RESEARCH ARTICLE

Peripheral nerve repair: a hot spot analysis on treatment methods from 2010 to 2014

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Abstract

Therapeutic strategies for neurological deficits and for promoting nerve regeneration after peripheral nerve injuries have received much focus in clinical research. Advances in basic research in recent years have increased our understanding of the anatomy of peripheral nerves and the importance of the microenvironment. Various new intervention methods have been developed, but with varying effectiveness. In the present study, we selected 911 papers on different repair methods for peripheral nerve injury from the Web of Science and indexed in the Science Citation Index from 2010 to 2014. We quantitatively examine new repair methods and strategies using bibliometrics, and we discuss the present state of knowledge and the problems and prospects of various repair methods, including nerve transfer, neural transplantation, tissue engineering and genetic engineering. Our findings should help in the study and development of repair methods for peripheral nerve injury.

***Key Words:** nerve regeneration; peripheral nerve injury; nerve repair; neural transplantation; nerve transfer; tissue engineering; genetic engineering; bibliometrics; Web of Science; neural regeneration*

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Introduction

Repair and reconstruction following peripheral nerve injury, especially long-segment nerve damage, is a major topic in neuroscience research and is of great clinical importance (Jiang et al., 2010). The peripheral nerve has the capacity to regenerate, but because of the low efficiency of regeneration, it is substantially impeded by the surrounding scar. As a consequence, regenerating axons are halted and may eventually form a neuroma (Jkema-Paassen et al., 2004).

Nerve autografts are considered the gold standard in the treatment of peripheral nerve injury. Recent studies have substantially increased our understanding of the role and importance of neurotrophic factors, laminin, interleukins and the immune response in peripheral nerve regeneration. Repair methods for peripheral nerve injury have used lasers, cell transplantation, and tissue and gene engineering approaches, in addition to microsurgical techniques. However, neurological recovery is still only approximately 70%. Consequently, novel strategies for enhancing the speed and extent of nerve regeneration are urgently needed.

Data and Methodology

Data source

Retrieval database: Science Citation Index (SCI).
Retrieval keywords: nerve injury, repair, anastomosis surgery, protection, nerve transfer, nerve graft.
Number of retrieved articles: 911.

Selection criteria

Inclusion criteria: Peer-reviewed articles on peripheral nerve injury; intervention studies on peripheral nerve injury; clinical application of different repair methods for peripheral nerve injury.
Exclusion criteria: Unpublished articles; obsolete research; repeated studies.

Indexes

Analyses were performed for: (1) citations of articles on peripheral nerve injury repaired using the same method; (2) the countries and regions where many relevant articles were published; (3) the institutions from which many of the articles were written; (4) the journals that published many of the articles; (5) the foundations that supported many of the studies; and (6) basic and clinical case studies.

Results

Analysis of articles indexed in the SCI on repair methods for peripheral nerve injury

A total of 1,125 articles indexed in the SCI from 2010 to 2014 on different repair methods for peripheral nerve injury were retrieved. However, only 911 original research reports and reviews were selected, because they can better reflect the academic level of the paper.

Temporal analysis of articles from 2010 to 2014 indexed in the SCI on repair methods for peripheral nerve injury

As shown in **Figure 1**, the greatest annual number of publications was 227 in 2014. From 2010 to 2014, the number of publications gradually increased. The number of publications on different repair methods for peripheral nerve injury exceeded 200 beginning in 2013. These findings suggest that repair methods for peripheral nerve injury continue to be of great concern globally.

Countries that have published articles indexed in the SCI on repair methods for peripheral nerve injury from 2010 to 2014

Numerous countries have published articles on different repair methods for peripheral nerve injury. In particular, China had the greatest number of publications at 269, accounting for 29.53% of the total number of articles, followed by the USA, with 249 publications. Germany was in third place (**Figure 2**).

