeneration.
NT-3	Neurotrophin-3	Stimulates growth and differentiation of neurons and Schwann cells.
GDNF	Glial cell line-derived neurotrophic factor	Enhances motor neuron survival and promotes axonal outgrowth.
VEGF	Vascular endothelial growth factor	Promotes angiogenesis; indirectly supports neuronal survival through improved blood supply.
IGF-1	Insulin-like growth factor-1	Facilitates nerve regeneration and myelination; reduces apoptosis.
HGF	Hepatocyte growth factor	Stimulates neurogenesis and axonal sprouting; exhibits anti-inflammatory effects.
FGF-2	Fibroblast growth factor-2	Promotes proliferation of neural stem cells; aids in neuroprotection.
TGF-β	Transforming growth factor beta	Regulates immune responses; modulates inflammation during nerve healing.

Notes: These neurotrophic factors are either secreted directly by UC-MSCs or encapsulated within their extracellular vesicles (EVs); their collective paracrine action contributes to axon guidance, remyelination, angiogenesis, and inflammation modulation, making UC-MSCs promising for treating peripheral and central nervous system injuries.

Umbilical cord-derived MSCs also contribute to remyelination, a critical aspect of nerve repair, by encouraging the differentiation and role of Schwann cells, which are responsible for wrapping the regenerating axons in myelin.[41] Remyelination not only speeds up nerve signal conduction but also stabilizes the regenerated axons, ensuring long-term functional recovery.[42] Additionally, UC-MSCs aid in the repair of synaptic connections between nerves and target tissues, further enhancing functional recovery following injury.[1]

Immunomodulation and inflammation control

Inflammation plays a dual role in peripheral nerve injury: it is necessary to start the repair process, but excessive or prolonged inflammation can result in secondary damage and scarring, impeding nerve regeneration.[43] Umbilical cord-derived MSCs have potent immunomodulatory properties, which permit them to fine-tune the inflammatory response at the site of injury.[44] Through the release of anti-inflammatory cytokines, like IL-10 and TGF-**β**, UC-MSCs suppress the action of pro-inflammatory immune cells, such as macrophages and T-cells, that could otherwise cause additional tissue damage.[26]

Umbilical cord-derived MSCs help generate an anti-inflammatory and pro-regenerative microenvironment by modulating the local immune response. This reduces the risk of fibrosis and scar formation, which are major barriers to nerve regeneration.[45] Moreover, UC-MSCs' capacity to regulate the activity of macrophages is particularly beneficial, as these immune cells play a pivotal function in both removing cellular debris and encouraging tissue repair.[46] UC-MSCs help convert macrophages transitioning from a pro-inflammatory to a pro-regenerative phenotype, consequently supporting nerve healing.[47]

Angiogenesis and support for vascularization

Adequate blood supply is necessary for successful nerve repair, as it provides oxygen and nutrients to revitalize tissues while removing waste products.[48] UC-MSCs participate in angiogenesis—the formation of new blood vessels—by secreting angiogenic factors such as VEGF and FGF. These factors encourage the creation of new capillaries in and around the injury site, ensuring a robust blood supply to the regenerating nerve.[49]

Umbilical cord-derived MSCs help sustain the newly formed tissue by enhancing vascularization, supporting axon survival and remyelination.[39] The increased blood flow also aids in the transport of essential nutrients and growth factors, further promoting the recovery process.[50] UC-MSCs' ability to stimulate angiogenesis is particularly critical in large or severe nerve injuries, where the lack of sufficient vascularization can hinder the repair process.[51] Thus, UC-MSCs not merely advertise nerve regeneration directly but also support the surrounding tissue environment by enhancing vascular support.[45]

The role of UC-MSC secretome in nerve regeneration

Definition and components of the UC-MSC secretome

The UC-MSC secretome refers to the array of bioactive molecules that are released by UC-MSCs. These molecules include exosomes, cytokines, growth factors, and neurotrophic factors (FIGURE 3), which play pivotal roles in the regeneration and repair of tissue.[9]

