REVİEW ARTICLE/ Derleme

Peripheral Nerve Regeneration and Stem Cell Therapies

Periferik Sinir Rejenerasyonu ve Kök Hücre Tedavileri

Aydin Him[1], Mehmet Emin Önger[2], Burcu Delibaş[2]

[1] Department of Biophysics, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[2] Department of Histology and Embryology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

Yazışma Adresi / Correspondence:
Aydin Him

Department of Biophysics, Faculty of Medicine, Ondokuz Mayıs University, 55139 Atakum, Samsun-Turkey

T: **+90 544 308 55 86** E-mail: **aydinhim@omu.edu.tr**

Geliş Tarihi / Received : **12.03.2018** Kabul Tarihi / Accepted : **30.05.2018**

Abstract

In this review, authors aimed to give information about the recent development about the use of stem cell transplantation in damaged nerve repair and highlight the key scientific studies. Although peripheral nerves show the potential of regenerating the axon and reinnerveting their target tissues, the recovery after intense nerve injury remains relatively poor. Schwann cells play important role in the regeneration success of peripheral nerves. Given that Schwann cells of the denervated peripheral nerve appear to become incapable in regeneration, it has been considered a reasonable approach to support the distal denervated nerve environment with exogenously derived host cells. The effects of various stem cells on peripheral nerve regeneration have been investigated. Skin, bone marrow and adipose derived stem cells were indicated as the most promising candidates with their potentials of converting into Schwann cells. Beside the application of pluripotent induced stem cell trials; recent studies have demonstrated that induced expression of growth factors in stem cells has more potential in regeneration. Although the stem cells were considered as efficient resources and promising agents in nerve regeneration there is no optimization of these therapies yet for their potential to be realized in a clinical setting. **(Sakarya Med J 2018, 8(2):182-192)**

Keywords Stem cell; peripheral nerve; regeneration; Schwann cell

Öz

Bu derlemede yazarlar kök hücre hücre transplantasyonunun sinir hasarlarının iyileştirilmesinde kullanımı ile ilgili yakın zamandaki gelişmeler ve bu alandaki başlıca çalışmalar hakkında bilgi vermeyi amaçlamaktadır. Periferik sinirlerin akson rejenerasyonu ve hedef dokularını tekrar innerve etme potansiyeline sahip olmalarına rağmen ağır sinir hasarı durumlarında düzelme sınırlı kalmaktadır. Denervasyona uğramış periferik sinirin Schwann hücrelerinin rejenerasyonda yeteri kadar rol alamayışlarından dolayı denerve olmuş distal sinir dokusu ortamının dış kaynaklı doku hücreleriyle desteklenmesi yaklaşımı gerçekçi görülmüştür. Çeşitli kök hücrelerinin periferik sinir rejenerasyonundaki etkileri çalışılmıştır. Deri, kemik iliği ve yağ doku kökenli kök hücreleri Schwann hücrelerine dönüşme kapasiteleriyle en ümit verici adaylar olarak belirlenmiştir. Pluripotent indüklenmiş kök hücre denemelerine ek olarak, yakın zamanlarda yapılan çalışmalar kök hücrelerinde büyüme faktörlerinin ifadesinin uyarılması da rejenerasyonda önemli potansiyele sahiptir. Kök hücrelerinin etkili kullanılabilecek kaynak olmaları ve sinir rejenerasyonunda ümit verici faktörler olduklarının düşünülmesine rağmen bu hücre tedavi potansiyellerinin klinikte kullanılması için gerekli ideal yöntemler henüz oluşturulamamıştır. **(Sakarya Tıp Dergisi, 2018, 8(2):182-192).**

Anahtar kelimeler Kök hücre; periferik sinir; rejenerasyon; Schwann hücresi

1. Peripheral Nerve Regeneration Process

A peripheral nerve injury is a case resulting with the paralysis, anesthesia and/or loss of motor function in the affected areas of the body. As a result of the injury, the proximal part of the axon, which is close to the damage, disintegrates in a small area and growth starts immediately after these residues are removed by macrophages and Schwann cells. Macrophages secrete Interleukin-1, which forces Schwann cells to release substances that facilitate nerve growth. Approximately 24 hours after the injury is inflicted, the axon tip at the proximal part generates a pedicle in the form of growth cone. This is the axoplasmic growth area that contains actin filaments and myosin, that helps in amoeboid-like contraction by means of filopodia.[1,2,3] The movement occurs by means of the adhesion to a suitable perceived substance through filopodia from the proximal stump to distal.[4,5] Approximately 24 hours later, a few sprouts reach the area of damage and the penetration to the injury area takes place on the second and third days. Schwann cells guide the axonal sprouting.[6] Through inter membrane differentiation, internal actin filaments become steady and when retraction occurs, the growth cone is pulled forward, axon and its contents are pushed to the involved filopodium and the axon stretches in the same direction.[1,2] If a sprout contacts the target organ, the other sprouts are degenerated and only one axon becomes mature. This axon is surrounded by Schwann cells. Only a few axons are observed to enter the old endoneurial layer. Regenerated sprouts move forward along the new Schwann cell interface. Myelination is determined by the main axon.[1] The size of the growth cone and the growth direction are influenced by mechanical factors. A scar that inhibits moving forward causes changes in the growth direction or leads branching in the growth direction.[6] However, there are reports that the growth cone increases the ability to penetrate through tissues by releasing protease [1]. Schwann cells function in the destruction of myelin and axonal debris during Wallerian degeneration and they are proliferated in the basal lamina of the remaining endoneurial connective tissue layer.[7] As a result of this, they are gathered as a longitudinal line known as Büngner band. These Schwann cell lines generate an important path for regenerated sprouts and function as guides. Schwann cells become ready to accept axon sprouts and the regenerated axons moving forward and get ready for remyelination.[8,9] Following the nerve lesion, between days 28 and 35, an extra endoneurial collagen layer accumulation occurs that causes the regrowth of required potential gap for axonal growth. This causes the diameter of the axon to decrease. Since the number of Schwann cells per unit length increases, this change causes a decrease in internodal length following the remyelination of regenerated axon.[9]

