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Human Peripheral Nerve Regeneration Using Stem Cells

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Abstract

Peripheral nervous system (PNS) is the most important system of the body that controls a wide range of organs and functions. When accidentally injured, PNS has long term consequences. Despite of the various surgical treatments, fully functional recovery is impossible and often results in some deficiency. Recent advances in stem cell technology have enabled to recover the full functional peripheral nervous injuries. Different stem cells have the potential to differentiate into "Schwann Cells". Schwann cells have great importance in peripheral nerve regeneration because it provides a good media for axon migration and also important in the release of neurotrophic factors which enhances nerve growth. Use of autologous stem cells reduces immunogenic reactions. Nerve regeneration using the different types of stem cells has been briefly discussed in this review.

Keywords: Peripheral nervous system (PNS), Stem cells, Schwann cells and Neurotropic factors.

INTRODUCTION

Peripheral nerves are essential connections between the central nervous system and muscles, autonomic structures and sensory organs. Injuries to the peripheral nervous system are common and results in functional deficits which has a long term penalties. Acute nerve injury reports can be traced back up to 3500 years ago in biblical story. The use of suture and agglutination to repair nerves was first reported by Paulus Aegineta in the seventh century. Technique of suturing stumps of transected nerve was described by Gabriele Ferrara, pioneer of peripheral nerve surgery.[1] For the improvement or repair of peripheral nervous system different strategies have been developed including therapeutic approaches e.g. nerve end-to-end suturing, fascicular suturing, nerve grafts, nerve conduits,[2] the use of fibrin glue, peripheral nerve allografts, polyethylene tubes, collagen chambers, silicone chambers,[3] basal lamina scaffolds, principles of artificial sensory function, gene technology, gangliosides, implantation of microchips, hormones, electromagnetic fields and hyperbaric oxygenation (HBO).[1] Regardless of remarkable advances in the microsurgical care, modifications of the surgical techniques greatly improve the functional outcomes of nerve injuries; testing of a cellular/ tissue bioengineering strategy is desirable.[4] Cell transplantation therapy has been shown to exert a beneficial effect on the peripheral nerve regeneration, and thus had been proposed as a new approach for the peripheral nerve regeneration. Different types of cells are used for the peripheral nerve regeneration but most important of which are the multipotent precursor or stem cells.

Multipotent precursor or stem cells are able to differentiate into myelinating cells, which support the nerve fibre regrowth, and can be used for nerve regeneration.[5] Stem cells transplantation has been used as a replacement therapy for central nervous system degenerative diseases.[6] Stem cells can be engineered to deliver appropriate support to the intrinsic cells in a diseased organ system.[7] Different types of stem cells, Schwann cells, embryonic stem cells, neuronal stem cells, bone marrow mesenchymal stem cells (MSCs),[8] bone marrow stromal stem cells (BMSCs) and CD133+ cells.[9,10] Although there are serious ethical and technical problems associated with the use of these cells.[11] In this review paper the importance of stem cells in the peripheral nerve regeneration have been discussed.

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Schwann cells

Schwann cells are peripheral glial cells that form the myelin of the peripheral nervous system (PNS) and have a major role in neuronal function including saltatory conduction. Schwann cells also have an essential role in the degeneration and regeneration of axons. In Wallerian degeneration, myelin is degraded and Schwann cells are activated which proliferate to produce a variety of neurotrophic factors, cytokines, and cell adhesion molecules, thereby providing a pathway for regenerating axons.[12] A series of reactions are involved in the peripheral nerve regeneration which are mainly activated by Schwann cells so that the axon of the proximal nerve stump grow through the distal stump in close contact with the Schwann cell bands. Because of these integrated functions nerve regeneration can be induced and the reinnervated Schwann cells can revert to axon-associated phenotype.[13] Biphasic electric current (BEC) enhanced the functional activity of Schwann cells via the induction of neurotrophic factor release and guide-increased axonal outgrowth in vivo.[14] Functional Schwann cells and neurons were specifically induced from bone marrow stromal cells (MSCs) and their effectiveness was evaluated by grafting them into peripheral nerve injury, spinal cord injury, or Parkinsons disease animal models. BMSCs-derived Schwann cells supported axonal regeneration and re-constructed myelin to facilitate the functional recovery in peripheral and spinal cord injury.[15,16] Wharton's jelly-derived mesenchymal stem cells (WJMSCs) can be differentiated into cells that are Schwann-like in terms of morphologic features, phenotype, and function and could be suitable Schwann-cell substitutes for nerve repair in clinical applications.[17] Induced Schwann cells are a valuable candidate source for cell therapy in peripheral nerve injury. Auto transplantation of MSC-derived Schwann cells is safe and effective for accelerating the regeneration of transected axons, functional recovery of injured nerves and spinal cord injury.[18] Schwann cells produce several types of neurotrophic factors such as NGF, BDNF, neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), CNTF, TGF-1b, b-2, and -b3, and bFGF. Schwann cells also produce extracellular matrices which includes fibronectin, laminin, tenascin-C, type IV and VI collagen, heparin sulfate, chondroitin sulfate proteoglycans, and entactin [19,20,21], and present with adhesion molecules such as NCAM, L1, and N-cadherin. These neurotrophic factors and extracellular matrices along with adhesion molecules help in the early peripheral nerve regeneration. But due to the limited availibility, prolonged expansion time in vitro, immunoreaction of allogenic Schwan cells hinders clinical use of these cells.