Institutions that have published articles indexed in the SCI on repair methods for peripheral nerve injury from 2010 to 2014

As shown in **Table 1**, among the top eight institutions that have published articles on various methods for the repair of peripheral nerve injury, the greatest number of articles was from Nantong University, China (33 articles), followed by the University of California system (26 articles). An article written by Gu et al. (2011) entitled "Construction of tissue engineered nerve grafts and their application in peripheral nerve regeneration" was published in *Progress in Neurobiology* in 2011 and has been cited 99 times. Yang et al. (2011) published an article entitled "Repair of rat sciatic nerve gap by a silk fibroin-based scaffold added with bone marrow mesenchymal stem cells" in *Tissue Engineering Part A* in 2011 that was cited 27 times. The authors of these two articles were from Nantong University in China, demonstrating that Nantong University is recognized internationally. Publications from Urmia University in Iran and the University of Manchester in the United Kingdom both numbered 25, but the average number of citations for the publications from Urmia University was less than five, suggesting that the academic level in Iran lags far behind the United Kingdom.

Citations for articles on various methods for the repair of peripheral nerve injury indexed in the SCI from 2010 to 2014

Bibliometrics shows that a major criterion for assessing the quality of an article is the number of citations that it receives. As shown in **Table 2**, the majority of the nine most-cited articles were written by authors from the USA, and were primarily on the repair of brachial plexus injury. An article entitled "Alginate: properties and biomedical applications" was written by Lee et al. (2012) from Harvard University, and has been cited 278 times. This article describes the application of alginate and its hydrogels in biomedical science and engineering, and provides new perspectives for future studies on peripheral nerve injury using these polymers.

Intervention methods for the repair of peripheral nerve injury in articles indexed in the SCI

As shown in **Figure 3**, nerve transfer is the first choice for treatment of peripheral nerve injury. Cell transplantation combined with nerve growth factors and other trophic factors has become a major intervention method for treating peripheral nerve injury. Tissue-engineered nerve grafts consist of a nerve scaffold containing seed cells and neurotrophic factors (Gu et al., 2011). The extensive application of bone marrow mesenchymal stem cells (Wakao et al., 2010) and adipose-derived stem cells (Zhang et al., 2010; Marconi et al., 2012; Tomita et al., 2013) has increased the bioactivity and supply of seed cells. Controlled release of neurotrophins in combination with a variety of other factors has increased the effectiveness of transplantation (Liu et al., 2011). Moreover, the combined application of multiple factors in tissue-engineered peripheral nerve grafts results in synergistic effects that exceed the effects of the factors individually (Erba et al., 2010; Ao et al., 2011; Reid et al., 2011; Luo et al., 2012).

The top eight countries that have published articles on various methods for the repair of peripheral nerve injury indexed in the SCI from 2010 to 2014 are disparities, generally, the USA ranks first in the fields of nerve transfer, cell transplantation and genetic engineering for the repair of peripheral nerve injury, followed by China and Brazil, however, the most articles on tissue-engineered material and neurotrophic factor for repairing peripheral nerve injury were mainly published by Chinese authors, and the Americans ranks second. As to using anastomosis for the repair of peripheral nerve injury, Japan is the leader, followed by the USA and France (**Table 3**).

Analysis of articles on nerve transfer for the repair of peripheral nerve injury indexed in the SCI from 2010 to 2014

As shown in **Table 4**, the nine most-cited articles on nerve transfer were mainly written by authors from the USA, and mainly focused on the repair of brachial plexus injury. An article entitled "Nerve transfers: indications, techniques, and outcomes" written by Tung et al. (2010) from the Division of Plastic and Reconstructive Surgery, Washington University School of Medicine, has been cited 52 times. In this article, the authors review current strategies using motor and sensory nerve transfers for peripheral nerve lesions of the upper extremities in the management of proximal and brachial plexus injuries. The authors also discuss recent developments in the treatment of more distal and isolated nerve injuries in the forearm and hand.

Garg et al. (2011) published an article entitled "Comparison of nerve transfers and nerve grafting for traumatic upper plexus palsy: a systematic review and analysis" that has been cited 32 times. These authors searched PubMed, EMBASE and the Cochrane Central Register of Controlled Trials for studies in which patients had surgery for traumatic upper brachial plexus palsy within 1 year of injury and with a minimum follow-up of 12 months, and compared the effects of nerve transfer and nerve transplantation. Their results suggest

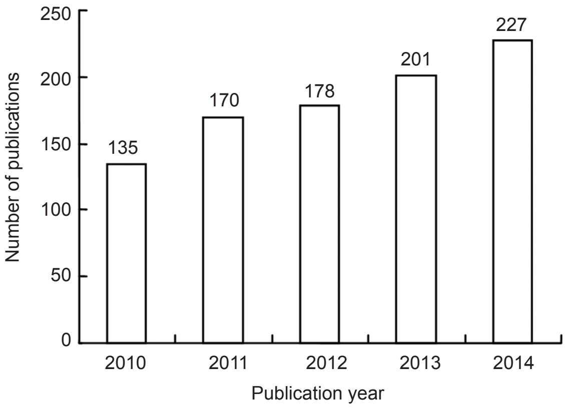

Figure 1 Quantitative analysis of articles indexed in the Science Citation Index from 2010 to 2014 on different repair methods for peripheral nerve injury.

