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Stem cell therapy for nerve injury

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Abstract

Peripheral nerve injury has remained a substantial clinical complication with no satisfactory treatment options. Despite the great development in the field of microsurgery, some severe types of neural injuries cannot be treated without causing tension to the injured nerve. Thus, current studies have focused on the new approaches for the treatment of peripheral nerve injuries. Stem cells with the ability to differentiate into a variety of cell types have brought a new perspective to this matter. In this review, we will discuss the use of three main sources of mesenchymal stem cells in the treatment of peripheral nerve injuries.

Keywords: Cell-based therapies, Peripheral nerve injury, Stem cells, Mesenchymal stem cells, Bone marrow mesenchymal stem cells, Adipose-derived mesenchymal stem cells, Umbilical cord mesenchymal stem cells

Core tip: Mesenchymal stem cells (MSCs) can differentiate into many kinds of cell types including Schwann cells (SCs). Since there are limitations for the use of SCs in nerve injuries, it is necessary to know about substitute cell types. So far, different sources of MSCs such as embryonic stem cells, bone marrow MSCs, adipose-derived stem cells, etc. have been studied and the existence of beneficial effects on nerve regeneration after injury has been confirmed. Here in this paper, we have collected the latest updates on the use of MSCs from different sources in peripheral nerve regeneration.

INTRODUCTION

Cell-based therapy in Peripheral nerve injuries (PNIs) has become an important intercession which amends clinical outcome. Contrary to the central nervous system, the peripheral nervous system has the potential for regeneration to a certain extent[1]. Nevertheless, complete functional recovery is strongly dependent upon the severity of the injury, anatomical site of the injury, and the delay before any kind of applied intervention[2].

What is PNI?

Any harm to the peripheral nerves interrupting their function would be classified as a PNI. In the case of PNI, the connection between the involved nerve fiber and the distal organ would be negatively affected and sometimes even lost, so, the distal organ undergoes atrophy due to denervation. In 1%-3% of patients with a traumatic accident, a PNI will almost always be involved[3,4]. It has been recognized in children suffering falls[5,6], as a consequence of medical procedures such as surgeries, chemotherapy, radiation[7-9] and sometimes it has been brought about some chronic conditions like diabetes and cancers[10,11]. It can also occur as an iatrogenic injury[12]. There are three main types of a condition causing PNI: Transection, tension, and compression[13,14]. First of which is commonly caused by penetrating trauma, the second one occurs when a nerve is over-stretched and the third can be reversed if the condition caused the injury is stopped within 8 h. In this article we have mainly focused on transection injuries.

What happens in cellular and molecular level?

A series of cellular and molecular events take place in response to nerve injury. In severe transection injuries (grade V in Sunderland classification or neurotmesis in Seddon classification[15,16]) caused by penetrating trauma, proximal and distal stumps of the injured nerve undergo pathological changes. “Wallerian degeneration” will occur in distal stump in which injured axons will turn into granule-like debris that will be later cleaned by macrophages[17]. Proximal stump also firstly retracts back to node of Ranvier[18] and then tries to reach the distal stump by giving rise to outgrowing axons[19,20] while activated Schwann cells (SCs) transform into regenerating phenotype and proliferate in the distal stump to form longitudinal columns called “bands of Büngner” which are essential to guide the outgrowing axons[21]. However, mentioned events along with the secretion of neurotrophic factors by SCs make a great environment for axonal stumps to meet, but the slow rate of axon regeneration which is location-dependent but is usually stated as 1 mm/d[22], almost always fails these processes and leads to impotency of activated SCs[23], misguidance of outgrowing axons and target organ atrophy due to prolonged lack of innervation[24].

