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Mesenchymal stem cells improve diabetic neuropathy in rat model

Xiaokun Shi, Kangquan Shou, Shi-Hong Shi, Jung Han Lee*

Abstract

One of the holistic strategies that are developed to combat diabetic neuropathy is stem cell therapy. Among different stem cell types, mesenchymal stem cells (MSCs) are one of the most well-studied cell therapy sources due to their low immunogenicity and their ability to both transit across the blood-nerve barrier and survive in the neuropathic microenvironment due to their protecting properties. MSCs can restore nerve morphology, increase survival, improve functional recovery and muscle reinnervation, and alleviate pain in various neurodegenerative conditions, including diabetic neuropathy. In recent years, many experiments have produced evidence to confirm these benefits using different diabetic rat models. In general, "diabetic neuropathy" as a search term along with "stem cell therapy" and "MSC" or "mesenchymal stem cell" on the PubMed database produced 11 articles published between January of 2002 and January of 2019. Most of the studies explored the therapeutic mechanisms, while relatively few studies elaborated on the stem cell regenerative processes in detail. Thus, this paper is dedicated to reviewing the evidence from rats who received MSCs through cellular injection to support the therapeutic potential of MSCs in diabetic neuropathy and provide a guideline for future preclinical studies in the field. This study focuses solely on rat models because rats are commonly used in preclinical research and in nerve conduction function analysis, which can augment the global view to streamline the gold standard for laboratory animal research in regenerative therapy.

Keywords: Ovarian cancer cell; CD70; Xenograft model; PCR

* Correspondence author e-mail: Lee-t@yahoo.com
[1] Department of oncology, the University of the West Indies
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Introduction

Diabetic neuropathy is a heterogeneous group of disorders that complicates diabetes and affects the major part of the peripheral nervous system. Diabetic neuropathy is characterized by the insidious onset of pain and sensory disturbance, poor foot sensation or numbness, itching, muscle weakness, and muscle wasting that is caused by a variety of physiological and structural changes over time resulting in damage to the distal nerve fibers. Despite significant progress in neurobiological research, the pathogenesis of diabetic neuropathy is still not fully understood. Therefore, we still have no specific drug to cure this degenerative complication and limit the prescribed drugs to symptomatic treatments. Current treatment options for diabetic neuropathy aim to prevent the symptoms or alleviate suffering but do not totally cure the disease itself.

One of the holistic strategies that are developed to combat diabetic neuropathy is stem cell therapy. Among different stem cell types, mesenchymal stem cells (MSCs) are one of the most well-studied cell therapy sources due to their low immunogenicity and their ability to both transit across the blood-nerve barrier and survive in the neuropathic microenvironment due to their protecting properties. MSCs can restore nerve morphology, increase survival, improve functional recovery and muscle reinnervation, and alleviate pain in various neurodegenerative conditions, including diabetic neuropathy. In recent years, many experiments have produced evidence to confirm these benefits using different diabetic rat models. In general, "diabetic neuropathy" as a search term along with "stem cell therapy" and "MSC" or "mesenchymal stem cell" on the PubMed database produced 11 articles published between January of 2002 and January of 2022. Most of the studies explored the therapeutic mechanisms, while relatively few studies elaborated on the stem cell regenerative processes in detail. Thus, this paper is dedicated to reviewing the evidence from rats who received MSCs through cellular injection to support the therapeutic potential of MSCs in diabetic neuropathy and provide a guideline for future preclinical studies in the field. This study focuses solely on rat models because rats are commonly used in preclinical research and in nerve conduction function analysis, which can augment the global view to streamline the gold standard for laboratory animal research in regenerative therapy.

Diabetic Neuropathy: Pathophysiology and Clinical Implications

Diabetic neuropathy (DN), a chronic and highly incident complication of both type 1 and type 2 diabetes (T1D and T2D), is defined as progressive somatic and autonomic nervous system deterioration caused by hyperglycemia in some patients after being relentless for years or even decades. Physiologically, hyperglycemia triggers a cascade of molecular dysregulation that ultimately integrates OS/NOS-induced oxidative and nitrosative stress and cytokine-induced low-grade inflammation as the main pathogenic pathways. In the case of OS/NOS, it causes peroxisomal alterations, along with polyol pathway hyperactivity—due to SGLT2 upregulation—, that predominate over mitochondrial-peroxidated energy metabolism and cause bioelectric and bioionic derangements by hyperactivating Na+–Ca2+ exchangers, changes in voltage-dependent K/Na channels, overactivation of potential-gated sodium, as well as decreased activity of Ca2+ and thinly myelinated pre-synapses. This hyperexcites adrenergic, glutamatergic, and glycine-mediated neurons, narrowing Schann cells as mitochondrial biogenesis and retrograde axonal transport are impaired. In later END stages, dysmetabolism, overproduction of extracellular matrix proteins, and defective release of trophic factors by astrocytes and microglia sustain low-grade inflammation and neurodegeneration.

