Mesenchymal Stem Cell Regenerative Therapy in the Spine - Recent Advancements and Possible Applications: A Review

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Abstract

A spinal cord injury (SCI) is an injury which damages the central nervous system, particularly the neurons and structures located in the spine. Treatment options involving mesenchymal stem cells (MSCs) have recently been recognized as possible repair solutions to an SCI. MSCs have multifaceted functionality which allows for a wide range of applications; and, specifically for usage in the spine, MSCs do not contain immunogenic response agents, which makes them suitable for treatment involving the central nervous system. Clinical usage of MSCs has been proven successful in other facets of medicine, but the exact mechanisms by which they repair SCIs is not fully understood (Xia et al., 2023). Recent research, however, suggests MSC involvement in reducing neuronal inflammation, regenerating axons, and repairing spinal blood vessels (Staff, 2022). These new findings anticipate future advancements in the usage of MSCs conjunctively with neurorehabilitation therapies (Xia et al., 2023). Further speculations could even involve treatment for reversing paralysis, inhibiting glial scarring, and reducing neurological symptoms of SCIs all within the spine.

Introduction

As strides in medical advancements occur across the frontier between health and illness, one area continues to elude reliable treatment: the nervous system. Particularly concerning substantial injuries to the spinal cord, modes by which to reverse and heal damage are currently underdeveloped. One possible solution to this "last frontier" of medicine is regenerative spinal cord injury (SCI) therapy using mesenchymal stem cells (MSCs). This novel development is currently the focus of a multitude of reviews, trials, and examinations; its efficacy in treatment is being revealed as having great promise. This is a relevant issue considering that treating the nervous system is considered to be one of the final areas of medicine for humans to conquer. Additionally, SCIs are life-altering injuries, often disabling those who sustain them. In the United States alone, "there were 17,810 new SCI cases reported in 2020, with a total of 294,000 Americans living with SCI," a number that could significantly decrease with MSC therapy (Ma et al., 2022). MSCs have shown efficacy in aiding in the regeneration of neuronal tissue in many clinical trials and have evidence backing their properties that allow for them to be a prime candidate for SCI treatment. Such properties include "neuroprotection, immunomodulation, axon sprouting and/or regeneration, neuronal relay formation, and myelin regeneration, among other mechanisms," which reinforce the assertion that MSC therapy is among the best approaches for treating the complex pathophysiology of SCIs (Shang et al., 2022). Furthermore, the use of MSC therapy in conjunction with other neurodegenerative-focused therapies is being explored due to the multimodal facets of an SCI and their complex pathological conditions.

Timing and the Immune System

Mesenchymal stem cells (MSCs) are cells harvested from various tissues and contain the ability to proliferate into different types of specialized cells, including neurons.

In the realm of the nervous tissue within the spine, MSCs have the distinct ability of aiding in overall regeneration thanks to their high proliferation abilities. This is fostered by their ability to release chemical factors that can influence cell interactions within the spinal cord, which is a useful tool in treating SCIs. Among cytokines and exosomes with anti-inflammatory abilities, MSCs also release "vascular endothelial growth factor (VEGF), nerve growth factor (NGF), glia-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF)", which not only allow for expedited nerve cell regeneration but also work to eliminate the effects of glial scarring, a major motor-inhibiting issue following SCI which can result in inflammation that stifles neuronal repairing and formation (Xia et al., 2023). Additionally, in major SCIs, the upregulation of endogenous neurotrophic factors often is not significant enough to produce meaningful regeneration or recovery in the trauma-affected areas. The need for an exogenous neurotrophic factor explains the effectiveness of GDNF and BDNF administered externally through MSC therapy.

Another important factor, VEGF, works in a different way to repair neuronal tissue through its vascularity; as an angiogenic factor, it promotes pericyte recruitment, which allows vascular tissues to mature and regenerate. Within the central nervous system (CNS), neurons and blood vessels work in units considered neurovascular units. These units allow VEGF to promote neuronal regeneration by enhancing the nutrient flow (Pan et al., 2013). Furthermore, VEGF mediates "vascular endothelial cell proliferation and migration, angiogenesis, and vascular permeability and leakage," enhancing the function of neuronal vascularity while appropriating the beneficial capacities of vascular components (Pan et al., 2013). Within the nervous system, vascular health is crucial due to the importance of blood supply for neuronal function and repairing sequences. Other growth factors such as NGF aid in the survival retention of neurons by enabling increased axonic regeneration.