Therapeutic strategies

In the case of transection injury, the Gold-Standard therapeutic strategy is to join the proximal and distal stumps of the damaged nerve through surgical interventions. Yet, when the gap is too wide to be repaired without stretching the nerve fiber, a nerve graft or a conduit is needed to bridge the gap. Although nerve grafting is the gold standard technique[20,25], this often leads to consequences such as donor site unwholesomeness for autologous grafts and graft rejection for heterologous grafts. On the other hand, conduits provide a guiding channel for axonal outgrowth and they can also serve as a vehicle to deliver essential growth factors and supporting cells[20,26-29]. In recent years, cell transplantation has been proposed as a method of improving peripheral nerve regeneration. SCs activated in response to nerve injury, as previously described play a key role in Wallerian degeneration and formation of bands of Büngner. These features make SCs the most suitable supporting cell candidate to transplant, but regarding other important features of SCs such as the difficulty of harvest, the slow expansion in culture and a high immunogenicity[30,31], SCs could not make the ideal

supporting cells. So attentions have moved towards the use of differentiated and undifferentiated types of stem cells which have the capacity to transform into a variety of different cell types in presence of particular factors.

Use of stem cells

Stem cells are undifferentiated cells of an organism being capable of giving rise to indefinitely more cells of the same type, and other types of cells by differentiation. Stem cells commonly come from two main sources: Embryos (embryonic stem cells), which can be harvested during embryonic period and adult tissues (adult stem cells) that are available in all the tissues in the body. Stem cells are classified by their capability to differentiate into other cell types. Unipotent stem cells (like muscle stem cells) can only give raise to cells of their own type. Oligopotent stem cells can differentiate into a few cell types, like myeloid stem cells. Multipotent stem cells have the ability to differentiate into a nearly related type of cells, like hematopoietic stem cells which not only can produce red blood cells but also can give rise to white blood cells and platelets. Pluripotent stem cells can differentiate into almost all cell types and the examples include embryonic stem cells and the cells from ectodermal, mesodermal and endodermal layers. Totipotent stem cells are the only ones which are able to give rise to all possible cell types, the example is the first few cells that result from the division of the zygote and the fertilized zygote itself.

Mesenchymal stem cells

In this review we mainly focused on mesenchymal stem cells (MSCs), the multipotent stem cells which can be obtained from various sources such as bone marrow, umbilical cord and amniotic fluid, adipose tissue, and also teeth. These cells are characterized morphologically by a small cell body containing a round nucleus with a clear appearance and a prominent nucleolus. Cells have a few long cell processes and the cytoplasm contains Golgi apparatus, mitochondria, rough endoplasmic reticulum and ribosomes. They are spread widely in the extracellular matrix containing a low amount of reticular fiber.

All-together, this paper will discuss the recent progress in the use of cell-based therapies and of interest the use of MSCs for peripheral nerve regeneration. It will summarize the perspectives of employing main sources of MSCs to speed up the healing process in injured peripheral nerves and involved mechanisms.

SURGICAL TECHNIQUES

The most common donor nerve used for autograft is Sural nerve which is a sensory nerve, hence it cannot be the proper choice for the repair of nerves with mixed motor and sensory or motor constituent[20,32]. Regarding to the complications of nerve autografts, researchers have focused on using substitute options to bridge the wide gaps with no harm to nerve ends. Various absorbable biomaterials have been used to make conduits and authors worldwide reported different results[20,26-29]. Conduits can be autogenous or synthetic. Autogenous conduits such as vein conduits sometimes accompanied by muscle or platelet-rich plasma components regardless of good outcomes require a donor site for harvesting[33,34]. A wide range of synthetic conduits made of collagen, polycaprolactone, polyglycolic acid and polyester have also been studied. Taras et al[35] used collagen conduits and reported good sensory nerves recovery. Wangensteen et al[36] and Ashley et al[37] showed that collagen conduits can have beneficial effects in clinical experiments as well as preclinical experiments with using them in trauma patients and infants with brachial plexus injuries respectively. They run a follow-up survey and monitored 5 infants with transplanted collagen conduits and reported significant motor recovery. Lohmeyer et al[38] also used collagen conduits for nerve reconstruction and reported a 55% of two-point discrimination and 77% of protective sensation recovery. Boeckstyns