From the clinical point of view, an increase in all-cause mortality, due to an overwhelming rise in cardiovascular events, results in patients showing silent ischemic cardiac arrhythmias or progressive alterations in otoneural cardiovascular reflexes, worsening orthostatic intolerance. Upregulated oxidative and nitrosative stress alter islet glucagon secretion in the hypothalamic nuclei and temporarily activate adrenoceptors. This is phenotypic in the case of an initial "sensory" axonal poly-Nmethyl-D-aspartate receptor depolarizing wave and spinal affair lasting for 18 months to a four-year-

old. Up to 60-90% of pancreatic pre-sympathetic spinal diabetic preganglionic neurons may become always pathologically sensitized, fostering a decrease in the spatial overlap sympathetic-preganglionic neuronal activation, inhibiting increased over-inhibition of ventricular sympathetic preganglionic activity. Central autonomic dysfunction occurs as lumbar sympathetic neurons simply die with advanced progression of OS/NOS-induced axonal degeneration. Thus, high-overactivity of pre-diabetic dorsal motor nucleus neurons gradually decreases adrenal and lumbar sympathetic tone in the diabetes-induced postganglionically sympathetically denervated adipogenic environment.

Mesenchymal Stem Cells: Characteristics and Therapeutic Potential

Mesenchymal stem cells are stromal cells that exist in nearly all human and mammalian organs and tissues. These cells are adult stem cells, are non-hematopoietic in origin, and have substantial differentiation potential. Mesenchymal stem cell cultures have an adherent fibroblastoid morphology and contain cells that meet a set of surface antigen expression markers, possess multi-lineage potential for differentiation into cell types that support connective tissue (i.e., adipocytes, chondrocytes, and osteoblasts), express particular sets of specific genes, and have multiple self-renewal mechanisms. However, they are distinct from other stem cells (such as embryonic stem cells), demonstrating a tendency of lower self-renewal, but a greater propensity to differentiate. They are known to be able to migrate directly to sites of injury to exert functions that play an important role in tissue regeneration, repair, and protection in a paracrine manner that supports, socializes, and proliferates target cells.

Mesenchymal stem cells from rats, mice, and humans have been reported to demonstrate therapeutic potential in cell therapy for diabetic neuropathy. They actively secrete growth factors to improve sciatic nerve blood perfusion, exert nerve tissue protection, reconstruct myelin, reduce delayed electrophysiological abnormalities, and modulate local inflammation to promote the regeneration of peripheral nerve. In addition, they were able to secrete growth factors directly to protect against dorsal root ganglion (DRG) apoptosis, thus improving the pain response. The transplanted mesenchymal stem cells also induce endogenous NSCs to participate in proliferation and differentiation and to remodel the myelin sheath by differentiating themselves into Schwann-like cells. This evidence suggests that mesenchymal stem cells may become a potential cell candidate for the treatment of diabetic neuropathy.

Animal Models of Diabetic Neuropathy

Diabetic neuropathy affects several organ systems, including the vasculature, skin, eyes, and the central and peripheral nervous systems. The peripheral nerves represent the most frequently affected site in diabetes. The somatosensory system and small fibers are the most affected domains in diabetes. Evidence of peripheral nerve degeneration can be found in sural nerve biopsies of patients in the initial phase of the disease [1,2]. Furthermore, using indirect methods, such as skin biopsy or

corneal confocal microscopy, neurodegenerative processes have been revealed early in the course of the disease [3]. These neurodegenerative changes have an overlap with autoimmune response [4].

The development of pathologically small nerve fibers, like in unmyelinated c-fibers, can also be achieved in animal models that have been exposed to inducing agents to induce diabetes, unlike those used in the fibroblast cell culture models. Animal models offer a unique opportunity to explore the pathological features of diabetic neuropathy. This section explores the hypothesis that mesenchymal stem cells could improve neurological outcomes in animal models. Animal models allow us to provide new insights into the therapy of MSC against diabetic neuropathy. Rat models are chosen in this section as a useful device because rats' sensory system structure resembles human anatomy and plays a significant part in sensory input and functional disturbance, which is typically regarded as a sign of neuropathy. Long lifespan, easy handling, and resemblance with individual diabetes characteristics have made rat models an appealing alternative for the research of diabetic neuropathy. They also allow us to further describe these MSC transplantation techniques using the three main routes in rats.