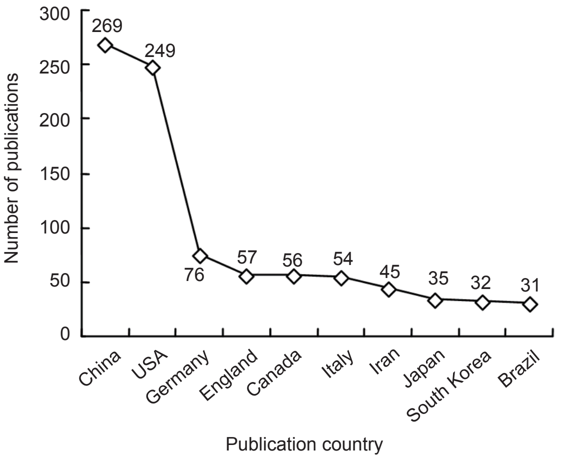

Figure 2 Countries that have published articles indexed in the Science Citation Index on different repair methods for peripheral nerve injury.

Table 1 The top eight institutions that have published articles on various methods for the repair of peripheral nerve injury

Institution	Number of publications	Percentage of publications (%)
Nantong University	33	3.62
University of California System	26	2.85
Urmia University	25	2.74
University of Manchester	25	2.74
University of Saskatchewan	23	2.53
China Medical University Taiwan	22	2.42
University of Turin	21	2.31
Hannover Medical School	21	2.31

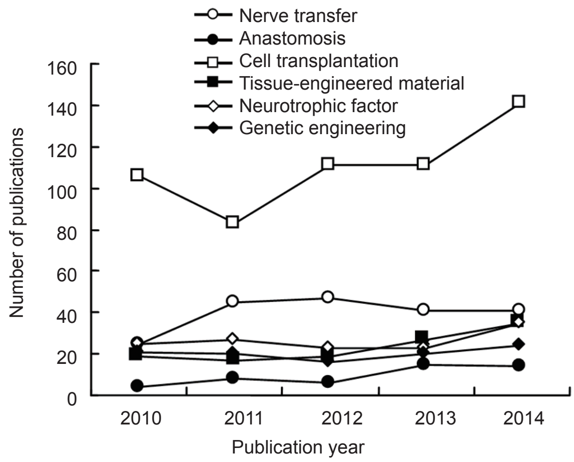

Figure 3 Different methods for the repair of peripheral nerve injury in articles indexed in the Science Citation Index.

that, compared with conventional nerve grafting, dual nerve transfer can substantially improve shoulder and elbow function in patients with complete traumatic C_{5-6} upper brachial plexus injuries and promote nerve regeneration. These data may be helpful to surgeons considering intraoperative options, particularly in cases in which the native nerve root or trunk may appear less than optimal.

Millesi (1982) pioneered microsurgery and made a significant contribution to the treatment of peripheral nerve damage. In microsurgery, surgeons usually use the same nerve branch for anastomosis to achieve the best repair effect. However, peripheral nerve injury is often accompanied by surrounding soft tissue defects, and the pathological process is complex. Therefore, the operation cannot fully restore function (Tinghog et al., 2013). In general, in patients with minor defects or no defects, end-to-end anastomosis can be used, and the epineurium and perineurium are sutured (Zhao et al., 1992; Weber et al., 2005). Neurolysis is needed if the nerves adhere to the surrounding tissue. The nerves should be dissociated from scar tissue to expose the normal nerve tract. Common anastomosis techniques include side-to-side anastomosis, end-to-side anastomosis and end-to-end anastomosis.