2. Molecules in Peripheral Nerve Regeneration

After axotomy, nucleus needs to produce new mRNA and thus cytoskeleton proteins such as actin and tubulin. Consequently, the production of growth associated proteins (GAPs) increases.[10] While axon develops in regeneration, GAP 43 phosphoprotein is present in the membrane, close to the growth cone. The production of this protein increases 10 times after axotomy. These phosphoproteins in the inner surface of neural membrane, which grow and become regenerated and provide axonal transportation, form the substrate of protein kinase C and play role in the progress of the growth area.[11] Laminin is a permanent element in the basal membrane and it is an integral network of glycoprotein, collagen IV and proteoglycans. It is primarily produced by Schwann cells and shows a wide spread in the peripheral nerve system. After peripheral nerve damage, laminin regulation in this area increases significantly by Schwann cells and this situation stimulates the development of axonal regeneration.[12] Glycoproteins such as laminin and fibronectin have positive

effects in the growth of the regeneration area. Thus, they are called "neurite-promoting factor" (NPF).[13] In other words, laminin has been shown to increase axonal regeneration.[14] Schwann cell basal membrane includes NPFs, like laminin. There are specific receptors for laminin in growth cone. In the presence of antibodies against laminin, the progress of regeneration area along the peripheral nerve tracers is inhibited.[15] Adhesion molecules such as L1, N-cadherin, neural cell adhesion molecule (NCAM) are found in Schwann cell membrane and these molecules have been shown to have positive contributions to regeneration.[16] In peripheral nerve damage, with the activation of intrinsic growth capacity, the level of cyclic adenosine monophosphate (cAMP) increases and protein kinase A (PKA) is activated. PKA enables the transcriptional upregulation of genes related with regeneration, such as Arginase I. Arginase I is an enzyme that is highly regulated by cAMP and PKA after peripheral damage. Arginase I stimulates the synthesis of polyamines that can directly regulate more advanced gene expression or cytoskeleton organization necessary for regeneration. High cAMP level increases IL-6, which in turn stimulates regeneration-related genes (for example GAP 43) through signal transducer and activator of transcription 3 (STAT3). Peripheral nerve damage also stimulates gene expression associated with c-Jun transcription factor such as integrin 7 1, CD44 and galanin.[15] Stimulation and reinforcement of the signal transduction pathways of phosphatidylinositol 3 kinase (PI3K), which is one of the intracellular regulators, increases myelin formation.[17] In the cell cycle of Schwann cells, "cyclin D1" plays the key regulator role and it is specific for Schwann cell proliferation.18 In peripheral nerve axon regeneration, myelin is quickly removed from the environment by Schwann cells and macrophages after damage. Schwann cells are dedifferentiated and they decrease all myelin proteins. ECM (extracellular matrix proteins) proteins such as laminin bind to integrin receptors in growth cone, activate PI3K and this in turn causes local accumulation of "activated Akt" in actin-laminin contact area. Activated AKT is phosphorylated and inhibits Glycogen Synthase Kinase-3 (GSK-3). This inhibition regulates cytoskeleton binding proteins and accelerates cytoskeleton organization. Peripheral nerve damage increases neural intrinsic growth capacity at the same time.[15]

Myelin Associated Glycoprotein (MAG) is a well-defined transmembrane protein in both central and peripheral nervous system. The early expression of MAG in myelination has brought to mind that it can play a role in the onset of myelination during growth. When oligodendrocytes and Schwann cells start to wrap around axons, they express MAG. Studies put forward that MAG is the major myelin-derived inhibitor of neurite growth.[19] During the effect of ECM proteins and regulatory molecules on Schwann cells, laminin separates axons radially during remyelination.[20] Dystroglycan and L-periactin regulate myelin sheath thickness and maintain the myelin sheath[21,22,23] It removes the fibrin for tPA/ plasminogen remyelination to progress. Fibrin inhibits remyelination.[24] Peripheral nerve system is known to have steroid receptors and thus these tissues are known to be targets for neuroactive steroids. Recent studies have shown that neuroactive steroids regulate the proliferation and cellular development of Schwann cells. P450scc (cytochrome) and 3 - hydroxysteroid dehydrogenase (3 -HSD), which turn pregnenolone into progesterone, have been shown to be released from Schwann cells.[25] Peripheral nerves and Schwann cells express neuroactive steroids and they are at the same time target cells and structures for these substances.

3. Stem Cells and Stem Cell Types

Multiple in vitro studies have shown the transformation in the morphology of different stem cell types under a range of stimuli to form tissues similar to neural tissue. Multiple animal studies have

been described using a large scale of stem cell types to treat a range of peripheral nerve damage conditions. To bridge the gap in the damaged peripheral nerves some authors used conduits combined with stem cell whilst others used cell therapy with nerve allografts. Since axons only grow a short distance beyond their own reparative matrix and an intact endoneurium is associated with better outcomes, there has been a strong research focus on bridging the gap via conduits as well as reconstruction of the extracellular matrix.

Stem cells, which originate from different parts of our body at different periods of life starting from embryological period, form the basis of each organ and tissue. All stem cells have the properties of renewing themselves and differentiate into other cells and they can be classified under two main groups as embryonic and mesenchymal stem cells based on the time and properties they are originated from.26 The use of different stem cell types in nerve regeneration in various injury models is summarized in Table 1.

Table 1. Advantages and disadvantages of using different stem cell types in nerve regeneration.