et al[39] used collagen tubules for recovery of the injured median and ulnar nerves and Sosa et al[40] used collagen tubules containing platelet-rich fibrin for a patient with ulnar neuroma and both of them reported significant motor and sensory recovery. Mackinnon et al[18] used polyglycolic acid tubes in 15 patients with 17 mm nerve gaps and found that despite 14% of them having poor recovery, 86% of them showed excellent (33%) and good (55%) signs of recovery. Battiston et al[27] used polyglycolic acid conduits and muscle-vein conduits to see their difference healing properties. Results showed no significant difference between two groups. Weber et al[41] evaluated the beneficial effects of polyglycolic acid tubes compared to neurorrhaphy and nerve autografts and reported that in gaps of less than 4 mm or more than 8 mm, polyglycolic acids provided better recovery. Despite great improvements in surgical techniques and instruments, this field will have to be more and more investigated to make an optimal combination of cells and neurotrophic factors accompany a conduit to amend clinical outcomes.

IMPORTANT ROLE OF NEUROTROPHIC FACTORS

Axonal outgrowths are very slow to form and in severe cases it takes a long time for them to reach the distal stump, and on the other hand it is critical for activated SCs to innervate quickly in order to remain in their active form. Thus, administration of exogenous neurotrophic and growth factor with the ability of speeding up the mentioned processes has gathered attention. Neurotrophic factors are proteins which are necessary for many vital neural activities particularly in the regeneration of neurons after injuries[42-45]. Some of the most important neurotrophic factors are listed in following sentences and their role in neural regeneration have been described in brief. Brain-derived neurotrophin factor (BDNF) plays a key role after neural injuries and showed to have advantageous effects on outgrowing axons[46,47]. Nerve growth factor (NGF) have also a beneficial effect on the elongation of outgrowing sensory axons additional to enhancing SCs motility[48-50]. Glial cell line-derived neurotrophic factor (GDNF) acts like a chemoattractant for SCs[48-50]. Sox11 is a very important transcription factor upregulating in response to PNI[51]. Its expression can affect myelination and axonal elongation and levels of BDNF[52-56]. It also can help with the survival of neurons through the expression of TNF receptor-associated factor-associated NF-κB activator (TANK)[51-55]. Vascular endothelial growth factor (VEGF) can improve outcomes of nerve regeneration through improving microcirculation[57]. Insulin-like growth factor (IGF) found to have stimulant effects on mitosis of SCs and axonal elongation[58] Mohammadi et al[59] used silicon tube with hepatocyte growth factor (HGF) filling and reported improved muscle atrophy. Li et al[60] also reported that same beneficial properties of HGF in combination with acellular nerve allograft. Mohammadi et al[61] reported improved recovery after using silicone tube filled with adrenocorticotropin hormone (ACTH). Emel et al[62] have reported that IGF-1 has a better effect on PNI compared to Platelet-rich plasma. Regardless of how much it could be helpful to use the combination of conduits and neurotrophins, it is still important to hold SCs at their active form, because over a short period of time they lose their capacity for remaining active.Researchers have had invented methods to transplant newly activated SCs to the site of injury or to use cell types which are able to transform into SCs or SC-like cells to support the healing process.

SCs IN NERVE REGENERATION

SCs actively produce cell adhesion molecules, neurotrophins and growth factors and they can also serve as a scaffold allowing axonal sprouts to grow through their basal lamina[63-66]. They can also produce regulatory factors to help axonal outgrowth[67,68]. Despite promising results in preclinical experiments, clinical studies did not gain good results because the difficulties with harvesting[68,69] and culture of SCs[70] and the fact that prolong denervated SCs lose their ability to stimulate regeneration[71].

