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Nerve Regeneration and Stem Cells

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ABSTRACT

Background: Peripheral nerve trauma results in functional loss in the innervated organ. Recovery without surgical intervention is seldom successful. Many surgical techniques can be used for repair in experimental models.

Objective: The authors investigated the source and delivery method of stem cells, their outcomes, and whether stem cells will be differentiated in the injured nerve and whether they improve the regenerative process.

Materials and Methods: The following key terms were used: nervous regeneration, nerve regeneration, facial nerve regeneration, stem cells, embryonic stem cells, fetal stem cells, adult stem cells, peripheral nerve, peripheral nerve trauma, and peripheral nerve traumatism. The inclusion criteria were the experimental studies that applied stem cell therapy and tissue engineering for nerve repair.

Results: Out of 197 studies, 52 studies meeting the inclusion criteria were reviewed. Different sources of stem and precursor cells were noticed (bone marrow mesenchymal stem cells, adipose-derived stem cells, dental pulp cells, umbilical cord, and neural stem cells) for their potential application in the patients with peripheral nerve injuries. Different material conduits (vases, collagen, and polyglycolic acid) were used as bridges between the two nerve endings. Immunochemistry and electrophysiology were used for analyzing regenerative effects. Although recent studies have shown that stem cells can act as a promising bridge for nerve repair, considerable optimization of these therapies will be required for their usage in a clinical setting.

Conclusion: The use of stem cells derived from different sources presents promising results for nerve regeneration and effective neural and functional results. The best choices are BMSC and ADSC. The use of conduit also help and maximize the nerve repair, and in this way induce better myelination and axonal growth of peripheral nerves. [Patent CA2958398A1, Patent WO2016023130A1, Patent EP1685832B1].

Introduction

Nerve traumas are very common in the world and complete disruption of the nerve trunks without treatment, would result in partial regeneration and repair, partial or total loss of function [1,2]. One of the treatments for these traumas, is direct repair of disrupted nerve, which is sometimes possible. In most of the cases, it needs urgent repair, normally before 6-12 hours after the accident. Other treatment is nerve graft, but it may not diagnosed in proper time, or is not possible, sometimes there is lack of enough donor nerve graft available and sometimes it would not result in complete healing because of the nature of trauma and nature of function of that particular nerve [3].

Currently new modality for treatment of these traumas is using stem cells. We know that pluripotential stem cell from bone marrow, adipose tissue, skin, dental pulp, umbilical cord or from nerve trunks can differentiate into the Schwann cells and nerve cells with axons. It could help in regeneration of the missing nerves. The function of these cells is supposed to be a combination of self-renewal function, production and release of many growth factors, preparing the environment for nerve growth and to provide a closed space for axons to grow [4-11]. The difference between Central Nervous System (CNS) and Peripheral Nervous System (PNS) is the presence of Schwann cells in PNS.

In this regard the PNS with the help of Schwann cells can grow and regenerate more properly and effectively [2,12]. Harvesting the Schwann cells, culturing and using them in proper time is not easy and we may not use them in the right and proper time after the trauma (delay in treatment). So, the other way is to use stem cells. Stem cells from bone marrow, adipose tissue, skin, dental pulp, umbilical cord and nerve tissue has been used for this purpose. The best, easiest (and cheapest) cells for cell culture and differentiation into the Schwann cells of nerve cells and axons are Bone Marrow Mesenchymal Stem Cells (BMSC) [1-3]. In this review article we are going to review the most recent and the most important researches about stem cells and usage of them in nerve repair.

Materials and Methods

With using two search engines, Pubmed and Embase. Following key terms were used: stem cells, embryonic stem cells, fetal stem cells, nervous regeneration, nerve regeneration, peripheral nerve regeneration, central nervous system regeneration; nerve repair; adult stem cells, Adipose derived stem cells; skin stem cells; nerve stem cells; facial nerve, dental pulp stem cells, and nerve trauma. The search was restricted to experimental studies that used stem cell and tissue engineering for nerve repair after trauma. All relevant papers were chosen and their data were used for the present manuscript. This review article has been written on the base of these researches.

Out of these studies, 13 were about using stem cells in nerve repair, 30 were about using BMSC, 9 were about ADSC, 17 were about MSC, 2 were about HSC, one was about skin SC, 12 were about NSC, 5 were discussed other stem cells origins. There were some studies (5 studies) about using growth factors and neurotrophic factors.

Results

We found 197 papers and some of them were not relevant, 52 papers were selected for our study. All the 52 papers were studies which meet the inclusion criteria. Different sources of stem and precursor cells were explored (bone marrow mesenchymal stem cells, adipose-derived stem cells, skin stem cells, dental pulp cells, umbilical cord cells and neural stem cells) for their potential application in the repair of nerve injuries or traumas. Different material conduits (veins, collagen, synthetic conduits, and polyglycolic acid) were used as bridges. Immunochemistry and electrophysiology were the principal methods for analyzing.