Stem CelSource	Research	Cell Type / Factor	Injury Type/ Experimental Model	Important Results	Advantage	Disadvantage
BMSCs	Zarbakhsh et al. (2016) 81	Bone marrow mesenchymal stem cells	Sciatic nerve gap in Wistar rats (10mm)	Successful nerve regeneration and myelination	Easy accessibility without ethical concerns	Low proliferation and differentiation capacity, invasive procedure is required for autologous source
SKP-SCs	McKenzie et al. (2006) 82	Skin-derived precursor cells differentiate into Schwann cells	Sciatic nerve defect in myelin deficit mice	Remyelination and functional recovery	Easily accessible	Takes a long time to differentiate
NSCs	Li et al. (2017) 83	Schwann cells differentiated from NSCs	Sciatic nerve injury mouse model	Improves motor recovery and increases the diameter up to 4.5-fold, at the medial site of the regenerated nerve	Give rise to al large number of neurons	Difficulty in obtaining
AMSCs	Cheng et al. (2010) 84	Mesenchymal stem cells derived human amniotic fluid	Sciatic nerve injury rat model	Nerve regeneration and functional improvement	Enhanced plasticity	Ethical considerations
ADSCs	Di Summa et al. (2010) 85	Nerve canal produced from adipose-derived stem cells	Sciatic nerve injury rat model (1.0 cm gap)	Increased peripheral nerve healing	Easily accessible	It has tendency to differentiae to adipose cell
ESCs	Magown et al. (2017) 86	Motor neurons derived from embryonic stem cells	Tibial nerve defect in mice	Functional recovery	No defect relevant to age and diseases, high proliferation capacity	Teratoma formation and ethical problems
HPSCs	Amoh et al. (2016) 87	Hair follicle-associated-pluripotent (HAP) stem cells	Injured peripheral nerve	HAP stem cells promoted the functional recovery of injured peripheral nerves and the spinal cord	Easily accessible in high amounts	Difficulties in isolating

Stem CelSource	Research	Cell Type / Factor	Injury Type/ Experimental Model	Important Results	Advantage	Disadvantage
DPSCs	Sanen et al. (2017) 60	Schwann cells derived from differentiated human dental pulp stem cells	15-mm rat sciatic nerve defect	d-hDPSCs are able to exert a positive effect in the regeneration of nerve tissue in vivo	Easily accessible, high proliferation capacity and high clonogenic potential	Require storage
MDSPCs	Lavasani et al. 57	Muscle-derived stem/progenitor cells (MDSPCs) isolated from adult human skeletal muscle	Critical-sized sciatic nerve injury	Increase in muscle mass after denervation, and reorganization of motor endplates at the postsynaptic sites	Easily accessible in high amounts	It is subjected to a small number of studies
iPSCs	Ikeda et al. 43	Induced pluripotent stem cells and basic fibroblast growth factor	Sciatic nerve gaps in mice	Successful nerve regeneration and myelination	Potential of inducibility from easily obtained somatic cells	The epigenetic memory from the original somatic cells is maintained

BMSCs: bone marrow stem cells; SKP-SCs: skin-derived precursor stem cells; NSCs: neural stem cells; AMSCs: amniotic fluid derived stem cells; ADSCs: adipose-derived stem cells; ESCs: embryonic stem cells; HPSCs: hair follicle associated pluripotent stem cells; DPSCs: dental pulp stem cells; MDSPCs: Muscle-derived stem/progenitor cells; iPSCs: induced pluripotent stem cells.

3.1. Embryonic Stem Cells

Embryonic stem cells are derived from the inner cell mass of blastocysts, which are formed between the third and fifth days following the fertilization of the egg by sperm and developed under laboratory conditions.[27] Since embryonic stem cells can differentiate to all cells and tissues except umbilical cord and placenta, they can also be called pluripotent stem cells. Stem cells which will differentiate to various organ and tissues of the body during the normal growth period can maintain their pluripotent properties under special laboratory conditions.[28]

Ziegler et al. developed a protocol that enabled to get Schwann cells at the rate of 60% from embryonic stem cells in order to replace Schwann cells required for nerve regeneration. They were generated hESC-derived neurospheres containing a mixture of neurons, neural and glial progenitors by means of PA6 induction.[29] The neurospheres were propagated for approximately 4 weeks in suspension and subsequently plated for further differentiation. They used co-culture of human embryonic stem cell-derived (hESC) schwann cells with hESC-derived axons in compartmentalized microfluidic chambers and they finally observed tight association of the Schwann cells with axons, also increased myelination.[30]

Chui et al. showed that naturally injected embryonic stem cells via microinjection method increased regeneration significantly. Immunostaining studies showed that embryonic stem cells survive and differentiate into Schwann cells after injection.[31] An alternative method is the studies to decrease the effects of muscle denervation by injecting embryonic stem cells to the muscle innerved by nerves during the damage formation process on the nerve.[32] In this study; mouse ESC-derived motor neurons were injected into transected tibial nerves and they observed newly formed neuromuscular junctions with the denervated triceps surae and they also observed 40% functional healing in contractile force.[33]

Besides its advantages, embryonic stem cell use still has disadvantages such as causing teratoma, limited source and ethical problems.

3.2. Mesenchymal Stem Cells

Approaches about nerve regeneration are mostly related with the differentiation of mesenchymal stem cells to neuron and glia. Experimental studies conducted with sciatic nerve have shown that after the injection of stem cells to undifferentiated culture, the migration and differentiation of mesenchymal stem cells occur on the side of nerve damage.[34,35,36] Transplantation of undifferentiated mesenchymal stem cells to a nerve tube has been reported to stimulate axonal growth and recovery in motor function.[37] Subtypes and practices of mesenchymal stem cells have been discussed.

