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RESEARCH ARTICLE

Research Progress in the Repair of Peripheral Nerve Injury with Adipose-Derived Stem Cell Exosomes

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ABSTRACT

The repair of peripheral nerve injury has always been a difficult clinical problem. Although a variety of treatment methods are available in clinical practice, their efficacy is limited. In recent years, the components carried by adipose stem cell exosomes and their functions have been increasingly discovered. A large number of experiments conducted around the world have shown that adipose-derived stem cell exosomes have a positive effect on the repair of peripheral nerve injury. This article reviews recent progress toward the use of adipose-derived stem cell exosomes in the repair of injured peripheral nerves and possible future research directions involving adipose-derived stem cell exosomes.

INTRODUCTION

Peripheral nerve injury is a common form of neurological injury and accounts for 2.8% of all trauma-related injuries [1]. Although the peripheral nerves have the ability to repair themselves, complete functional recovery is often difficult, especially for longer nerve injuries and proximal nerve defects [2]. At present, various methods are employed to treat peripheral nerve injury in clinical practice [3,4]. Unfortunately, the current methods still do not provide good functional recovery [5] and are associated with disadvantages such as expensive repair materials and high risks of complications of failure [6]. Thus, trauma-related nerve injury imposes a considerable economic burden on societies as while negatively affecting the quality of life of patients and their families [7].

In recent years, the Adipose-Derived Stem Cell Exosomes (ADMSC-Exos) have been widely investigated for their utility in the treatment of many diseases, including in the repair of peripheral nerve injury [8,9]. In the present review, recent research progress achieved toward the application of ADMSC-Exos in the treatment of peripheral nerve injury is reviewed, and relevant application strategies and prospects for ADMSC-Exos in the field of nerve repair are discussed.

Exos are lipid membrane vesicles that contain a variety of non-coding RNA and protein substances that are actively secreted by cells [10]. Research has confirmed that Exos can mediate signal transduction between cells [11] and influence the repair of injured nerves and other pathological processes [12]. Since 1981, when the concept of Exos was first proposed [13], these vesicles have been a hotspot in many research

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fields. Exos were once considered a redundant component in cellular activities, but more in-depth research revealed that Exos transmit substances between cells, such as RNAs and proteins, and in doing so participate in the occurrence and development of a variety of diseases (such as tumors and genetic diseases) [14,15]. In normal physiological processes, Exos play a role in mediating cell–cell communication [16]. In addition, Exos can also regulate host-pathogen interactions [17]. Studies have also shown that Exos can serve as valuable markers in the clinical diagnosis of various diseases due to the presence of specific proteins [18] or microRNAs (miRNAs) [19] on their surface and can be secreted into the serum, cerebrospinal fluid, urine, saliva and other body fluids [20]. Their specific contents (proteins or miRNAs) enable Exos to play a diagnostic role in the clinic [21].

Research into the clinical potential of Adipose-Derived Mesenchymal Stem Cells (ADMSCs) became a hot topic after Zuk, et al. [22] first extracted these cells from autologous adipose tissue in 2001. Because they can be extracted easily and in abundant numbers from adipose tissue, ADMSCs have been regarded as an ideal source of cells for tissue repair in the treatment of a variety of diseases [23]. A large number of studies have shown that Exos derived from MSCs can regulate cell proliferation and differentiation, limit tissue and cell damage, regulate the immune response, and promote tissue regeneration and cellular repair [24,25]. Owing to these functions, ADMSC-Exos have great potential for clinical application in the repair of damaged nerve tissue.

ADVANTAGES OF ADMSC-EXOS

Adipose-derived stem cells and their Exos

Adipose cells have many advantages such as easy access, rapid growth, high genetic stability, low antigenicity [26,27], and multidirectional differentiation ability. Qian, et al. [28] detected signature proteins unique to neurons after applying a specific inducer to ADMSCs, indicating that ADMSCs have the potential to differentiate into nerve cells. In addition, the cell adhesion ability of ADMSCs is strong, making them easy to culture *in vitro*, and their nutrient requirements are low, with vigorous growth occurring in the medium [28]. ADMSCs are not only pluripotent and plastic [29], but also abundant within adipose tissue. ADMSCs make up approximately 2% of all adipocytes, which is much higher than the proportion of stem cells in bone marrow (1/25,000–1/100,000) [30,31]. Because of their accessibility and low maintenance requirements, ADMSCs hold great potential for use in many clinical applications. In addition to ADMSCs, Exos are also relatively easy to isolate *in vitro* at normal or slightly lower oxygen levels [32,33].