NGF overproduction has been shown to improve functional recovery in a mouse model when administered following a SCI (Wang et al., 2021). After chemically modifying neural stem cells (NSCs) to overproduce NGF following a SCI, researchers found the motor functions of the affected limbs were generally improved, and, at the site of the trauma, the affected cells did not retain extreme pathological states over a prolonged timeline. This can be observed in Figure 1, which displays data showing the regenerative properties of NGF-modified NSCs. The introduction of NGFs appears to have shrunk the affected area of an SCI lesion and improved the motor function of the hindlimbs. This reinforces the assertion that NGF can regulate the neuronal environment and increase endogenous responses from certain neurons such as NSCs (Wang et al., 2021).

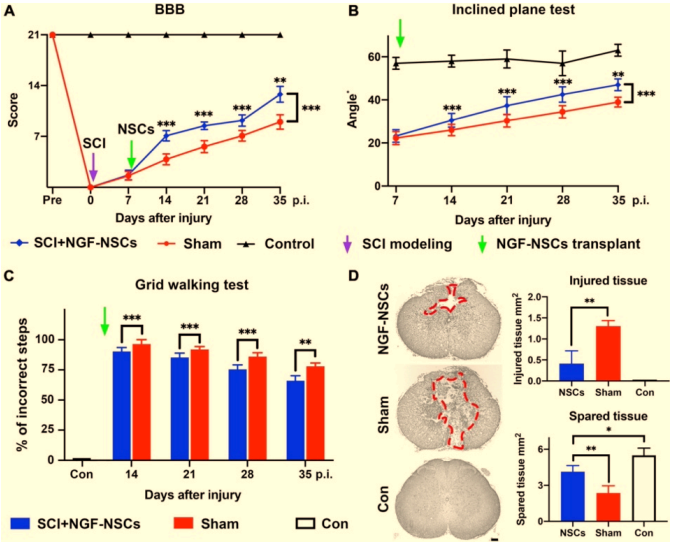

Figure 1. NGF-Modified NSCs

Figures A-C highlight the benefits of NGF-modified neural stem cells (NSCs) on "functional recovery of hindlimbs and alleviated histopathological damage after SCI" by analyzing the angular and quantitative improvements. Figure D shows the area of injured tissue 4 weeks after initial injury, circled by red dotted lines. This shows the minimized histopathological damage contained within the epicenter of the lesion when utilizing NGF-NSCs. After transplantation, rats with significant SCIs regained improved function of hindlimbs once they received treatment from NGF-NSCs.

Exogenous factors of the same chemical makeup have similar effects in regulating microenvironments and increasing regenerative ability. GDNF and BDNF are often linked with "β III tubulin, enolase 2, and microtubule associated protein 1b" (Xia et al., 2023). These neuromarkers have been shown to encourage microtubule health, axon regeneration, appropriate neuronal aging, and overall maintenance of synaptic areas. High level dosages of BDNF may also improve motor function, help maintain the recovering blood spinal cord barrier after SCIs, and improve neuronal regeneration (Muheremu et al., 2021). Sequentially, when GDNF is introduced to the SCI site, nerve cell density and motor function can increase. These neurotrophic factors, when paired with "recombinant proteins such as osmotic pumps, nanoparticles, viral vectors, as well as polymer scaffolds," can encourage the regeneration of the SCI-affected area of the spine by providing it with ample neurotrophic support (Muheremu et al., 2021). These various factors secreted by MSCs within the microenvironments of the neural tissue in the spinal cord chemically support regenerative capabilities and are therapeutic in the case of SCIs. Each factor in combination can change the effects of a SCI and be applied to regenerative therapies in humans. And, when paired with other therapeutic methods of inter-neural intervention, their positive effects can be amplified.