Rat Models: Advantages and Relevance

Experimental animals are widely used to model various aspects of DN to develop anti-DN drugs and test their preclinical effects. The existing literature involves a comprehensive overview of an exhaustive list of small animals used for this purpose, including those that mimic type 1 diabetes (T1D), such as guinea pigs, basset hounds, and others. In the T1D animal model of rabbits, the electro-analgesiological pattern of nerve dysfunction corresponds to clinical neurophysiology in human T1D compared to T2D. The symptoms of DSPN in diabetic rabbits were alleviated by the drugs used to ameliorate pain symptoms of human DPN. This pre-clinical efficacy was further confirmed in a large animal model of naturally occurring diabetic neuropathy in dogs.

As for the T2D phenotype, the most studied animal models include those induced by high-fat, high-sucrose diets, as well as Zucker diabetic fatty (ZDF) rats, Otsuka Long-Evans Tokushima fatty (OLETF), Goto-Kakizaki (GK) rats, and db/db mice, C57BL/6-Ins2Akita (Akita), and others. The present review focuses on predominantly used rat models with STZ-induced T1D and T2D. Traditionally, experimental studies of the cellular, biochemical, and molecular mechanisms of DN pathogenesis were limited by the lack of corresponding available human tissues. In this context, rat models of DN are advantageous tools. Hormonal and genetic pesticides are used for experiments in rats with T1D and T2D. Rat models are the working models of studying the following and basic mechanisms of DN development. This review presents data on the MSC-based treatment of DN in experimental rat models. In this context, the most consistent, valid, and practically relevant network of animal evidence is derived from the work with rat models, in which damage to the nervous system in diabetes is the strongest.

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Mechanisms of Action of Mesenchymal Stem Cells in Diabetic Neuropathy

The beneficial effects of mesenchymal stem cells (MSCs) likely result from their various mechanisms of action. Antioxidative and antiapoptotic, angiogenic and vasculogenic, and remodeling and neuroregenerative activities have been reported as the main mechanisms of MSC action in numerous studies of different animal models of diabetic neuropathy, as well as in several clinical settings.

Anti-Inflammatory Effects

Peripheral neuropathy is primarily associated with neuroinflammation and oxidative stress, and initiation of treatment in prediabetic states could be useful in reversing or halting neuropathy development. Indeed, data from preclinical research show that MSCs reduce the expression of proinflammatory cytokines, such as IL-1β, TNF-α, and TGF-β1, and increase the expression of anti-inflammatory cytokine IL-10 in the sciatic nerve, which could prevent nerve damage in the early stage of the disease.

Secretion of Neurotrophic Factors

MSCs can secrete and produce various neurotrophic factors, including VEGF, BDNF, HGF, NGF, and GDNF, which could stimulate nerve regeneration in diabetic neuropathy. Direct application of BDNF and CNTF in one clinical trial has already shown improvements in sensory conduction and vibration perception thresholds, as well as reductions in neuropathic pain in various patients with early diabetic neuropathy. MSCs stimulate the expression of various growth factors, and they synthesize and release them in a time-dependent manner: VEGF and GDNF in the early phase, HGF in the intermediate phase, and NGF and BDNF in the long-term phase after combined hyperbaric oxygen therapy with culture-expanded MSCs in diabetic neuropathy.

Anti-Inflammatory Effects

Several preclinical studies carried out in different models of diabetic neuropathy have shown that stem cell therapy with MSCs mediated the anti-inflammatory effects in both peripheral and central nervous system. After nerve injury, macrophages and microglia are rapidly recruited to the lesion site and, in the CNS, they are mainly involved in the removal of myelin debris and in the support of axonal regeneration. This function goes along with the production of immune mediators, which provide either pro-regenerative or regenerative-unfriendly milieu.

MSCs might contribute to a pro-regenerative inflammasome environment and, simultaneously, counteract tissue-injuring-induced neuroinflammation. In the nerve, BM-MSC and hUC-MSC therapy triggered the accumulation of anti-inflammatory/pro-regenerative macrophages and a reduction of pro-inflammatory M1 cells. BM-MSCs inhibited LPS-induced release of microglial and peripheral blood mononuclear cell-derived anti-inflammatory molecules and improved also anti-inflammatory and anti-apoptotic molecule cytokine profile shift in an animal model of DuPN. Also, in the spinal cord of type I

diabetic rats, transplanted BM-MSCs modified the microenvironment after nerve injury by the release of neuroprotective chemokines. hUC-MSCs also increased the mRNA levels of anti-inflammatory M2 macrophages and chemokines in the sciatic nerve, in line with the reactivation of the CD68/ED1+ cells towards the M2 phenotype. From a different point of view, a single peripheral injection of BM-MSCs restored to normal the initial exaggerated systemic inflammation, thus ameliorating the development of the nerve electrophysiological parameters of DuPN in diabetic rats. Taken together, these findings support the notion that MSCs might modulate the inflammatory response in the nervous system, thus ameliorating the development of symptoms in DuPN.