Yuksel et al. (1999) investigated the effect of side-to-side anastomosis on peripheral nerve regeneration in the rat. A total of 30 rats were equally divided into three groups. End-to-end anastomosis, end-to-side anastomosis and side-to-side anastomosis were utilized to repair the injured peroneal nerve. The authors found that nerve regeneration was better in the side-to-side anastomosis group than in the end-to-side anastomosis group, suggesting that side-to-side anastomosis can be used to promote nerve regeneration after tumor resection or nerve graft removal. This article has been cited 25 times.

Wan et al. (2014) concluded that end-to-side anastomosis was not suitable for incomplete facial paralysis. Facial paralysis was induced by transecting the facial nerve in the rat. Nine weeks later, repair was performed using hypoglossal-facial nerve anastomosis, and the nerve gap was bridged using a pre-degenerated peroneal nerve graft. Four months later, muscle action potential recording and retrograde labeling revealed successful establishment of connections between the hypoglossal and facial nerves. This study demonstrates that hypoglossal-nerve side-to-side anastomosis combined with nerve transplantation can be used to treat incomplete facial paralysis, and that it does not impact the function of

Table 2 Highly-cited articles on different methods for the repair of peripheral nerve injury indexed in the SCI

Title	Author	Total citations	Average citations per year	Year of citations				
				2010	2011	2012	2013	2014
Alginate: properties and biomedical applications	Lee (2012)	278	69.5	0	1	16	85	132
Current applications and future perspectives of artificial nerve conduits	Jiang (2010)	119	19.83	1	26	22	28	30
Construction of tissue engineered nerve grafts and their application in peripheral nerve regeneration	Gu (2011)	99	19.8	0	6	18	21	43
EphB signaling directs peripheral nerve regeneration through Sox2-dependent Schwann cell sorting	Parrinello (2010)	91	15.17	4	11	23	23	23
Adipose-derived stem cells enhance peripheral nerve regeneration	di Summa (2010)	89	14.83	1	16	24	18	24
Electrospun nanofibers for neural tissue engineering	Xie (2010)	77	12.83	1	8	22	20	23
FDA approved guidance conduits and wraps for peripheral nerve injury: A review of materials and efficacy	Kehoe (2012)	68	17.00	0	1	6	18	30
Trophically and topographically functionalized silk fibroin nerve conduits for guided peripheral nerve regeneration	Madduri (2010)	65	10.83	3	9	23	12	17
Silk fibroin biomaterials for tissue regenerations	Kundu (2013)	64	21.33	0	0	0	8	36

Table 3 The top eight countries that have published articles on various methods for the repair of peripheral nerve injury

Nerve transfer		Anastomosis		Cell transplantation		Tissue-engineered material		Neurotrophic factor		Genetic engineering	
Country	Number	Country	Number	Country	Number	Country	Number	Country	Number	Country	Number
USA	65	Japan	18	USA	144	China	32	China	42	USA	44
China	38	USA	17	China	129	USA	23	USA	32	China	24
Brazil	23	France	16	Japan	66	Canada	11	Japan	16	Japan	8
Canada	11	China	12	Germany	41	Germany	8	Germany	10	England	7
Spain	10	Germany	11	England	34	Australia	6	Iran	9	Netherlands	5
France	9	Turkey	8	Canada	28	South Korea	5	England	9	Spain	4
Japan	8	Italy	7	Italy	23	Italy	5	Turkey	6	Canada	4
India	7	Brazil	7	Sweden	22	Canada	11	Sweden	5	Australia	4

Table 4 Highly-cited articles on nerve transfer for the repair of peripheral nerve injury

Title	Author	Total citations	Average citations per year
Nerve transfers: indications, techniques, and outcomes	Tung (2010)	52	8.67
Comparison of nerve transfers and nerve grafting for traumatic upper plexus palsy: a systematic review and analysis	Garg (2011)	32	6.40
Nerve root grafting and distal nerve transfers for C_5–C_6 brachial plexus injuries	Bertelli (2010)	26	4.33
Clinical outcomes following median to radial nerve transfers	Ray (2011)	23	4.60
Comparison of single versus double nerve transfers for elbow flexion after brachial plexus injury	Carlsen (2011)	22	4.40
Double fascicular nerve transfer to the biceps and brachialis muscles after brachial plexus injury: clinical outcomes in a series of 29 cases	Ray (2011)	21	4.20
The motor nerve to the masseter muscle: an anatomic and histomorphometric study to facilitate its use in facial reanimation	Borschel (2012)	20	5.00
Reverse end-to-side nerve transfer: from animal model to clinical use	Kale (2011)	19	3.80
Behavioural and anatomical analysis of selective tibial nerve branch transfer to the deep peroneal nerve in the rat	Kemp (2010)	17	2.83