Clinical Applications and Recent Advancements

When an SCI occurs, endogenous repair is induced and cells, such as Schwann, myelinating, and regenerative cells, migrate to the trauma site to repair damaged tissue. There are positive benefits to this process, but the main problem stemming from endogenous repair is that axon growth is inhibited, and glial scarring often occurs due to oligodendrocyte myelin debris from the trauma (Nandoe Tewarie et al., 2009). Logistically, the introduction of MSCs to treat SCIs and combat the negative endogenous effects appears legitimate, but the methodology behind achieving similar results to the expected outcome in clinical trials is actually much more complicated. There are multiple factors to address regarding the introduction and transplantation of MSCs to an area of trauma including "mode of transplantation, dose and frequency of MSCs, timing of SCI, and type of SCI," which complicate the process of clinical research and require further studies to apply MSCs to SCI treatment effectively(Xia et al., 2023). This is due to the diversity in proliferation and differentiation that MSCs contain, as illustrated by Figure 2. With the exponential number of possibilities that MSCs contain, the implicating factors, such as the mode and timing of transplantation, complicate this even further. The standard mode of transplantation is a local injection within the site of a SCI, but MSC transplant injections into the subarachnoid space and intravenously are also common in clinical trials (Xia et al., 2023).

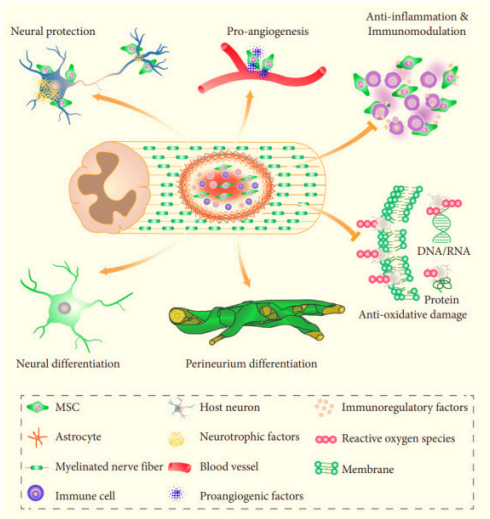

Figure 2. Properties of MSCs

A figure illustrating the multifaceted properties of MSCs, showing their ability to target various pathological conditions within a SCI (Ma et al., 2022). This emphasizes the proliferation abilities of MSCs to differentiate and offer support to various aspects of the neuronal and spinal tissues. Each image stemming off the initial stem cell source represents a unique use that they can serve within the human body.

The idea of enhancing MSCs through additive therapy and procedures is also being explored clinically. Methods such as pre-conditioning, three-dimensional cultures, genetic modifications, and pairing with neurorehabilitation show promise in enhancing capabilities of MSCs (Ma et al., 2022). One example of pre-conditioning, IFN-γ pretreatment, has been observed to aid in the release of chemical factors that give MSCs their immunosuppressive and immunomodulatory abilities (Ma et al., 2022). This is an important aspect within the spinal cord due to immunogenic complications common in the neural system, like glial scarring and microglia activity, as immunogens retroactively damage the neural tissue following an SCI. Alterations with oxygen levels of MSCs, such as hypoxic treatment followed by reoxygenation, seem to improve proliferative abilities and migratory actions of MSCs, allowing them to regenerate numbers and relocate to affected areas. Additionally, similar preliminary oxygen treatments have proved to enhance survival rates of MSCs, a common downfall when examining prolonged timelines and chronic SCIs. It is believed that within the spine, these benefits are due to an “up-regulation of cytokines,” like VEGF, which promote neuronal regeneration among other therapeutic effects (Ma et al., 2022). Similarly, using certain types of tissue engineering, the proliferation and survival of MSCs can be altered; one mode by which to achieve this is biomaterialistic scaffolding. Biomaterials within scaffolding can aid in cell survival, intercellular interactions, proliferation, and protection (Blando et al., 2022). By using certain gels, as well as synthetic and biological materials, the microenvironments in which MSCs are comfortable reproducing and releasing chemical factors in can be replicated (Xia et al., 2023). These “neurotrophic factor co-delivery” assisters can increase production of cytokines, promoting the regeneration of targeted areas of the spinal cord (Xia et al., 2023). Biomaterial scaffolds, such as “block copolymer of PLGA and poly-l-lysine (PLL) with a highly interconnected porous structure (approximately 250–500-μm-diameter pores),” when paired with MSC therapy, have clinically been proven to regenerate nerve tissue in rat models with SCIs as well as restore motor function (Ashammakhi et al., 2019). Additionally, Figure 3 shows the wide range of scaffolding methods available, and what benefits might come with each. The combinations of what materials to use and how to assemble them are numerous. This offers a view on how beneficial this method could be and how adaptable the possibilities are to address many distinct types of SCIs and lesions. A large factor in the dangers of spinal cord lesions and trauma is the loss of cells in the affected area and the following necrosis of tissue. This environment makes it hard to encourage cell-proliferation, and neuronal microenvironments of cell necrosis-affected tissues do not make suitable areas to introduce new cells. So, scaffolding MSCs with biomaterial can promote proliferation and tissue regeneration whilst inhibiting glial scarring and inflammation (Blando et al., 2022). The creation of a habitable extracellular matrix (ECM) can support “regenerative environment, differentiation, and trophic support” in the form of releasing factors that can regenerate tissues (Blando et al., 2022).