Molecular characteristics of ADMSC-Exos

With the expansion of Exo research, it became clear that different Exos carry different molecular markers, which can be used for the diagnosis and detection of clinical diseases [34,35]. Sonoda, et al. [36] found in a rat model of acute kidney injury that miRNA-16, miRNA-24 and miRNA-200C levels are increased in urinary exosomes in the state of kidney injury, and their increases were associated with a reduction of target mRNA in the glomerular medulla. Zhang, et al. [37] analyzed the miRNA profile of ADMSC-Exos and found 148 known miRNAs, and proteomic analysis of ADMSC-Exos identified 1466 proteins involved in various cellular functions [38]. Baglio, et al. [24] showed that Exos of MSCs derived from adipose tissue and bone marrow have highly overlapping miRNA expression profiles and identified differences in only a few transporter RNAs between the Exos from these two MSC types.

Effectiveness of ADMSC-Exos for the repair of peripheral nerve injury *in vivo*

Multiple studies [39-41] have shown that Exos derived from bone marrow MSCs can promote the repair of nerve defects and improve the quantity and quality of regenerated nerve fibers. Therefore, it is speculated that the ADMSC-Exos may have the same effect in the process of nerve injury repair. In recent years, many studies on ADMSCs have found that their Exos play an active role in the repair of peripheral nerves. Ghoreishian, et al. [42] isolated undifferentiated ADMSCs from the adipose tissue of dogs and showed that undifferentiated ADMSCs immersed in alginate hydrogels could be applied to successfully repair a 7-mm nerve defect that caused facial nerve injury. Orbay, et al. [43] cultured ADMSCs in an induction solution containing various growth factors and found that the cells differentiated into cells similar to Schwann cells in morphology. Moreover, compared with treatment with a silicone catheter only, transplantation of ADMSCs and differentiated ADMSCs into a damaged sciatic nerve resulted in greater improvements of nerve function indexes such as the conduction velocity of the sciatic nerve in a rat peripheral nerve gap model. Marconi, et al. [44] injected ADMSCs into rats through the tail vein to study the effect on the injured sciatic nerve, and their results showed that, compared with those in the phosphate-buffered saline–treated control group, the sciatic nerve function index and the number of nerve fibers regeneration were significantly greater. Allbright, et al. [45] placed ADMSCs in hydrogel for their use to repair the damaged sciatic nerve and reported promising results. In the study of stress urinary incontinence, Ni, et al. [38] found that the density of skeletal muscle fibers and peripheral nerve fibers in the urethra of rats treated with ADMSC-Exos was higher than that in the untreated group. In an experimental study of the bilateral cavernous nerve injury rat model, Li, et al. [46] found that ADMSC-Exo treatment could significantly reduce pathological changes, including distortion of normal nerve anatomy, atrophy of smooth muscle and collagen deposition, resulting in improvement of erectile function.

The role of exosomes in protecting neurons

Considerable evidence indicates that many different types of Exos can promote nerve regeneration [47,48]. For example, Schwann cell-derived exosomes were shown to promote neurite outgrowth [49]. However, the isolation of Exos from many sources can require damage to the source tissue, whereas the collection of ADMSCs to obtain ADMSC-Exos is relatively convenient and minimally harmful [50]. In 2018, Lin, et al. [51] applied ADMSC-Exos for the treatment of a sciatic nerve injury model and observed a reduction in the inner injury of the nervous tract, a complete and orderly nervous tract membrane, and promotion of repair of the sciatic nerve injury via reductions in Schwann cell apoptosis and autophagy. In 2019, Ren, et al. [52] found that the ADMSC-Exos modified to carry miRNA-133b significantly promoted the recovery of neural function in animals with spinal cord injury by influencing a signaling pathway related to axonal regeneration and the expression of Neurofilament (NF), Growth Associated Protein 43 (GAP43), Glial Fibrillary Acidic Protein (GFAP) and Myelin Basic Protein (MBP). Wei, et al. [53] identified many insulin-like growth factors and hepatocyte growth factors within human ADMSC-Exos and showed that ADMSC-Exos had a positive effect on the proliferation of PC12 cells after the induction of neuronal injury, reflecting a protective effect of ADMSC-Exos. Di, et al. [54] applied ADMSCs and a fibrin bio-catheter to a sciatic nerve injury model, and this treatment combination achieved an axon regeneration length and proximal stem cell movement distance that were superior to those achieved with only the bio-catheter. Together, these experimental studies confirm that ADMSC-Exos can play an important role in the protection of neurons and the occurrence of neurites.

Mechanism of nerve regeneration by ADMSC-EXOs

Exosomes affect a variety of nerve regeneration pathways. Some studies have shown that neurotrophic factors combine with exosomes to promote nerve regeneration. For example, ADMSC-Exos modified with Pigment-Epithelial Derivative Factor (PEDF) can activate autophagy and inhibit neuronal apoptosis, thereby reducing cerebral ischemia-reperfusion injury [55]. Recently, it has been confirmed that ADMSC-Exos transmit exosomal miRNA-30d-5p to inhibit autophagy among microglia and ultimately promote the polarization of microglia into an anti-inflammatory phenotype and reverse neuronal damage [56]. In addition, the blood supply to injured nerves is an important factor affecting nerve regeneration. Reconstruction of the vascular network provides a conducive microenvironment for axon growth during peripheral nerve repair [57,58]. Kang, et al. [59] found that ADMSC-Exos induce angiogenesis by affecting the expression of the anti-angiogenic gene Hypoxia Inducible Factor-1 (HIF-1) in endothelial cells through miRNA-31. Liang, et al. [60] found that ADMSC-Exos can deliver miRNA-125a to endothelial cells and reduce the expression of angiogenesis inhibitor Delta-like 4 (DLL4), thereby promoting angiogenesis at damaged sites. Other studies have shown that ADMSC-Exos play a neuroprotective role through the PI3K/AKT signaling pathway [53] (Figure 1).