Table 5 Analysis of articles on tissue-engineered materials for the repair of peripheral nerve injury

Author	Animal	Damage type (defect length)	Repair material	Observation time	Outcomes
Zhu (2011)	Rat	Sciatic nerve gap (10 mm)	Seamless bi-layer nanofibrous conduits	12 months	Bi-layer nanofibrous conduits are better than nanofibrous conduits, and can remarkably promote the regeneration of injured nerve.
Liu (2011)	Rat	Sciatic nerve gap (10 mm)	Poly (lactic acid-caprolactone)/nerve growth factor conduits	12 weeks	Poly (lactic acid-caprolactone)/nerve growth factor conduits present good mechanical function and biocompatibility, can effectively contribute to the regeneration of rat sciatic nerve.
Huang (2012)	Rat	Sciatic nerve gap (10, 13 mm)	Silk conduits	12 weeks	Spidrex(®) silk conduits can well promote axonal regeneration and functional recovery.

Table 6 Analysis of articles on cell transplantation for the repair of peripheral nerve injury

Author	Animal	Damage type (defect length)	Cell	Observation time	Outcomes
Tomita (2013)	Rat	Tibial nerve crush	Tibial nerve treated with ADSCs	8 weeks	ADSCs can improve myelinization in rats with tibial nerve crush.
Marconi (2012)	Mouse	Sciatic nerve crush	1-week post-crush intravenous injection of ADSCs	5 weeks	ADSCs lessen inflammation, improve the recovery of motor function, and elevate the number of regenerated myelinated fibers.
Wakao (2010)	Monkey	Median nerve (20 mm)	Monkey bone marrow stromal cell-derived Schwann cells	12 months	Transplantation of monkey bone marrow stromal cell-derived Schwann cells promotes the recovery of neurological function, and the regeneration of injured nerve in monkey models of median nerve injury.
Zhang (2010)	Rat	Sciatic nerve gap (10 mm)	Xenogeneic acellular nerve matrix + ADSCs	3 months	Transplantation of xenogeneic acellular nerve matrix + ADSCs improves microenvironment surrounding the injury site, and promotes nerve regeneration.

ADSCs: Adipose-derived stem cells.

Table 7 Analysis of articles on cell transplantation combined with tissue-engineered materials for the repair of peripheral nerve injury

Author	Animal	Damage type (Defect length)	Material	Observation time	Outcomes
di Summa (2010, 2011)	Rat	Sciatic nerve defect (10 mm)	Fibrin conduit + ADSCs	2, 16 weeks	ADSCs increase nerve regeneration (2 weeks), fiber diameter, and reduce muscle atrophy (16 weeks).
Ao (2011)	Rat	Sciatic nerve defect (12 mm)	Chitosan conduits + bone marrow stem cells	3 months	Chitosan conduits + bone marrow stem cells increases nerve conduction velocity and the number of myelinated axons.
Erba (2010)	Rat	Sciatic nerve defect (10 mm)	Poly-3-hydroxybutyrate conduits + ADSCs	12 months	Transplantation of monkey bone marrow stromal cell-derived Schwann cells promotes the recovery of neurological function, and the regeneration of injured nerve in monkey models of median nerve injury.
Luo (2012)	Rat	Sciatic nerve defect (50 mm)	Acellular nerve allograft + ADSCs	6 months	Acellular nerve allograft + ADSCs improves myelination and reduces muscle atrophy.
Reid (2011)	Rat	Sciatic nerve defect (10 mm)	ADSCs + PCL conduit	2 weeks	ADSCs reduce the expression of apoptotic gene in the dorsal root ganglion.

ADSCs: Adipose-derived stem cells; PCL: polycaprolactone.

residual normal axons.