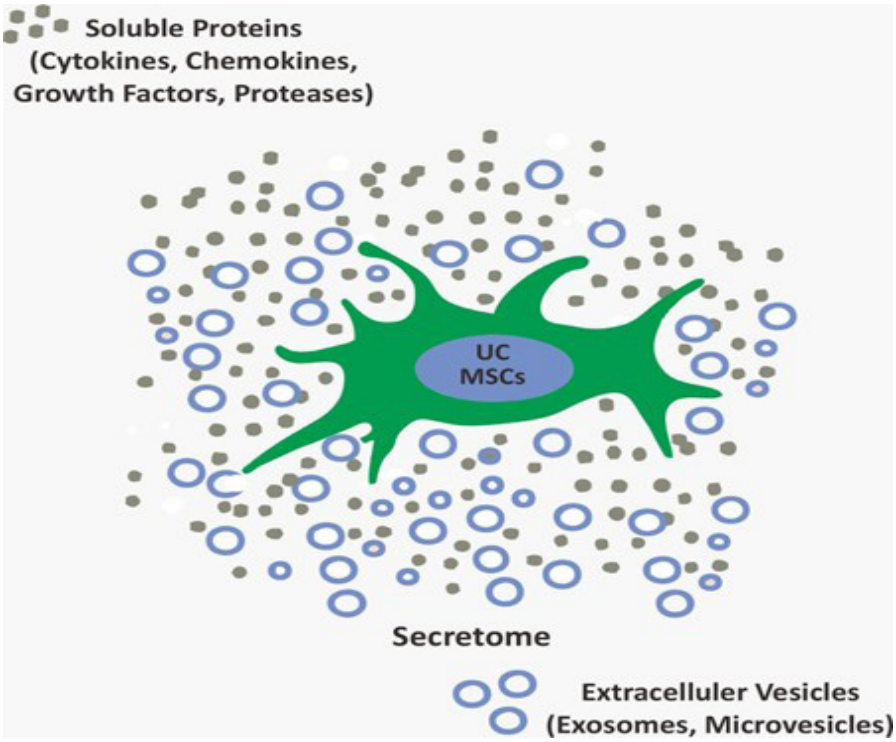

FIGURE 3. This diagram shows the secretome of UC-MSCs), composed of two main components: (1) Soluble proteins such as cytokines, chemokines, growth factors (VEGF, HGF, IGF, TGF-**β**), and proteases that regulate inflammation, angiogenesis, and tissue repair; and (2) Extracellular vesicles (EVs), including exosomes and microvesicles, which carry proteins, lipids, and RNAs to mediate intercellular communication and systemic regenerative effects. Together, these elements underpin the regenerative and immunomodulatory potential of UC-MSCs, supporting their use in cell-free therapies

Exosomes, which are small extracellular vesicles, carry proteins, lipids, and nucleic acids, including microRNAs (miRNAs), that control gene expression and encourage recovery.[52] Along with exosomes, the UC-MSC secretome is rich in cytokines IL-10, NGF, BDNF, and VEGF.[9] These molecules contribute to nerve regeneration by promoting cell survival, axonal growth, and vascularization, as well as modulating the immune response to reduce inflammation.[53]

Paracrine mechanisms in nerve repair

The UC-MSC secretome facilitates nerve regeneration primarily through paracrine signaling, where bioactive molecules act on nearby cells to initiate healing.[21] Unlike direct cell therapy, the paracrine effects of the secretome allow it to exert regenerative actions without the need for the cells themselves to integrate into the damaged tissue.[54] The secretome's exosomes and soluble factors influence the behavior of neurons, Schwann cells, endothelial cells, and immune cells, promoting a regenerative environment in injured peripheral nerves.[55] This paracrine mechanism enhances neuroprotection, supports axonal regrowth, and stimulates the proliferation and differentiation of Schwann cells, that are critical for remyelination and nerve repair.[56]

The UC-MSC secretome exhibits potent anti-inflammatory properties by releasing IL-10 and TGF-**β** that reduce the recruitment and activation of pro-inflammatory immune cells.[46] By controlling inflammation, the secretome helps to minimize secondary damage to nerve tissues following injury.[57] Furthermore, the secretome demonstrates anti-apoptotic effects, preventing the programmed cell death of neurons and supporting cell survival during the critical stages of nerve regeneration.[58] The secretome's angiogenic factors, like VEGF, promote the creation of new blood vessels, ensuring a sufficient blood supply to the regenerating nerve, which supports tissue repair and enhances the provision of nutrients and oxygen to the location of injury.[59]