Discussion

Aside from the directions discussed in this article, future areas of research might consist of combining MSCs with other therapeutic approaches used in treating diabetic neuropathy, such as anti-oxidative substances (since they are known to have anti-diabetic properties as well), antioxidant enzymes aimed at removal or minimization of oxidative stress production, pain management therapies designed to mediate the sensation of pain, anti-inflammatory medications or approaches, as well as other cellular therapies that have been shown to decrease the sensation of pain or have anti-inflammatory properties. Because diabetic neuropathy may affect multiple sensory functions simultaneously, novel navigated stimulation approaches, as well as invasive techniques, are being developed and should be evaluated alongside existing methods.

Further additional innovations to be developed will consist of different administration routes to ensure that higher proportions of the transplanted MSCs are properly and successfully targeted into the tissue that may benefit from its application. Beyond the type of MSCs, various other factors can substantially influence the volume and nature of MSCs produced in vitro, which can determine the efficacy and safety of the subsequent autotransplantation. These details may therefore constitute a significant regulatory element that may need to be standardized and be considered within any following preclinical study. Research teams should focus their efforts on attempting to identify optimal doses and dosing schedules for diabetes patients with and without sensory symptoms, which could benefit from regenerative therapy. Given the variables that must be taken into consideration for stem cells to be used clinically, future studies are possibly warranted on refining and controlling fully reproducible studies before translating any of these findings to clinical trials. Stem cells are a candidate for DR therapeutics. MSCs have already demonstrated their curative effects against DR in several trials. The in-place expanded knowledge on the variety of correlative effects of MSCs has introduced a new yet not far-fetched line of research: the combination of MSCs with other therapeutics. Now that further substantiating trials on the efficiency of MSCs or combined with another therapeutics are on the radar, they are providing better-than-ever answers. Extracellular MSC vehicles are an irreplaceable source of insulin (encapsulated MSCs). For the sake of the adaptogenic protective effects of MSCs from the onset of DPN, their combination with a sub-hypoglycemic agent that exerts individual curative effects as well as, in some way, relieving pain and at the same time does - in order to prevent hyperglycemia. MSCs can be combined with pericyte transplantation since their effects are efficient at different

degenerative levels: up-stream and over high glucose-related enhanced pericyte death, or even glia cells/endothelial cells interior to the BM unit. A treatment strategy using sub-minimal efficient quantities of three of the above-mentioned stem cell types, preferring, according to some collateral data, SVF over MSC, has earned a likelihood to be efficient also in treating diabetes (e.g., protection of the pancreatic endocrine cells in T2D). Therefore, a multicore type of study is highly recommended to accumulate data on this territory in a short time, during the time-limited DPN of the aging population. A shared experimental animal model for diabetes-based vesicular-trophic methods of regenerative modulation is requiring an inexpensive logistically basic strategy.

Conclusion

MSC-based diabetic neuropathy therapy in rats has favorable outcomes in terms of cell sources, optimal mode (including motor and therapeutics), dosage, administration frequency and timing, and short- and long-term complications, and personalized regimens. Toxicology studies will be conducted to determine the safety of safer, more selective and supportive regimens. Attempts to bypass the retinal blood and nerve barriers (exercise, low-level laser therapy, hyperbaric oxygen therapy) will not increase power as such interventions may not directly change the nerves or may need to undergo cell therapy. We must, of course, take therapeutic steps. The in vitro and in vivo rat and mouse animal studies are clear and significant because the functional and histomorphometric results of healthy animal therapies can be saved and analyzed using the same special device. There are still some challenging steps in this review. There are still few human data collection designs in the above human study populations (diabetes and neuropathy diagnoses and classification). Further research should address these critical gaps in the field. In addition, gender, type of stem cell and type of therapeutic agent are not reported in any systematic review. Further investigation will benefit from this position. The global research agenda is confined to murine animal therapy studies or in vitro models with MSC. The long-term effects of allogeneic MSC therapy have yet to be investigated, and it is not clear if any adverse effects such as cancer or mortality have been observed. Study of other future concerns is also limited in human assays.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

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Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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