Clinically these assertions have shown merit as well. In a clinical trial involving patients with advanced SCIs, Yannan Zhao et al. found that biomaterial scaffolding paired with MSCs regenerated motor function of spinal cord transmission through the peripheral nervous system (PNS) (Blando et al., 2022). One patient, with a major thoracic SCI eventually regained the ability to walk after experiencing MSC scaffolding therapy, and another regained lower body control after losing it to a major cervical SCI. By using electrophysiology, researchers were able to determine that following treatment, the patients were able to conduct electrical transmission through the spinal cord more effectively than when paralysis was sustained.

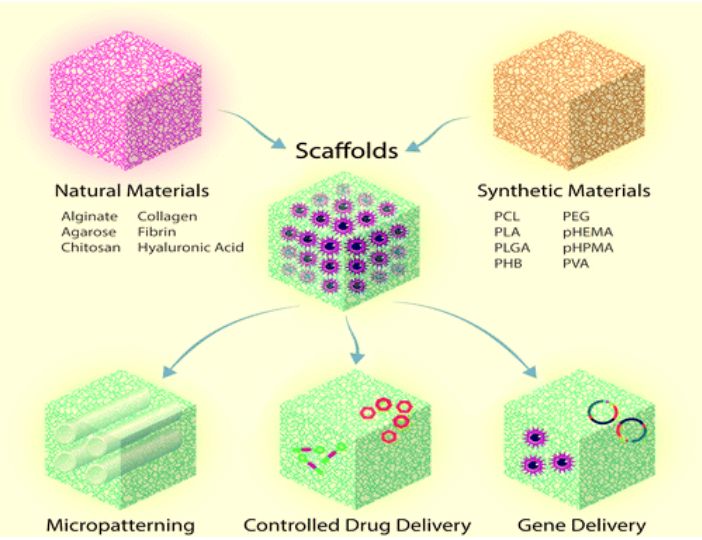

Figure 3. MSC Scaffolding

A figure displaying the ways by which scaffolds could be used to enhance the functionality of MSCs and allow for positive implications (Ashammakhi et al., 2019). Additionally, it illustrates the ways other therapy options like gene or controlled drug delivery can be utilized to enhance these effects. The three images following the arrows below the Scaffolds figure in the middle represent implementations of scaffolding. The two images above the middle image represent the materials (both synthetic and natural) used in scaffolding.

Another mode by which to influence the effectiveness of MSCs in treating SCIs is through pre-injection gene modification. After genetically modifying rat MSCs to express MNTS1, “a multineurotrophin that binds TrkA, TrkB and TrkC, and p75(NTR) receptors or MSC-MNTS1/p75(-) that binds mainly to the Trk receptors,” Gentaro Kumagai et al. injected the genetically modified MSCs to the central affected area of a contusive SCI (Kumagai et al., 2013). This resulted in promotion of angiogenesis, enhanced axonal growth, reduced inflammation and glial scarring, and various other positive factors after regenerative SCI therapy (Kumagai et al., 2013). Additionally, MSCs genetically modified to release growth-factor-1, an insulin-like factor, exhibit better survival and capacity to improve myelination (Xia et al., 2023). As found by Yuan-haun Ma et al., the use of genetic modifications and tissue engineering like biomaterial scaffolding, produced greater functionality and motor rehabilitation in animal spine models (Xia et al., 2023). Additionally, related to the secretions of MSCs that give them regenerative properties, three-dimensional scaffolding and tissue engineering can increase the expression of specialized neurotrophic factors like BDNF and GDNF, which expedite