3.2.1. Bone marrow derived stem cells

There are a great number of studies in literature about the peripheral nerve regeneration with stem cell use originating from various sources such as embryonic, hematopoietic, epithelial, mesenchymal, amniotic fluid, cord blood and skin.[38,39,40] In addition, stem cell populations different from adult tissues such as bone marrow, fatty tissue and nerve tissue have been defined. These are defined as multipotent stem cells which have the potential to differentiate into different cell types.[41] Bone marrow stroma cell, which is also called mesenchymal stem cell, can differentiate to mesenchymal progenitor cells for structures such as bone, cartilage, tendon, fatty tissue and muscle.[42]

Especially in peripheral nerve damage model, we can frequently come across literature records which describe the application methods of bone marrow mesenchymal stem cell transplantation. The expression of glial cell markers, which are typical of Schwann cells, have been defined in vitro in rat mesenchymal stem cells and have produced effective results in peripheral nerve regeneration.[43,44]

Differentiated mesenchymal stem cells synthesize and secrete neurotrophins.[45] Similarly, it has been reported that differentiated mesenchymal stem cells have the potential to influence the expression of growth factors and myelination of axons in different levels.4[6,47] However, Wang et al., 2009, reports that bone marrow induced stem cells increase peripheral nerve regeneration not only by secreting neurotrophic factors, but also indirectly by affecting Schwann cell proliferation rate.[36]

Although bone marrow stem cells are more easily obtained when compared with embryonic stem cells, their proliferation capacity is less when compared with embryonic stem cells. In addition, since the method to obtain them is invasive and painful, it generally requires anesthesia and the fraction of the obtained stem cells are less when compared with other sources.

3.2.2. Adipose derived stem cells

Adipose derived stem cells have the same properties with bone marrow derived stem cells both phenotypically and in terms of gene expression.[48] On the other hand, differentiation of adipose derived stem cells to osteoblasts, chondrocytes and adipocytes has been reported to be the same with that of mesenchymal stem cells.[49] However, the stem cell intensity in fatty tissue is 100 to 1000 times more when compared with bone marrow.[50] This is an important advantage because

the more intense stem cell is in the material transplanted to nerve tube, the shorter the period of spread of stem cells will be during the process before differentiation. There are also studies in literature which reveal that adipose derived undifferentiated stem cell transplantation increases peripheral nerve regeneration.[51] Based on the results that the intensity of blood vein in fatty tissue is directly associated with adipose derived stem cell amount, some researchers claim that the stem cells in these tissues are originated from vascular precursors.[52] Although there are differences in humans and primates in terms of the differentiation capacity between adipose derived stem cell and bone marrow derived mesenchymal stem cells, it has been reported that adipose derived stem cells have faster reproduction capacity.[53,54] In a study by Georgiou et al., adipose derived stem cells isolated from rats were differentiated to Schwann-like cells in vitro. Differentiated cells were implanted in absorbable collagen tubes and the 15 mm gap in the sciatic nerve was bridged. The results of the immunofluorescent and electron microscopic assessment at the end of 8 weeks showed that the axon rate was 3.5 times more in the group that contained adipose derived stem cell when compared with the other group without stem cells.[55] In another study conducted with adipose and bone marrow derived stem cells and Schwann cell transplantation in sciatic nerve regeneration, each of the three materials was reported to increase regeneration while Schwann cell transplantation was reported to be significantly successful when compared with others.[56] Adipose and bone marrow derived stem cell transplantation was reported not to have any statistical advantage to each other in regeneration.

3.2.3. Muscle derived stem cells

A study by Lavasani et al. showed that stem cells isolated from human skeletal muscle could differentiate to glial and neuronal phenotypes in vitro and could repair clinical sciatic nerve damage.[57] Researchers examined the differentiation capacity of human Sk-SCs in severely crushed sciatic nerves of nude rats by means of injecting them into the long-gap transected nerve model with an acellular conduit bridge. They showed that human Sk-SCs are a potential practical source for autologous stem cell therapy following severe nerve injury.[58]

3.2.4. Dental stem cells

Beigi et al. (2014) showed that, electrospun poly (-caprolactone)/gelatin (PCL/Gel) nanofibrosis beds were produced to fill in 10 mm sciatic nerve gap in rat models, they were wrapped around copper wire and adhered with medical purpose adhesive to obtain tubular shaped bio-graft.[59] In another study, roots were taken from dental pulpa and it was emphasized that neurodegenerative capacities of Schwann cells were promising.[60]

In a study conducted by Yamamoto et al. (2016), a granulocyte colony with high neurotrophic/angiogenic potential was isolated by using stimulation factor gradient and the effects of mobilized dental stem cells on peripheral nerve regeneration were examined. The results showed that the use of dental pulpa root cells compared with autograft and control groups increased the number of myelinated fiber and axon significantly.[61]

3.2.5. Skin derived stem cell precursors

A valuable number of studies have shown increases in acute and delayed peripheral nerve regeneration when skin derived precursor Schwann cell were used.[62,63,64,65] However, in nerve damage, the use of Schwann cells obtained from autologous culture is not very practical in terms of

technical difficulties and the fact that it requires a long time. Schwann cells grow slowly. It takes 10 weeks for Schwann cells to reach a suitable number of transplantation under culture medium, during which neuronal cell death may occur.[66]

3.3. Amniotic tissue derived stem cells

Amniotic tissue derived stem cells (ATDSC) are derived from amniotic fluid or amniotic membrane. ATDSCs show the properties of both mesenchymal cells and neural stem cells and they have the property of differentiating to neural stem cells. The survival of ATDSCs after transplantation is the most difficult obstacle during clinical application.[67,68]

Chen et. al. showed that intramuscular injection of ATDSCs can protect muscle apoptosis and likely does so through the secretion of various neurotrophic factors and also this protection furthermore improves the nerve regeneration in a long-term nerve anastomosis model.[69] In another study Yang et al showed that intravenous administration of AFMSCs may be a promising alternative treatment strategy in peripheral nerve disorder and led to improvements in neurobehavioral and expression of regeneration markers.[70]

3.4. Cord blood derived stem cells

Cord blood stem cells are frequently preferred due to their capacity of differentiation and proliferation. Due to their property of being obtained easily from postnatal tissue after birth, they cause less ethical problems. Despite high proliferation capacity of cord blood cells, there are few resources showing that they trigger tumorigenesis after transplantation. Several studies emphasize that human umbilical cord blood-derived stem cells modulate the immune/inflammatory response to injury and inhibit the apoptotic cascade.[71,72] Sung et. al. showed that transplantation of human umbilical cord blood-mesenchymal stem cells into the rat sciatic nerve following crush injury promoted functional recovery and axonal regeneration.[73] Studies show the positive effect of human umbilical cord blood-mesenchymal stem cells therapy in peripheral nerve regeneration but the underlying molecular mechanism of regeneration remains poorly understood.[74,76]