Secretome-based therapy for nerve injury

The UC-MSC secretome presents a promising cell-free therapy for handling peripheral nerve injuries because its capacity to mimic the regenerative effects of cell-based therapies without the potential complications connected to live cell transplantation, like immune rejection or tumorigenicity.[60] Secretome-based therapies leverage the bioactive molecules that UC-MSCs naturally produce to promote neuroprotection, reducing cell death and preserving the functional integrity of injured nerves.[61]

Studies have indicated that the UC-MSC secretome have the ability to stimulate axonal regeneration, supporting the growth of severed nerve fibers and the recovery of motor and sensory functions.[21] The secretome also enhances remyelination, aiding Schwann cells in wrapping regenerated axons with myelin, which is essential for restoring nerve conduction and improving functional outcomes.[62] Via modulation of the immune response, decreasing inflammation, and promoting angiogenesis, the UC-MSC secretome creates a favorable environment for nerve regeneration and functional recovery in the injury of peripheral nerve cases.[21,39]

Preclinical and clinical evidence

Preclinical studies in peripheral nerve injury

Numerous preclinical studies using animal models have proven the effectiveness of UC-MSCs and their

secretome in encouraging peripheral nerve repair.[63] In rodent models of sciatic nerve injury, UC-MSCs have been demonstrated to significantly enhance nerve regeneration, functional recovery, and motor coordination compared to untreated control groups. These studies indicate that UC-MSCs contribute to axonal outgrowth, remyelination, and synaptic restoration, often attributed to their neurotrophic factor release and paracrine signaling.[9,64]

Studies focusing on the UC-MSC secretome have highlighted the ability of secreted factors, such as exosomes and cytokines, to accelerate the regeneration process in nerve injuries.[65] For instance, in models of crushed or transected peripheral nerves, the administration of UC-MSC-derived exosomes has been associated with improved axon regeneration, enhanced Schwann cell proliferation, and increased angiogenesis in the injured tissues.[36] These preclinical investigations indicate that both UC-MSCs and their secretome could offer a potent, non-invasive therapeutic approach for treating peripheral nerve injuries.[7]

Clinical trials and emerging applications

Clinical studies evaluating the use of treatments based on UC-MSC in peripheral nerve injuries are still in the early stages, but there is growing interest in their application for nerve repair and regenerative medicine.[51le] Certain clinical trials are exploring the possibility of the UC-MSC secretome, particularly the application of exosome-based therapies, as a cell-free alternative for whole-cell therapies. Early findings from these studies imply that UC-MSC-derived exosomes may be able to promote regeneration of the nerve without the problems that come with cell transplantation, such as immune rejection or tumor formation.[66]

Preliminary clinical data from trials involving UC-MSC-based therapies for nerve repair have demonstrated promising safety and tolerability, with minimal adverse events reported.[67] Patients treated with UC-MSCs or their secretome have shown improvements in nerve function, including enhanced sensory perception, recovery of motor function, and reduced pain.[19] These outcomes are ascribed to the neuroprotective, anti-inflammatory, and pro-regenerative effects of UC-MSCs and their secreted factors.[64]

The emerging clinical evidence suggests that UC-MSC-based therapies could provide a safe and effective therapeutic alternative for patients with peripheral nerve injuries, particularly those who have limited options for conventional nerve repair.[39in] More research is needed to validate these results and expand the application of UC-MSC therapies to more complex or severe cases of nerve damage.[68]

DISCUSSION

Regulatory and ethical considerations

One of the main challenges in advancing UC-MSC and secretome therapies to widespread clinical use is the lack of standardization in their production, characterization, and administration.[69] The isolation, expansion, and storage of UC-MSCs, as well as the preparation of their secretome, can vary between laboratories, resulting in inconsistencies in therapeutic outcomes.[70]

Regulatory agencies, such as the FDA and EMA, require strict guidelines for cell-based and biologic therapies, but establishing universal protocols for UC-MSC therapies is complex because of differences in donor tissue, culture conditions, and the techniques used to isolate and expand cells.[71]