nerve cell axonal regeneration and minimize the effects of glial scarring. Furthermore, neurorehabilitation can be paired with these modes by which to transplant MSCs to enhance their regenerative capabilities. Studies have shown that physical and mental activities such as “treadmill training, electrical stimulation, electroacupuncture, transcranial magnetic stimulation (TMS), ultrashort wave therapy, and swimming training,” enhance the effects of MSC transplant therapy after a SCI (Xia et al., 2023). The hypothesis that CNS controls aspects of the PNS can promote rehabilitation within the neural tissue of the spine that controls muscle motor activity. Another important aspect of understanding the importance of the mode by which to transplant MSCs is the form of injection. The most used is intravenous (IV), intrathecal (IT), and intralesional (IL) injections, each with their own benefits and drawbacks (Xia et al., 2023). While IL injections have been observed to be effective in locating MSCs to the site of the initial SCI trauma, it is normally an intricate procedure with a lot of room for error, especially when dealing with already damaged cell tissue. The risks of further damage or contamination of spinal tissue outweigh the efficacy of an IL injection of MSCs, pushing for the exploration of other injection modes. IT and IV injections are not only less invasive but also easier operations to perform. Furthermore, IT injections are generally more effective “in terms of cell engraftment and safety” (17). Additionally, it has been established that IT injections can be a noninvasive and safe therapy when trying to improve neuronal functioning and motor capabilities in humans, including the general rehabilitation of spinal cord tissue (Bydon et al., 2019). According to Mohamad Bydon et al., IT injections improved both objective and subjective measures of recovery in patients, as established in a human clinical trial involving 14 patients suffering from SCIs (Bydon et al., 2019). With each MSC transplantation method having different benefits and drawbacks, there is no end-all, best method. Each method can be utilized in many ways, and through clinical research, the consensus is in favor of the idea that in cases of SCIs, it is more advantageous to utilize multiple different injection methods to transplant MSCs.

Clinical Applications and Recent Advancements

While there are plentiful examples of clinical studies, not many are standardized or contain large enough sample sizes to draw supported conclusions. One study, however, unified a large quantity of results regarding MSC therapy in SCIs into a single meta-analysis using data from 62 clinical trials. To address “how much scientific evidence there is to support the sufficiency of stem cell therapy in preclinical and clinical studies of SCIs”, Zhinzhong Shang et al. analyzed 62 clinical trials involving 2,439 patients (Shang et al., 2022). After extracting data, it was observed that in 48.9% of patients receiving MSC therapy, their American Spinal Injury Association (ASIA) impairment scale score, a neurological assessment that takes sensory and motor ability of the spinal cord into account, improved by at least one grade. There are mechanisms by which MSCs work that are not understood due to the discrepancy between expected success and actual success of the treatment.

Additionally, Zhinzhong et al. found that side effects such as “neuropathic pain, abnormal feeling, muscle spasms, vomiting, and urinary tract infection were (the most) common, with an incidence of > 20%.” The likelihood and inexplicable nature of these side effects are most concerning (Shang et al., 2022). This demonstrates the premature excitement regarding MSC transplantation therapy, as there is still so much more to address and understand, especially regarding the effectiveness and risks. Currently, the main problem in analyzing contemporary data is its scarcity. This highlights the importance of promoting research; with time, sufficient data will become available to make accurate conclusions without doubts.

Overall, these current clinical applications make integration of MSCs in the cases of SCIs, more realistic and feasible when regenerating tissue and restoring function. However, the exact mechanisms are not fully understood. Additionally, while the clinical data sounds promising, it is still debatable whether certain data is conclusive due to controversial methods or studies that take novel approaches. Furthermore, certain risks should not be ignored concerning MSC therapy. Serious effects have been observed in patients, like a “large tumor-like mass inside the spinal cord after 8 years of olfactory mucosa cell transplantation,” due to the MSC therapy the patient was receiving (Lukomska et al., 2019). Moreover, in neurological applications of MSCs, there have been even further negative side-effects observed. After injection, unintended symptoms consisting of fevers, headaches, and pain were common, while definitive positive results were quite rare (Lukomska et al., 2019).