4. Induced stem cell applications

In 2012, John B. Gurdon and Shinya Yamanaka found that mature and specialized cells could be reprogrammed to turn into pluripotent-differentiated cells via viruses, this discovery won the Nobel Prize in Physiology or Medicine. This in turn increased the number of studies to analyze the effect of induced pluripotent stem cells on peripheral nerve damage.[77,78,43]

The application of induced pluripotent stem cells to cover the internal surface of the tubes used in binding disconnected nerve ends increased motor and sensory recovery to a great extent. In addition, it was proved histologically that induced pluripotent stem cells increased axonal renewal.78 Using induced pluripotent stem cells combined with fibroblast growth factors was reported to increase regenerative effect.[43]

Wang et al. formed non-fibrosis tubular graft by using neural crest stem cells obtained from induced and embryonic stem cells and thus aimed to form a bridge between disconnected nerve ends. The results of the electrophysiological analyses conducted one month after surgical procedure

showed that the graft material used increased nerve regeneration. As a result of histological analyses, it was found that neural crest induced stem cells differentiated to Schwann cells that formed myelin sheath to guiding axons. No teratogenic effect was found even one year after transplantation. [79] Similarly, in a study by Uemura et al., it was found that induced stem cell transplantation did not create any teratogenic effects in the nerve in the long run and increased axonal regeneration and myelination.[80]

In a study by Ikeda et al., which aimed to treat peripheral nerve damage by using induced pluripotent stem cells and tubes that included basic fibroblast growth factor, it was reported that 12 weeks after transplantation there were increases in regeneration and functional recovery.[80]

The use of somatic cell induced pluripotent stem cells in patient specific special cell treatments is a big potential in terms of inhibiting the formation of immune reaction. The use of cell induced pluripotent stem cells brings together requirements such as understanding the differences between populations of induced pluripotent stem cells and determining suitable basis of differentiation.