Neuroglial cells in the peripheral nervous system are called Schwann cells and originate from neural crest cells in dorsal tubular nerve cords. Schwann cells gradually differentiate under specific microenvironmental conditions and encapsulate axons to form the nerve fiber myelin sheath. In the process of the growth and development of nerves, Schwann cells are closely related with axons [61]. In addition to providing a protective sheath for axons, Schwann cells secrete nerve growth factors and exosomes to promote the extension of axons [62]. Research has shown that the repair of injured peripheral nerve heavily depends on the proliferation and migration of Schwann cells [63]. Therefore, Schwann cells play a significant role in repairing the peripheral nerve after injury. In 2019, Bucan and colleagues [64] found that ADMSC-Exos can stimulate the proliferation of Schwann cells and increase the expression of cyclin Ki67, which indicates that Exos can enhance the length of neurites of Dorsal Root Ganglia (DRG) neurons. First, they demonstrated that ADMSC-Exos contain a variety of growth factors that facilitate nerve regeneration. Other researchers also demonstrated obvious changes in the expression level of miRNAs in Schwann cells after nerve injury, suggesting that exosomes carrying miRNAs secreted by Schwann cells may play a certain role in nerve regeneration [65,66]. Co-culture of ADMSCs and Schwann cells increased the mRNA expression levels of Epidermal Growth Factor Receptor 3 (EGFR3/ErbB3), Neuregulin 1 (NRG1), early growth response protein 2 (Egr2/Krox20), and MBP, as well as the corresponding protein expression levels of ErbB3, NRG1 and Krox20. In Schwann cells to promote the repair of the injured nerves [67] (Figure 1).

PROSPECTS

With more in-depth research on Exos, evidence has emerged that ADMSC-Exos can avoid problems related to stem cell transplantation and offer advantages such as the ease of collection in large quantities. With more investigators and clinicians in more fields recognizing the potential of ADMSC-Exos, these vesicles are gaining a broad future in the field of neuranagenesis. However, application method, application dosage and safety of exosomes in the human body still need in-depth study in the process of tissue repair after nerve injury. Additionally, any possible long-term or adverse side effects need to be determined. Although the current experimental evidence shows that MSC-derived Exos are safe and effective for the treatment of peripheral nerve injury, the problem of how exosomes are widely used in clinical practice has not been resolved. Safe dosage for use in humans is also unknown [38]. Moreover, combination of

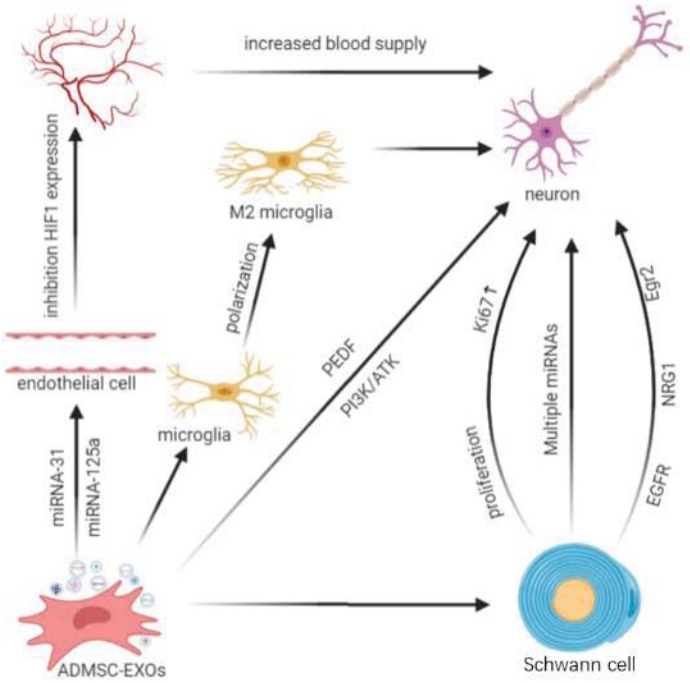

Figure 1 As shown in the figure, adipose stem cell-derived exosomes promote the repair of nerve damage through variety of ways.

ADMSC-Exos with other nerve repair methods needs to be explored. Therefore, continued research to characterize the effects of ADMSCs and their Exos is warranted, and more clinical studies are needed to determine the potential benefit of ADMSC-Exos for nerve repair.

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Data availability statement

The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

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