Regeneration results of the treatment. Recent studies have shown that stem cells can act as a promising bridge for nerve repair, considerable optimization of these therapies will be needed for them to be used in a clinical setting. Out of these studies, 13 were about using stem cells in nerve repair, 30 were about using BMSC, 9 were about ADSC, 17 were about MSC, 2 were about HSC, 2 were about skin SC, 12 were about NSC, 5 were discussed other stem cells origins. There were some studies (5 studies) about using growth factors and neurotrophic factors.

Discussion

For repairing the nerve injuries, we have three options available; direct nerve suturing, nerve graft and stem cell or Schwann cell repair [1,3]. Although some of the results of the first two options are acceptable, but none of them are excellent and always we would have some remaining defects in the nerve function.

Schwann Cells

According to numerous studies, using Schwann cells has a very good result in most of the reports. But their harvesting would result to injury to the other nerves. Time for culture of Schwann cells is somehow long, reproduction of these cells is very long and we cannot re-produce enough Schwann cells in proper time [4].

Stem Cells

The next option is to use precursor stem cells, many studies promoting using the stem cells, culture them and use them after differentiation into nerve cells or Schwann cells [4,5,13-16]. According to studies and literature, stem cells can differentiate into the special cells that are needed for the repair of the defective tissue, can produce growth factors for growth of these cells [4,17-19], can produce regenerative factors, bioactive molecules [14], special growth factors [14], regulating molecules [20], trophic molecules [2,11,19,21-25], special extracellular matrix molecules [21], cytokines for differentiation of the stem cells into proper cells [4,18,19,26,27], promoting re-myelination [4,21], Structural support [11], increase in plasticity [11], reduction in retrograde degeneration [11], they are neuro-protective [19,28], they modulate the bed tissues [22], can modulate the immune system and produce proper environment for the regeneration of nerves [5,11,19,21,29,30]. Some of the cells would differentiate into endothelial cells to re-vascularize the tissue or have neo-vascularization effects [31-33]. These cells can reverse and remodel the injured tissue [34]. In this way they have neuro-regenerative and neuro-protective potentials [19,28].

Embryonic Cells

The embryonic cells and fetal cells are multi-potential cells that can be used for this issue, but usage of them has ethical problems and in most of the centers their usage is prohibited [6,7,35].

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Therefore, the best option is adult stem cells. Adult stem cells can be harvested from Bone Marrow (BMSC), Adipose Tissues (ADSC), umbilical cord, skin, dental pulp and nerve tissues [1,3,36,37] (Table 1).

Table 1: Comparison of different stem cells in regeneration of nerve tissue.

Type of stem cells	Advantages	Disadvantages	References
BMSC	-Easy to harvest -Expandable -Better differentiation to the nerves - highly proliferative -neurotrophic effect -neurogenesis	-harvest by inward admission	[1,4,5, 6,11,14,20,23,25,32,38]
ADSC	-Easy to harvest -Expandable - good colonization effects - no functional loss -Abundant amount -fast culture	- Not possible in thin patients	[2,31,37,39]
Neural stem cells	-good differentiation to the nerve tissue	-trauma to normalnerves -difficult to harvest	[1]
Olfactory ensheating cells	- neurotrophic and neuroprotective effects -myelinization	-very difficult to harvest -Donor deficit	[19,26]
Dental pulp progenitor cells	- dedifferentiate into Schwann cells and nerve cells	-difficult to harvest -Donor deficit	[3,31]
Small embryonic stem cells	- potential stem cells for all tissues	- difficult to harvest - very few in number	[19,26,30]
Epiblast stem cells	- pluripotential potential	- difficult to harvest - very few in number	[19]
Umbilical stem cells	- can produce the Schwann cells, neural cells and axons	-No source if it is not banked earlier	Umbilical stem cells
- if used earlier, it is not expandable	5, 7		- if used earlier, it is not expandable

Bone Marrow Stem Cells

There many Studies about using BMSC for Nerve Repair: BMSC are pluripotential and can be easily harvested, they are highly proliferative and can differentiate into other lineage of the tissues, for example from mesoderm into ectoderm derive tissues. They also have neurotrophic effects for the injured nerves. It has been shown that Mesenchymal Stem Cells (MSC), specially BMSC are best candidate for regeneration of the nerve tissues. They can easily differentiate into Schwann cells and axons [1,4,5]. They have low immunogenicity and have proper immunomodulation effects [5,11]. Most of the studies about repair with stem cells are based on BMSC. The BMSCs have been used for bone fusion, treatment of cartilage degeneration, spinal cord repair and degeneration of discs, bone defects, non-unions and osteoblast reproduction [6,14,20,32]. They have also been used for reproduction of myocardial cells, kidney, liver and for insulin-producing cells of pancreas [6,14,38]. It has been postulated that BM stem cells can give neurotrophic factor gene (s) to the genome of the neurons [23]. So this is a kind of gene delivery and can induce neurogenesis [25].