1. Letourneau PC. Immunocytochemical evidence for colocalization in neurite growth cones of actin and myosin and their relationship to cell--substratum adhesions. Dev Biol. 1981;85(1):113-122.
2. Napoli I, Noon LA, Ribeiro S, Kerai AP, Parrinello S, Rosenberg LH, et al. A central role for the ERK-signaling pathway in controlling Schwann cell plasticity and peripheral nerve regeneration in vivo. Neuron. 2012;73(4):729-742.
3. Marconi S, Castiglione G, Turano E, Bissolotti G, Angiari S, Farinazzo A, et al. Human adipose-derived mesenchymal stem cells systemically injected promote peripheral nerve regeneration in the mouse model of sciatic crush. Tissue Eng Part A. 2012;18(11-12):1264-1272.
4. Forman DS, Berenberg RA. Regeneration of motor axons in the rat sciatic nerve studied by labeling with axonally transported radioactive proteins. Brain Res. 1978;156(2):213-225.
5. Daly W, Yao L, Zeugolis D, Windebank A, Pandit A. A biomaterials approach to peripheral nerve regeneration: bridging the peripheral nerve gap and enhancing functional recovery. J R Soc Interface. 2012;9(67):202-221.
6. Webber CA, Christie KJ, Cheng C, Martinez JA, Singh B, Singh V, et al. Schwann cells direct peripheral nerve regeneration through the Netrin-1 receptors, DCC and Unc5H2. Glia. 2011;59(10):1503-1517.
7. Satinsky D, Pepe FA, Liu CN. The Neurilemma Cell in Peripheral Nerve Degeneration and Regeneration. Exp Neurol. 1964;9:441-451.
8. Ladak A, Olson J, Tredget EE, Gordon T. Differentiation of mesenchymal stem cells to support peripheral nerve regeneration in a rat model. Exp Neurol. 2011;228(2):242-252.
9. Cragg BG, Thomas PK. The Conduction Velocity of Regenerated Peripheral Nerve Fibres. J Physiol. 1964;171:164-175.
10. Shen Y, Mani S, Donovan SL, Schwob JE, Meiri KF. Growth-associated protein-43 is required for commissural axon guidance in the developing vertebrate nervous system. J Neurosci. 2002;22(1):239-247.
11. Fawcett JW, Keynes RJ. Peripheral nerve regeneration. Annu Rev Neurosci. 1990;13:43-60.
12. Sun WJ, Sun CK, Zhao H, Lin H, Han Q, Wang J, et al. Improvement of Sciatic Nerve Regeneration Using Laminin-Binding Human NGF-beta. Plos One. 2009;4(7): e6180.
13. Davis GE, Manthorpe M, Williams LR, Varon S. Characterization of a Laminin-Containing Neurite-Promoting Factor and a Neuronotrophic Factor from Peripheral-Nerve and Related Sources. Ann Ny Acad Sci. 1986;486:194-205.
14. Madison R, Dasilva CF, Dikkes P, Chiu TH, Sidman RL. Increased Rate of Peripheral-Nerve Regeneration Using Bioresorbable Nerve Guides and a Laminin-Containing Gel. Experimental Neurology. 1985;88(3):767-772.
15. Nie X, Zhang YJ, Tian WD, Jiang M, Dong R, Chen JW, et al. Improvement of peripheral nerve regeneration by a tissue-engineered nerve filled with ectomesenchymal stem cells. Int J Oral Max Surg. 2007;36(1):32-38.
16. Widerberg A, Kanje M, Dahlin LB. Tourniquet compression: a non-invasive method to enhance nerve regeneration in nerve grafts. Neuroreport. 2002;13(4):371-375.
17. Ogata T, Iijima S, Hoshikawa S, Miura T, Yamamoto S, Oda H, et al. Opposing extracellular signal-regulated kinase and Akt pathways control Schwann cell myelination. J Neurosci. 2004;24(30):6724-6732.
18. Atanasoski S, Notterpek L, Lee HY, Castagner F, Young P, Ehrengruber MU, et al. The protooncogene Ski Schwann cell proliferation controls and myelination. Neuron. 2004;43(4):499-511.
19. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, et al. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. J Neurosurg. 1998;89(5):699-706.
20. Chen C, Hill LD, Schubert CM, Strauss JF, Matthews CA. Is laminin gamma-1 a candidate gene for advanced pelvic organ prolapse? Am J Obstet Gynecol. 2010;202(5): 505.e1-5.
21. Masaki T, Matsumura K, Saito F, Sunada Y, Shimizu T, Yorifuji H, et al. Expression of dystroglycan and laminin-2 in peripheral nerve under axonal degeneration and regeneration. Acta Neuropathol. 2000;99(3):289-295.
22. Saito F, Moore SA, Barresi R, Henry MD, Messing A, Ross-Barta SE, et al. Unique role of dystroglycan in peripheral nerve myelination, nodal structure, and sodium channel stabilization. Neuron. 2003;38(5):747-758.
23. Williams AC, Brophy PJ. The function of the Periaxin gene during nerve repair in a model of CMT4F. J Anat. 2002;200(4):323-330.
24. Akassoglou K, Yu WM, Akpinar P, Strickland S. Fibrin inhibits peripheral nerve remyelination by regulating Schwann cell differentiation. Neuron. 2002;33(6):861-875.
25. Melcangi RC, Cavarretta IT, Ballabio M, Leonelli E, Schenone A, Azcoitia I, et al. Peripheral nerves: a target for the action of neuroactive steroids. Brain Res Brain Res Rev. 2005;48(2):328-338.
26. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001;414(6859):105-111.
27. Thomson JA. Embryonic stem cell lines derived from human blastocysts. Science. 1998;282(5395):1827-1827.
28. Jiang YH, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature. 2002;418:41-49.
29. Pomp O, Brokhman I, Ziegler L, Almog M, Korngreen A, Tavian M, et al. PA6-induced human embryonic stem cell-derived neurospheres: a new source of human peripheral sensory neurons and neural crest cells. Brain Res. 2008;1230:50-60.
30. Ziegler L, Grigoryan S, Yang IH, Thakor NV, Goldstein RS. Efficient Generation of Schwann Cells from Human Embryonic Stem Cell-Derived Neurospheres. Stem Cell Rev Rep. 2011;7(2):394-403.
31. Cui L, Jiang J, Wei L, Zhou X, Fraser JL, Snider BJ, et al. Transplantation of embryonic stem cells improves nerve repair and functional recovery after severe sciatic nerve axotomy in rats. Stem Cells. 2008;26(5):1356-1365.
32. Kubo T, Randolph MA, Groger A, Winograd JM. Embryonic Stem Cell-Derived Motor Neurons Form Neuromuscular Junctions In Vitro and Enhance Motor Functional Recovery In Vivo. Plastic and Reconstructive Surgery. 2009;123(2):139s-148s.
33. Yohn DC, Miles GB, Rafuse VF, Brownstone RM. Transplanted mouse embryonic stem-cell-derived motoneurons form functional motor units and reduce muscle atrophy. J Neurosci. 2008;28(47):12409-12418.
34. Carrier-Ruiz A, Evaristo-Mendonca F, Mendez-Otero R, Ribeiro-Resende VT. Biological behavior of mesenchymal stem cells on poly-epsilon-caprolactone filaments and a strategy for tissue engineering of segments of the peripheral nerves. Stem Cell Res Ther. 2015;6:128.
35. Plock JA, Schnider JT, Solari MG, Zheng XX, Gorantla VS. Perspectives on the use of mesenchymal stem cells in vascularized composite allotransplantation. Front Immunol. 2013;4:175.
36. Zhang JY, Deng ZH, Liao J, Song C, Liang C, Xue H, et al. Leptin attenuates cerebral ischemia injury through the promotion of energy metabolism via the PI3K/Akt pathway. J Cerebr Blood F Met. 2013;33(4):567-574.
37. Lakshmipathy U, Hart RP. Concise review: MicroRNA expression in multipotent mesenchymal stromal cells. Stem Cells. 2008;26(2):356-363.
38. Weiss JN, Levy S, Malkin A. Stem Cell Ophthalmology Treatment Study (SCOTS) for retinal and optic nerve diseases: a preliminary report. Neural Regeneration Research. 2015;10(6):982-988.
39. Tremp M, Schwabedissen MMZ, Kappos EA, Engels PE, Fischmann A, Scherberich A, et al. The Regeneration Potential After Human and Autologous Stem Cell Transplantation in a Rat Sciatic Nerve Injury Model Can Be Monitored by MRI. Cell Transplant. 2015;24(2):203-211.
40. Sakar M, Korkusuz P, Demirbilek M, Cetinkaya DU, Arslan S, Denkbaş EB, et al. The effect of poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHx) and human mesenchymal stem cell (hMSC) on axonal regeneration in experimental sciatic nerve damage. Int J Neurosci. 2014;124(9):685-696.
41. Napoli I, Noon LA, Ribeiro S, Kerai AP, Parrinello S, Rosenberg LH, et al. A Central Role for the ERK-Signaling Pathway in Controlling Schwann Cell Plasticity and Peripheral Nerve Regeneration In Vivo. Neuron. 2012;73(4):729-742.
42. Muraglia A, Todeschi MR, Papait A, Poggi A, Spano, Strada P, et al. Combined platelet and plasma derivatives enhance proliferation of stem/progenitor cells maintaining their differentiation potential. Cytotherapy. 2015;17(12):1793-1806.
43. Ikeda M, Uemura T, Takamatsu K, Okada M, Kazuki K, Tabata Y, et al. Acceleration of peripheral nerve regeneration using nerve conduits in combination with induced pluripotent stem cell technology and a basic fibroblast growth factor drug delivery system. J Biomed Mater Res A. 2014;102(5):1370-1378.
44. Choi SA, Lee JY, Kwon SE, Wang KC, Phi JH, Choi JW, et al. Human Adipose Tissue-Derived Mesenchymal Stem Cells Target Brain Tumor-Initiating Cells. Plos One. 2015;10(7):e0129292
45. Montaville P, Jamin N. Determination of Membrane Protein Structures Using Solution and Solid-State NMR. Methods Mol Biol. 2010;654:261-282.
46. Keilhoff G, Goihl A, Langnase K, Fansa H, Wolf G. Transdifferentiation of mesenchymal stem cells into Schwann cell-like myelinating cells. European Journal of Cell Biology. 2006;85(1):11-24.
47. Kratchmarova I, Blagoev B, Haack-Sorensen M, Kassem M, Mann M.