STEM CELLS USED IN PNIs

Because of stem cells' potentials they have become a source of cells which act s an alternative for SCs in peripheral nerve regeneration[70,72-74]. Stem cells as previously described, are biological progenitor cells which are undifferentiated and are able to produce more undifferentiated stem cells like themselves through mitosis. In addition, they can differentiate into almost all kinds of cell type depending on trophic and tropic factors they are exposed to. In the case of nervous system, stem cells have the ability to differentiate into supporting cells including oligodendrocytes, astrocytes, microglia, SC-like cells, and neurons themselves[75]. They can be differentiated *in vitro* before transplantation, and can also be transplanted in their undifferentiated form allowing to differentiate *in vivo* at the site of injury. An ideal choice of stem cell would be depended on the important features of the cells, like the ease of harvesting through noninvasive procedures, rapid expanding in culture and low immunogenicity[30,31]. Many kinds of stem cells with different sources have been studied, among them, MSCs having mentioned features, have been suggested as a potential cell type to enhance nerve regeneration. MSCs are multipotent stromal cells which can differentiate into a variety of cell types. Three main sources of MSCs will be discussed in following sections.

Bone marrow mesenchymal stem cells

Several studies have reported that bone marrow mesenchymal stem cells (BMSCs) can be induced to differentiate into mesodermal, ectodermal and endodermal lineage[76-80]. Interestingly they can differentiate into SC-like cells and ameliorate neural regeneration by releasing neurotrophic and growth factors, BDNF, GDNF, myelin basic protein[81] and by regulating SCs behavior[82]. These good effects seem to be irrelevant to their differentiation state because both differentiated and undifferentiated BMSCs represent positive molecular, electrophysiological, histological and behavioral effects in preclinical experiments[83]. Regarding some problems in harvesting BMSCs like the need of performing invasive and painful procedures that might yield a low number of cells, BMSCs have some disadvantages in clinical studies. Wang et al[84] compared the combination of BMSC-SCs and Adipose-derived stem cell SCs (ADSC-SCs) with acellular grafts to bridge the sciatic gaps of 15 mm and reported the greater regeneration recovery at the presence of BMSC-SCs and ADSC-SCs. Hu et al[85] used BMSC seeded grafts for the recovery of 50 mm median nerve injury in monkeys and found that the healing process with good functional and morphological outcomes was close to autografts. Cuevas et al[86,87] found that using BMSCs have beneficial effects on rat models of PNI with injured sciatic nerves. They have also run a follow-up experiment to assess the healing process and reported a significant improvement in sciatic nerve-injured rats with transplanted BMSCs compared to control group. Chen et al[81] used silicon conduits filled with BMSCs and assessed the recovery process measuring the number of growing axons and muscle atrophy along with walking test and reported their beneficial effects on mentioned indices highlighting the role of neurotrophic factors and myelin basic protein upregulation and not the increase in the number of SCs. Haghighat et al[88] and Mohammadi et al[89] also showed that using vein conduits with undifferentiated BMSCs can cause a significant increase in the number and diameter of growing axons and functional improvement consequently. Studies showed that differentiated BMSCs can have a better impact when used in combination with acellular nerve allografts rather than undifferentiated BMSCs[90]. It has been demonstrated that using BMSCs in PNIs can have similar outcomes as in use of autografts. Studies showed that BMSCs can possibly improve the outcome of nerve regeneration by modulating the behavior of SCs along with expressing neurotrophins[82]. Caddick et al[79] found that BMSCs can be induced to differentiate into SC-like cells representing SCs markers such as S100, P75, and GFAP. It has been reported that with the use of cytokines, rat BMSCs can be transformed into SC-like cells which were capable of myelinating PCl2 cells *in vitro* after 2 wk as well as increasing the myelinated axons in a rat model of PNI after 3 wk[91]. It has been shown that BMSCs apply their beneficial effects in a dose-dependent manner[92].