Furthermore, the secretome, which consists of a mixture of exosomes, cytokines, and growth factors, poses additional regulatory challenges

because it is a cell-free product with complex biological activity that must be standardized for clinical application.[9] Developing methods to ensure consistent potency and safety of UC-MSC secretome products is critical for regulatory approval.[72]

There are still ethical considerations to be resolved, even if UC-MSCs are considered ethically favorable because their non-invasive sourcing from donated umbilical cords. The collection of umbilical cords requires informed consent from mothers, and there must be clear guidelines to prevent exploitation or commercialization of this biological material.[73] In addition, some concerns may arise regarding the long-term safety and biological consequences of using UC-MSCs in therapies, particularly in terms of potential genetic modifications or unintentional alterations to cells during the expansion process.[74i]

Taking care of these ethical concerns through clear regulatory frameworks and transparency in the sourcing and handling of UC-MSCs is essential to gain public and clinical trust.[75]

Safety and efficacy concerns

There are still concerns about tumorigenesis (formation of tumors) and immune reactions, despite UC-MSCs low immunogenicity and relative safety in clinical applications.[76] As MSCs have the capacity to differentiate into several kinds of cells, there is a potential risk that, under certain conditions, they could lead to uncontrolled cell growth or transformation into malignant cells. This risk is a concern, especially in the context of long-term treatments or in patients with pre-existing cancer conditions.[77]

The potential for immune reactions in cases where patients may have specific sensitivities to allogeneic cells or proteins secreted by UC-MSCs is another concern.[78] Even though UC-MSCs are regarded as having minimal immunogenicity, patients can develop adverse immune responses to these foreign cells.[79] To mitigate these risks, the topic of ongoing study is focused on better quality control measures, developing genetically stable cell lines, and optimizing the conditions under which UC-MSCs are administered.[80] Preclinical safety testing, alongside long-term clinical follow-ups, is essential to assess tumorigenic potential and immune-related risks in patients receiving UC-MSC therapies.[81]

Challenges in large-scale manufacturing

Scaling up the production of UC-MSCs and their secretome for clinical use presents significant manufacturing challenges. The need to generate large numbers of high-quality cells and secretome products for therapeutic applications is a complex task that requires rigorous quality assurance to ensure dependability, potency, and security of each batch.[82]

Differences in cell culture conditions, donor differences, and the techniques for isolating and expanding the cells can lead to inconsistencies in the final product, potentially affecting therapeutic outcomes.[83]

The secretome itself is a complex mixture of molecules that requires careful characterization to ensure each therapeutic batch contains the necessary components (e.g., exosomes, cytokines, and growth factors) in the right proportions. Developing reproducible and scalable manufacturing protocols that meet regulatory standards is critical for moving these therapies from preclinical to clinical stages.[84]

Producing UC-MSCs and their secretome at a commercial scale is both technically and financially challenging. The scalability of MSC-based therapies involves not only the extensive cell growth but also maintaining their biological characteristics and

therapeutic efficacy.[69] Traditional cell culture techniques may not be efficient for large-scale production, and the cost of maintaining good manufacturing practices (GMP)-compliant facilities for UC-MSC expansion and secretome collection can be prohibitively high.[85]

The downstream processing of UC-MSC secretome, including exosome isolation, purification, and storage, further contributes to the overall cost of production. To make UC-MSC-based therapies widely accessible, efforts must be directed towards developing cost-effective and scalable bioprocessing methods that maintain product quality while reducing production expenses.[86]

Future directions and innovations

Enhancing UC-MSC therapies for nerve repair

As research into UC-MSCs progresses, one encouraging area of innovation involves genetic engineering to enhance their neuroregenerative potential. By modifying specific genes in UC-MSCs, scientists aim to improve their ability to secrete key neurotrophic factors and growth signals that accelerate nerve regeneration.[87] For example, UC-MSCs may be engineered to overexpress proteins such as BDNF or NGF, which are known to encourage axon regeneration and synaptic repair in damaged nerves.[88]

Another approach involves preconditioning UC-MSCs to optimize their therapeutic efficacy before transplantation. This can be done by exposing the cells to specific environmental conditions, such as hypoxia or certain chemical signals, which boost their proliferation, secretion of bioactive factors, and overall regenerative potential.[89]