Mechanism of divergent growth factor effects in mesenchymal stem cell differentiation. Science. 2005;308(5727):1472-1477.
48. De Ugarte DA, Morizono K, Elbarbary A, Alfonso Z, Zuk PA, Zhu M, et al. Comparison of multi-lineage cells from human adipose tissue and bone marrow. Cells Tissues Organs. 2003;174(3):101-109.
49. Nagata H, Ii M, Kohbayashi E, Hoshiga M, Hanafusa T, Asahi M. Cardiac Adipose-Derived Stem Cells Exhibit High Differentiation Potential to Cardiovascular Cells in C57BL/6 Mice. Stem Cell Transl Med. 2016;5(2):141-151.
50. Muschler GF, Matsukura Y, Nitto H, Boehm CA, Valdevit AD, Kambic HE, et al. Selective retention of bone marrow-derived cells to enhance spinal fusion. Clin Orthop Relat R. 2005(432):242-251.
51. Kolar MK, Kingham PJ. Regenerative effects of adipose-tissue-derived stem cells for treatment of peripheral nerve injuries. Biochem Soc T. 2014;42:697-701.
52. Lin G, Garcia M, Ning H, Banie L, Guo YL, Lue TF, et al. Defining Stem and Progenitor Cells within Adipose Tissue. Stem Cells Dev. 2008;17(6):1053-1063.
53. Izadpanah R, Trygg C, Patel B, Kriedt C, Dufour J, Gimble JM, et al. Biologic properties of mesenchymal stem cells derived from bone marrow and adipose tissue. J Cell Biochem. 2006;99(5):1285-1297.
54. Kingham PJ, Kalbermatten DF, Mahay D, Armstrong SJ, Wiberg M, Terenghi G. Adipose-derived stem cells differentiate into a Schwann cell phenotype and promote neurite outgrowth in vitro. Experimental Neurology. 2007;207(2):267-274.
55. Georgiou M, Golding JP, Loughlin AJ, Kingham PJ, Phillips JB. Engineered neural tissue with aligned, differentiated adipose-derived stem cells promotes peripheral nerve regeneration across a critical sized defect in rat sciatic nerve. Biomaterials. 2015;37:242-251.
56. di Summa PG, Kingham PJ, Raffoul W, Wiberg M, Terenghi G, Kalbermatten DF. Adipose-derived stem cells enhance peripheral nerve regeneration. J Plast Reconstr Aes. 2010;63(9):1544-1552.
57. Lavasani M, Thompson SD, Pollett JB, Usas A, Lu A, Stolz DB, et al. Human muscle-derived stem/progenitor cells promote functional murine peripheral nerve regeneration. J Clin Invest. 2014;124(4):1745-1756.
58. Tamaki T, Hirata M, Nakajima N, Saito K, Hashimoto H, Soeda S, et al. A Long-Gap Peripheral Nerve Injury Therapy Using Human Skeletal Muscle-Derived Stem Cells (Sk-SCs): An Achievement of Significant Morphological, Numerical and Functional Recovery. Plos One. 2016;11(11).
59. Beigi MH, Ghasemi-Mobarakeh L, Prabhakaran MP, Karbalaie K, Azadeh H, Ramakrishna S, et al. In vivo integration of poly(epsilon-caprolactone)/gelatin nanofibrous nerve guide seeded with teeth derived stem cells for peripheral nerve regeneration. J Biomed Mater Res A. 2014;102(12):4554-4567.
60. Sanen K, Martens W, Georgiou M, Ameloot M, Lambrichts I, Phillips J. Engineered neural tissue with Schwann cell differentiated human dental pulp stem cells: potential for peripheral nerve repair? J Tissue Eng Regen Med. 2017; 11(12):3362-3372.
61. Yamamoto T, Osako Y, Ito M, Murakami M, Hayashi Y, Horibe H, et al. Trophic Effects of Dental Pulp Stem Cells on Schwann Cells in Peripheral Nerve Regeneration. Cell Transplant. 2016;25(1):183-193.
62. Stratton JA, Shah PT, Kumar R, Stykel MG, Shapira Y, Grochmal J, et al. The immunomodulatory properties of adult skin-derived precursor Schwann cells: implications for peripheral nerve injury therapy. Eur J Neurosci. 2016;43(3):365-375.
63. Sparling JS, Bretzner F, Biernaskie J, Assinck P, Jiang Y, Arisato H, et al. Schwann Cells Generated from Neonatal Skin-Derived Precursors or Neonatal Peripheral Nerve Improve Functional Recovery after Acute Transplantation into the Partially Injured Cervical Spinal Cord of the Rat. Journal of Neuroscience. 2015;35(17):6714-6730.
64. Mozafari S, Laterza C, Roussel D, Bachelin C, Marteyn A, Deboux C, et al. Skin-derived neural precursors competitively generate functional myelin in adult demyelinated mice. J Clin Invest. 2015;125(9):3642-3656.
65. Khuong HT, Kumar R, Senjaya F, Grochmal J, Ivanovic A, Shakhbazau A, et al. Skin derived precursor Schwann cells improve behavioral recovery for acute and delayed nerve repair. Exp Neurol. 2014;254:168-179.
66. Mosahebi A, Wiberg M, Terenghi G. Addition of fibronectin to alginate matrix improves peripheral nerve regeneration in tissue-engineered conduits. Tissue Eng. 2003;9(2):209-218.
67. Pan HC, Yang DY, Ho SP, Sheu ML, Chen CJ, Hwang SM, et al. Escalated regeneration in sciatic nerve crush injury by the combined therapy of human amniotic fluid mesenchymal stem cells and fermented soybean extracts, Natto. J Biomed Sci. 2009;16:75.