Adversities and Current Limiting Factors

While the attractiveness of mesenchymal stem cell therapy, specifically in neural systems, has led to many valuable studies, there seems to be an overstatement regarding the actual applicability and current understanding of MSC therapy. As a novel topic, there has been a recent influx in interest regarding MSC therapy in combating SCIs, but the conclusions made are not in support with each other. There also seems to be a degree of confirmation bias in the current state of public opinion. With the recent increase of interest in stem cell therapies, many Phase I studies, reports, and reviews have been published; however, significant clinical data is yet to be attained. A large-scale meta-analysis focused on adverse events (AEs) or negative side effects of a MSC treatment of a SCI. Zhizhong Shang et al. discovered that clinical trials and research have produced approximately 28 possible AEs (Shang et al., 2022). Additionally, it was also found that the development of viable SCI treatment using stem cells is still in the early, infantile, stages. Not only do the ideal parameters for injection and treatment need to be established, but the exogenous effects of MSC introduction to a site of trauma also need to be better understood. Better clinical trials, research on large mammals, and early-stage human trials need to be further studied for the advancement of the stem cell field. Currently, knowledge is limited on both the interactions between neuronal tissue and MSCs as well as the optimal operations on a SCI trauma site.

In addition, clinical trials are not closely regulated. Therefore, more research on MSCs and their functions is needed for the current interest and excitement surrounding this topic to be justifiable and within reason.

Ethical Concerns of Stem Cell Therapy

While the ethics of using MSCs, cells often derived from tissues like adipose, bone marrow, or other general tissue groups, is not disputed, there have been concerns raised in the scientific community surrounding stem cell research and its morality. This conversation is often centered around the idea of scientific misuse of stem cells, immoral genetic manipulation, and human cloning. An example of scientific misuse of stem cells can be seen with Rishi S. Nandoe Tewarie et al.'s research done in the field of human asexual or same-sex reproduction through the use of oocytes proliferated from male stem cells, which can enable one male or two males to produce a human embryo (Nandoe Tewarie et al., 2009). While this is entirely possible and within the realms of scientific reason, it has been debated whether this would be an ethical action. There is no way of knowing the detrimental effects this could have on a child due to the pairing of strictly male DNA. This leap, while scientifically relevant, would be concerning ethically and could eventually lead to the degradation of human moral laws. Additionally, cloning human cells follows the same line of reasoning: while scientifically possible, it is still ethically questionable. Many believe that there needs to be a line drawn in how deeply science interferes with natural human development and evolution over time. The implications of cloning open doors that generate additional issues. Another ethical concern regarding stem cell research is genetic modification and human germline engineering. By utilizing stem cells to produce artificial gametes, the expression of certain genes can possibly be altered, thus allowing human intervention within the genomic sequence of embryos (Nandoe Tewarie et al., 2009). This is ethically concerning because it would essentially enable humans to design the type of child they wish to bear, eliminate all genetically expressed diseases, and change the physical appearance of their future child. This is concerning on various levels and would lead to the dissolution of countless social, economic, and cultural values.

Conclusion

As a novel method of approaching SCI regenerative therapy, MSC transplantation is a promising and exciting solution. Not only are the factors secreted by MSCs beneficial for neuronal repair and regrowth, but their effectiveness is amplified when paired with other enhancing. Multiple studies and clinical trials have shown that the factors secreted by MSCs can enable tissue repair and neuronal regeneration in the spine. However, MSC therapy can also come with concerning side effects. The promise of MSC therapy is offset by its inconsistency, risks, and ineffectiveness in current clinical trials. It is hard to find substantial and valid research supporting large-scale MSC transplantation in the human spine that does not include many failures and low success-rates. This puts into check the current excitement surrounding MSC therapy and applications within the nervous system of the spine. While there are obviously possibilities in the future, at the current state of research and clinical trials, the effectiveness of MSC therapy is questionable at best. There are still many factors that need to be addressed as progress is made, such as standardizing methods, developing lower-risk results, and exploring the mechanism of MSC therapy. With a better understanding of these intricate modes by which MSCs work to regenerate neurons and enhance the microenvironments within tissues following a SCI, future trials in humans could be seen as safer and more realistic.

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