Combining UC-MSCs with advanced biomaterials is another innovative strategy to improve outcomes in peripheral nerve repair.[90] These biomaterials, such as scaffolds or hydrogels, can serve as supportive structures that imitate the natural extracellular matrix, enhancing the survival and integration of transplanted UC-MSCs at the injury site.[91] Biomaterials also provide a controlled-release system for growth factors or drugs that promote nerve healing, ensuring sustained therapeutic effects over time.[92]

Growth factors like FGF or VEGF can be delivered alongside UC-MSCs to promote angiogenesis and establish an advantageous environment for nerve regeneration. These combination approaches, integrating biotechnology and cell therapy, hold great prospect of improvement nerve repair outcomes.[14]

Innovations in secretome delivery

The UC-MSC secretome, composed of bioactive molecules like exosomes, cytokines, and growth factors, offers a powerful cell-free approach to nerve regeneration. However, delivering the secretome in a targeted and sustained manner remains a key challenge. To address this, researchers are developing novel delivery systems like hydrogels and nanoparticles that improve the retention and targeting of the secretome at the site of injury.[93]

Hydrogels can be designed to offer a controlled-release mechanism for secretome components, allowing the gradual release of therapeutic molecules over time. This prolonged delivery helps ensure continuous support for axonal growth, inflammation control, and tissue repair during the recovery process.[94]

Similarly, nanoparticles can be used to encapsulate specific components of the secretome, improving their stability and enabling precise targeting to the injured area. These nanoparticles may be functionalized to react to particular biological signals at the site of injury, releasing their cargo when and where it is needed most. Innovations in these delivery technologies could significantly increase the efficacy of secretome-based therapies for nerve repair.[95]

Potential for personalized medicine

One of the most exciting future directions for UC-MSC therapies lies in their potential for personalized medicine. Each patient's nerve injury and regenerative capacity are unique, impacted by factors like age, genetics, and the extent of nerve damage. UC-MSC-based therapies could be designed to satisfy the particular needs of individual patients, optimizing their recovery outcomes.[96] Personalized UC-MSC therapies, for example, could involve selecting specific cell populations with enhanced regenerative abilities according to a patient's genetic profile.[97] Similarly, secretome-based therapies could be customized to include a specific mix of growth factors and cytokines that best match the patient's injury and biological characteristics.[98]

Advances in biomarkers and diagnostic tools will also enable more precise monitoring of a patient's response to UC-MSC therapy, allowing for real-time adjustments to the treatment plan. Personalized medicine has the capacity to greatly enhance the success rate of nerve repair therapies, offering more effective and targeted treatments according to each patient's particular biology.[99]

The pathways involved in peripheral nerve regeneration mediated by the UC-MSCs have been summarized and compared with those from other stem cell sources in the (TABLE 2).[21,39,100]