68. Liao W, Zhong J, Yu J, Xie J, Liu Y, Du L, et al. Therapeutic benefit of human umbilical cord derived mesenchymal stromal cells in intracerebral hemorrhage rat: implications of anti-inflammation and angiogenesis. Cell Physiol Biochem. 2009;24(3-4):307-316.
69. Chen CJ, Cheng FC, Su HL, Sheu ML, Lu ZH, Chiang CY, et al. Improved Neurological Outcome by Intramuscular Injection of Human Amniotic Fluid Derived Stem Cells in a Muscle Denervation Model. Plos One. 2015;10(5):e0124624.
70. Rutka JT. Dual regeneration of muscle and nerve by intravenous administration of human amniotic fluid-derived mesenchymal stem cells regulated by stromal cell-derived factor-1 alpha in a sciatic nerve injury model (vol 116, pg 1357, 2012). Journal of Neurosurgery. 2015;123(6):1605-1605.
71. Hao L, Zhang C, Chen XH, Zou ZM, Zhang X, Kong PY, et al. Human umbilical cord blood-derived stromal cells suppress xenogeneic immune cell response in vitro. Croat Med J. 2009;50(4):351-360.
72. Vendrame M, Gemma C, de Mesquita D, Collier L, Bickford PC, Sanberg CD, et al. Anti-inflammatory effects of human cord blood cells in a rat model of stroke. Stem Cells Dev. 2005;14(5):595-604.
73. Sung MA, Jung HJ, Lee JW, Lee JY, Pang KM, Yoo SB, et al. Human umbilical cord blood-derived mesenchymal stem cells promote regeneration of crush-injured rat sciatic nerves. Neural Regen Res. 2012;7(26):2018-2027.
74. Yan-Wu G, Yi-Quan K, Ming L, Ying-Qian C, Xiao-Dan J, Shi-Zhong Z, et al. Human Umbilical Cord-Derived Schwann-Like Cell Transplantation Combined with Neurotrophin-3 Administration in Dyskinesia of Rats with Spinal Cord Injury. Neurochem Res. 2011;36(5):783-792.
75. Veeravalli KK, Dasari VR, Fassett D, Dinh DH, Rao JS. Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells Upregulate Myelin Basic Protein in Shiverer Mice. Stem Cells Dev. 2011;20(5):881-891.
76. Matsuse D, Kitada M, Kohama M, Nishikawa K, Makinoshima H, Wakao S, et al. Human Umbilical Cord-Derived Mesenchymal Stromal Cells Differentiate Into Functional Schwann Cells That Sustain Peripheral Nerve Regeneration. J Neuropath Exp Neur. 2010;69(9):973-985.
77. Lopatina T, Bruno S, Tetta C, Kalinina N, Porta M, Camussi G. Platelet-derived growth factor regulates the secretion of extracellular vesicles by adipose mesenchymal stem cells and enhances their angiogenic potential. Cell Commun Signal. 2014;12:26.
78. Uemura T, Takamatsu K, Ikeda M, Okada M, Kazuki K, Ikada Y, et al. Transplantation of induced pluripotent stem cell-derived neurospheres for peripheral nerve repair. Biochem Biophys Res Commun. 2012;419(1):130-135.
79. Wang A, Tang Z, Park IH, Zhu Y, Patel S, Daley GQ, et al. Induced pluripotent stem cells for neural tissue engineering. Biomaterials. 2011;32(22):5023-5032.
80. Uemura T, Ikeda M, Takamatsu K, Yokoi T, Okada M, Nakamura H. Long-term efficacy and safety outcomes of transplantation of induced pluripotent stem cell-derived neurospheres with bioabsorbable nerve conduits for peripheral nerve regeneration in mice. Cells Tissues Organs. 2014;200(1):78-91.
81. Zarbakhsh S, Goudarzi N, Shirmohammadi M, Safari M. Histological Study of Bone Marrow and Umbilical Cord Stromal Cell Transplantation in Regenerating Rat Peripheral Nerve. Cell J. 2016;17(4):668-677.
82. McKenzie IA, Biernaskie J, Toma JG, Midha R, Miller FD. Skin-derived precursors generate myelinating Schwann cells for the injured and dysmyelinated nervous system. J Neurosci. 2006;26(24):6651-6660.
83. Lee DC, Chen JH, Hsu TY, Chang LH, Chang H, Chi YH, et al. Neural stem cells promote nerve regeneration through IL12-induced Schwann cell differentiation. Mol Cell Neurosci. 2017;79:1-11.
84. Cheng FC, Tai MH, Sheu ML, Chen CJ, Yang DY, Su HL, et al. Enhancement of regeneration with glia cell line-derived neurotrophic factor-transduced human amniotic fluid mesenchymal stem cells after sciatic nerve crush injury. J Neurosurg. 2010;112(4):868-879.
85. di Summa PG, Kingham PJ, Raffoul W, Wiberg M, Terenghi G, Kalbermatten DF. Adipose-derived stem cells enhance peripheral nerve regeneration. J Plast Reconstr Aesthet Surg. 2010;63(9):1544-1552.
86. Magown P, Rafuse VF, Brownstone RM. Microcircuit formation following transplantation of mouse embryonic stem cell-derived neurons into peripheral nerve. J Neurophysiol. 2017;117(4):1683-1689.
87. Amoh Y, Katsuoka K, Hoffman RM. Peripheral-Nerve and Spinal-Cord Regeneration in Mice Using Hair-Follicle-Associated Pluripotent (HAP) Stem Cells. Methods Mol Biol. 2016;1453:21-32.