Adipose-derived mesenchymal stem cells

Adipose-derived mesenchymal stem cells (ADSCs) are another source of multipotent stem cells with the ability of transforming into all three germinal layers[93,94] and additionally, has been showed to give much greater numbers of cells compared to other adult tissues[95], with minimally invasive surgical procedures and a very simple isolation protocol including washing; diffusing with the aid of enzymatic agents; centrifugation and remotion of red blood cells (RBCs). This protocol gives a cellular fraction containing various cell types. Among them, ADSCs of interest adhere to the plastic wall of the container and proliferate quickly, so it can be easily recognized and separated from other cells. Studies showed that ADSCs can be induced to express glial cell markers such as S100B, GFAP and P75 neurotrophin receptors *in vitro*[69]. Also in the case of ADSCs, it has been demonstrated that *in vitro* differentiation into SCs could not bring any further melioration probably because of ADSCs natural capacity of *in vivo* differentiation into SCs[65]. Di summa et al[65] demonstrated that ADSC-SCs, as well as BMSC-SCs, can be used for the repair of rat sciatic nerve injury and since unlike the BMSCs, ADSCs can be easily harvested and expanded, they would be a better choice in PNI injuries. Erba et al[96] transplanted undifferentiated ADSCs in poly-3-hydroxybutyrate conduit to assess the axonal outgrowth and the transplanted cells capacity to transform at the site of injury. They reported the increase in the number of SCs and regeneration however researchers could not detect any transformation into neither glial nor neural cells. A similar result has been reported by Santiago et al[97] and the possible mechanism suggested by the authors through which the regeneration has been enhanced, was the expression of neurotrophins. Other similar results have been reported by other researchers[98,99]. Wei et al[100] showed that ADSC filled conduits have the same regenerative effects in rat sciatic nerve injury as SC filled conduit. Researchers found that ADSCs cannot be differentiated into SCs *in vivo* despite *in vitro* differentiation[101]. It has been demonstrated that undifferentiated ADSCs can release neurotrophins but at a lower extent[102]. Oliveira et al[103] used polycaprolactone conduits seeded with MSCs and showed the improvement of myelination and function compared with empty conduits. Another research group used collagen conduits with collagen gel containing ADSCs filling and results showed that improvement was similar to nerve autografts[104].

Umbilical cord mesenchymal stem cells

Regardless of ethical concerns with the use of umbilical cord mesenchymal stem cells (UC-MSCs) and limitation of its availability, there is still proofs which show they are superior to other adult stem cell with different sources: First, they can be collected in great numbers without causing any harm to donor simply from discardable tissues after childbirth; second, as they will be collected at the perinatal period, they are less likely to have genetic damages[105]; third, they are younger than other adult stem cells so they can undergo higher number of mitosis and can be much more expanded in culture[106]; fourth, while they lack HLA-II, they have much lower immunogenic properties compared to other adult stem cells[107]. Matsuse et al[108] used tubes filled with SC-like cells which have been previously formed as a result of UC-MSCs differentiation and showed that they can promote axonal regeneration. Same results have been demonstrated by Kuroda et al[109] and Pereira et al[110]. Peng et al[111] demonstrated that SC-like cells can secrete BDNF, Neurotrophin-3, and NGF *in vitro* and when combined with PCl2 cells, axonal growth was seen.

CONCLUSION

To improve peripheral nerve regeneration for better sensory and motor recovery, the use of stem cells and especially MSCs would be greatly helpful. These cells are not only able to differentiate into SCs in vitro, but they can also transform into SCs directly at the site of injury. Furthermore, administration of stem cells, can regulate the activity of native SCs, modify the inhibitory regenerative environment, improve myelination and cell survival and enhance neurotrophic activity. In summary, MSCs with such suitable properties as the ease of harvesting, especially in the case of ADSCs, and the low risk of

immunogenic activities have got a great potential to improve the regeneration process. Thus, for sure by further investigations, significant improvements in neural regeneration by the help of MSCs will be obtained.

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