Adipose-Derived Stem Cells

The ADSCs are numerous and can be easily harvested from the excess fat tissues in the body. Adipose-Derived Stem Cells (ADSC) can be harvested very easily, are expandable, and can be easily differentiated into Schwann cells. They have good nerve colonization effects. The donor sites are expandable and there would be no functional loss after harvesting the fat tissue. The amount of fat stem cells in the adipose tissue is abundant. Harvesting is easy, fast and culturing of the cells is also fast [2,31,37,39]. They have very good results in nerve repair with good functional results.

Neural Stem Cells

Neural stem cells are other option. These cells are very capable in re-producing the nerve and neural tissue, but they are difficult to harvest, the amount of harvest is not high, and it always results in damage to the donor nerves. So, in most of the trauma cases it cannot be used [1]. But the results are very good, and the surgeon can rely on the results with NSCs.

Olfactory Ensheating Cells

Olfactory ensheating cells are some sort of Schwann cells that are present both in PNS and CNS. They have neurotrophic and neuroprotective effects. They can secret cytokines. They can be used in regeneration of the nerves. These cells can bridge the defect and provide a good environment for nerve growth. Also, they can induce myelinization of the axons. So, they are very powerful in nerve repair [19,26].

Dental Pulp Progenitor Cells

Dental pulp progenitor cells can also be used for cell culture and treatment of nerve injuries. These are MSC and dedifferentiate into Schwann cells and nerve cells. It is said that they have characteristic of MSCs so can be used for repair of injured nerves [3,31]. Harvesting is easy and with abundant stem cells.

Small Embryonic-like Stem Cells

Very small embryonic-like stem cells are the cells that are normally found in bone marrow and they can migrate to the peripheral blood. They are potential stem cells for all part of the human body. They are also present in the brain. These cells are very few and can go to any part of the body and begin the tissue repair [19,26,30]. The studies about these cells are few. And it needs more researches to confirm its results.

Epiblast/Germ Line-Derived Stem Cells

Epiblast/germ line –derived stem cells are the cells that have pluripotential potential and can differentiate into many lines of cells and start to regenerate the whole organ [19].

Umbilical Cord Stem Cells

Umbilical cord stem cells (endothelial progenitor cells, hematopoietic stem cells) are a kind of MSCs and can produce the Schwann cells, neural cells and axons. Fortunately, their use has not any ethical issue [5,7]. Their results are very promising and good results have been reported.

Skin Stem Cells

Skin-derived precursor cells also have been used for wound healing and skin defects. They can also be used for regeneration of the nerves. The function of these progenitor cells is that they work according to the cell differentiation, type of delivery, number of the injected cells and differentiation into other progenitor cells [40].

Conduits

For having complete effects of stem cells during the repair of neural tissues, some authors recommend using conduits, fibrin glue, immune-modulator drugs, scaffolds, biomaterials and rehabilitation, functional electrical stimulation, and physiotherapy [2,3,11,14,32,41-43]. Four mechanism has been postulated for the action of stem cells; resident stem cells, circulating stem cells, transient dedifferentiation of local paranchyma and neuroneogenesis [23,25,44]. With these mechanisms the stem cells can have a good to excellent results for nerve repair.

Although recent studies have shown that stem cells can act as a promising bridge for nerve repair, considerable optimization of these therapies will be needed for them to be used in a clinical setting. Limitations of our study were that only papers with English language have been selected. The most of studies have been done on animals and human researches are few.

Current and Future Development

Currently most of investigations are focused on the nerve promoter or stem cell promoters. These compounds can help in differentiation of stem cells into neuroblast and also can help in regeneration of the injured nerves. The resulted nerves are much thicker after the regeneration with much more axons and a better function. With the invent of these growth factors, we can have a rather complete recovery after nerve injury. Some examples are promoters of growth factors that are added to the conduits for better nerve regeneration. Patent CA2958398A1, Patent WO2016023130A1, Patent EP1685832B1 [45-47].

Conclusion

Stem cells have very high potentials in repair and regeneration of neural tissues. BMSC and ADSC are the best options. They can have complete healing effects by adding functional cells, differentiation to neural tissue, producing proper environment, secreting cytokines, trophic factors and immunomodulators. The best choice of stem cells for neural regeneration is BMSC. They can be easily harvested, are highly proliferative and have neurotrophic e**ffects.**

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