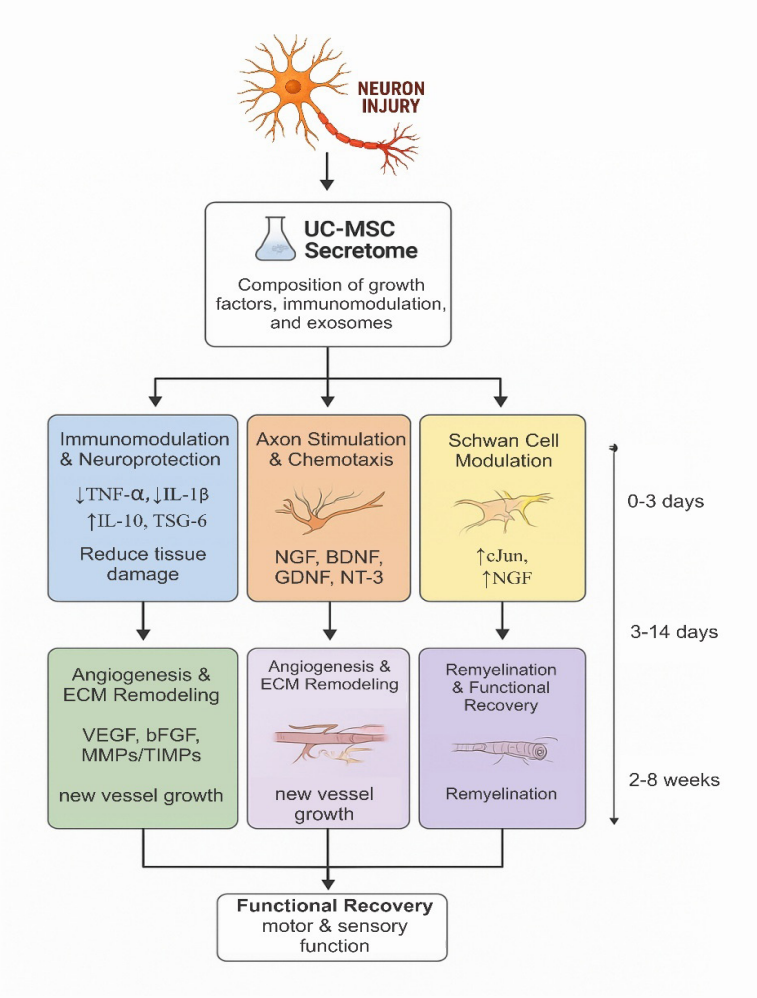

FIGURE 4. Peripheral nerve regeneration mediated by UC-MSC secretome

TABLE 2. Mechanistic strengths and regenerative pathways of various mesenchymal stem cell sources

Source	Main mechanistic strength	Dominant pathway in regeneration
UC-MSC (Umbilical cord mesenchymal stem cells)	Broad-spectrum paracrine signaling	Immunomodulation + Axonal regeneration
BM-MSC (Bone marrow mesenchymal stem cells)	ECM remodeling & repair support	Structural repair + moderate neurotrophic signaling
AD-MSC (Adipose-derived mesenchymal stem cells)	Angiogenesis & metabolic support	Vascular remodeling + indirect neuroprotection
DP-MSC (Dental pulp mesenchymal stem cells)	Neurotrophic specificity	Direct neurite outgrowth + Schwann modulation

This narrative review has limitations including potential selection bias due to its non-systematic approach, which may affect the comprehensiveness of included studies. Clinical translation of UC-MSCs secretome therapy faces challenges such as lack of standardized production protocols, variability in therapeutic products, and limited clinical trial data. Regulatory and ethical hurdles also remain, and long-term safety and optimal dosing strategies are yet to be fully established. Additionally, complex factors inherent to peripheral nerve injuries further complicate therapeutic evaluation. Future research should focus on standardization, rigorous clinical trials, and detailed mechanistic studies to validate and optimize this promising therapy.

CONCLUSIONS

The UC-MSCs and their secretome have a lot of potential in the field of peripheral nerve repair because of their potent regenerative properties. The UC-MSCs offer several advantages, including minimal immunogenicity, a high rate of proliferation, and a capacity to differentiate into key cell types like neurons and glial cells. Moreover, their immunomodulatory, anti-inflammatory, and anti-apoptotic effects contribute greatly to enhancing the regeneration of the nerve. The UC-MSC secretome, abundant in exosomes, cytokines, and growth factors, plays an essential role in nerve repair by promoting axonal regeneration, reducing inflammation, and supporting angiogenesis at the injury site.

Both preclinical and clinical studies have proven the potential of UC-MSCs and their secretome to promote neuroprotection and recovery of functional in various peripheral nerve injuries. These findings underscore UC-MSCs as a promising alternative to traditional therapies in peripheral nerve regeneration.

There is still much to be done despite the advancements in UC-MSC-based therapies for nerve injuries, much work remains to be done. Upcoming research should keep investigating ways to enhance the regenerative capacity of UC-MSCs through genetic engineering, combination therapies with biomaterials, and innovations in secretome delivery systems such as nanoparticles and hydrogels. Further clinical trials are necessary to establish long-term advantages, safety, and effectiveness of UC-MSC therapies in peripheral nerve repair.

Personalized medicine approaches, in the coming years, could revolutionize

nerve repair treatments by tailoring UC-MSC-based therapies to the individual needs of patients, optimizing outcomes according to their unique biology. Overall, UC-MSCs and their secretome show promise as a frontier therapy of peripheral nerve injuries, having the capacity to significantly improve recovery and patients' quality of life.

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