Embryonic stem cells

Embryonic stem (ES) cells are the stem cell derived from the embryo. They can be maintained in vitro without any apparent loss of differentiation potential. These pluripotent cells can differentiate into virtually any cell lineage, including germ line, neurons, and non-neuronal nervous system cells.[22] When compared with Schwann cells, ES cells proliferate actively; the doubling times of human and mouse ES cells are only 30–35 hours and 12–15 hours, respectively. Transplantation of neurally induced ES cells differentiates into myelin-forming cells and provides a potential therapy for severely injured peripheral nerves. ES cell-derived neural progenitor cells (ES-NPCs) transplantation into the severely injured peripheral nerve could promote axonal regeneration, remyelination, and functional recovery.[23] Human embryonic stem cells (hESC)-derived PA6-induced NSP (neurospheres) cells are also an excellent potential source of human peripheral sensory neuron-like cells (PSN) for study of differentiation and modeling of PNS disease.[24] Embryonic stem cells have been successfully used for the regeneration of nerve injuries but the main drawback being some what difficult to obtain.[23]

Bone marrow stromal cells (BMSCs)

Bone marrow stromal cells (BMSCs) are multipotential stem cells that under specific environmental condition differentiate into different types of cells, for example, osteoblasts, adipocytes and chondrocytes.[9] BMSCs comprise of a heterogeneous population of cells, which includes those with small rounded, large flattened and fibroblast-like morphology, with distinct plasticity and characterization [25, 26]. BMSCs also differentiate into myelinating cells, for example Schwann cells, which are capable of supporting nerve fibre regeneration.[5] Human BMSCs can be used as a substitute for Schwann cells that may be applied for nerve regeneration.[27] A population of HSCs with in the human bone marrow has neurogenic potential and is capable of differentiating into neurons when placed under appropriate environmental condition.[28] Bone marrow stromal cells (BMSCs) can be induced to form Schwann cells by sequentially treating the cells with beta-mercaptoethanol and retinoic acid, followed by forskolin and neurotrophic factors including heregulin. BMSC-DSCs have great potential to promote regeneration of peripheral nerves. The artificial graft made with BMSC-DSCs represents an alternative method for the difficult reconstruction of a long distance gap in a peripheral nerve [13]. BMSCs have the advantage of being easily accessible through aspiration of the bone marrow from patients without serious ethical problems, and can be readily expanded in large scale for

Autotransplantation.[9] Regeneration of transected axons and functional recovery of injured nerves is accelerated in auto-cell therapy by using BMSC-derived Schwann cells.[18]

Bone marrow mesenchymal cells (MSCs)

Bone marrow MSCs are relatively available from noninvasive and autologous harvest method and are the most promising choice in most clinical nerve injuries. They have been widely used with artificial conduits and acellular grafts to improve electrophysiological, morphometric, and/or behavioral recovery outcomes [29]. Human mesenchymal stromal cells (hMSC) promote tissue repair, by local differentiation to replace lost cell types, by production of growth factors that may support remyelination of demyelinated axons, recruiting endogenous progenitor cells and by the generation of neoangiogensis, so it is clear that undifferentiated hMSC are capable of supporting and directing axon growth. The availability of such a versatile population of autologous donor cells demonstrates their potential for promoting repair after CNS or PNS injury.[30] Clinically approved Gd-DTPA together with fluorescence-conjugated transfection reagent can be successfully used for MSCs labeling, by which the distribution and migration of the labeled MSCs could be tracked in vivo by MRI in a relatively short-term period after transplantation into peripheral nerves with acute traction injury.[8]

CD133+ cells

CD133+ cells are easily purified from peripheral blood and possible autologous candidate for peripheral nerve injuries. These cells have potential for enhancement of histological and functional recovery from peripheral nerve injury.[10] CD133+ cells derived from cord blood are able to differentiate into neural cells in vitro.[31]

Neurotrophic factors

Neurotrophins can stimulate neuronal survival, function and axonal growth. They also enhance regeneration of peripheral and central nervous system after injury [32]. Neurotrophic factors that are expressed after nerve injury are important for neuronal survival, and may also be important for axonal regeneration [33]. Neurotrophic factors and extracellular matrix proteins promote early peripheral nerve regeneration, particularly regeneration of long nerve defect.[34] Several types of neurotrophic factors are necessary for the nervous system development which influence differentiation, support cell survival, and stimulate neurite outgrowth. These neurotrophic factors include nerve growth factor (NGF), fibroblast growth factor (FGF) and glial cell line – derived neurotrophic (GDNF),[3] BDNF, neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), CNTF, TGF-1b, b-2, and -b3 and bFGF.[16] Long term administration of lowdoses of neurotrophic factors, such as GDNF and BDNF can promote axonal regeneration of chronically axotomized motoneurons, thus improving the poor functional recovery after traumatic peripheral nerve injury.[35] Vascular endothelial growth factor, an angiogenic factor, was thought to act on the blood vessel endothelium only, but recently it was shown to have a direct action on Schwann cells, neurons, and neural progenitor cells.[36] MSCs differentiation into myelinating cells was effectively induced by the sequential administration of various factors BME, RA, followed by a mixture of FSK, bFGF, PDGF and HRG, thus support the regeneration of nerve fibers.[5] The administration of neurotrophic factors and/or extracellular matrix proteins can promote early peripheral nerve regeneration, particularly for the regeneration of long nerve defect.[34] The addition of fibronectin to alginate hydrogel matrix contributed to improve nerve regeneration, supporting SC viability and augmenting their effect on axonal growth when transplanted in a bioengineered nerve conduit.[37]

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