Cage et al. (2013) reported a case of biceps muscle reinnervation after side-to-side anastomosis of an intact median nerve to a damaged musculocutaneous nerve. Nine months after surgery, electromyographic and nerve conduction studies showed that the biceps muscle was reinnervated partly by donor axons from the healthy median nerve and partly by the recovering musculocutaneous nerve. This demonstrates that side-to-side anastomosis of an intact median to an injured musculocutaneous nerve provides dual reinnervation of the biceps muscle, and simultaneously minimizes injury to both donor and recipient nerves.

Analysis of articles on tissue-engineered materials for the repair of peripheral nerve injury indexed in the SCI from 2010 to 2014

Composite bioengineered material containing an acellular nerve matrix and synthetic biodegradable material can be used as an ideal scaffold for the repair of peripheral nerve injuries. Acellular nerve scaffolds are not limited by availability as are autologous nerves or by graft rejection, and strength and plasticity are similar to autologous nerves. Moreover, the microenvironment is more conducive to peripheral nerve regeneration. Synthetic biodegradable materials have a number of advantages such as biodegradability, plasticity and greater permeability. Analysis results are shown in **Table 5**.

Analysis of articles on cell transplantation for the repair of peripheral nerve injury indexed in the SCI from 2010 to 2014

Nerve autografts are considered the gold standard for the repair of nerve defects that are greater than 50-mm long or cannot undergo tension-free suturing (Doolabh et al., 1996; Valero-Cabre et al., 2001). The use of nerve scaffolds has reasonable success for short-segment nerve defects (shorter than 10 mm in rats). Nevertheless, when the length of the injured nerve exceeds a certain limit, the use of a nerve scaffold alone blocks nerve regeneration, because of the lack of support cells in the scaffold (Doolabh et al., 1996). Functional seed cells implanted in the nerve scaffold secrete growth factors and extracellular matrix molecules, which provides a favorable microenvironment for nerve regeneration. The most-studied functional seed cells are Schwann cells, olfactory ensheathing cells, neural stem cells, mesenchymal stem cells and embryonic stem cells. Analysis results are shown in **Table 6**.

Analysis of articles on cells combined with tissue-engineered materials for the repair of peripheral nerve injury indexed in the SCI from 2010 to 2014

Analysis results are shown in **Table 7**.

Analysis of articles on gene therapy for the repair of peripheral nerve injury indexed in the SCI from 2010 to 2014

Gene therapy is the therapeutic delivery of nucleic acid into cells to treat disease by overcoming protein deficiency or inhibiting overexpression of certain genes *in vivo*. Mason et al. (2011) published an article entitled "Gene therapy for the peripheral nervous system: a strategy to repair the injured nerve?" in 2011 in *Current Gene Therapy* that has been cited 21 times. The authors discuss the potential of gene therapy as an adjunct strategy alongside surgical repair techniques for promoting peripheral nerve regeneration in rodent models. Hu et al. (2010) observed that the accuracy of sensory axon reinnervation is enhanced by overexpression of nerve growth factor distal to the bifurcation. They used the femoral nerve as a model. Recombinant adenovirus encoding nerve growth factor was injected along the saphenous branch close to the bifurcation 1 week after injury to enhance sensory axon targeting. The accuracy of axon reinnervation was assessed by retrograde tracing at 3 or 8 weeks after nerve injury. Nerve growth factor overexpression increased the accuracy of saphenous branch axon reinnervation to the appropriate nerve branch, independent of its effect in enhancing the speed and extent of axonal regeneration. This finding provides *in vivo* evidence that the expression of a neurotrophin enhances the targeting of distal peripheral axons into the appropriate nerve branch. Gene therapy is still in the early experimental stage, but it is expected to have substantial therapeutic potential for nerve damage in the near future.

Discussion

Long-term basic and clinical studies show that techniques for the repair of peripheral nerve injury are constantly developing and that hot points constantly evolve.

In summary:

(1) Nerve transfer is the first choice for repairing peripheral nerve injuries. Nerve autografts are considered the gold standard for the treatment of long-segment nerve injuries. With the development of tissue engineering and gene therapy, the number of articles on nerve transfer has decreased. The institutions where many of the articles on nerve transfer were written are in China.

(2) The number of articles on cell transplantation combined with tissue-engineered materials has increased. Most of the articles focus on the recovery of function in animal models. Combined application is a hot point in present surgical treatment.

(3) Many of the relevant articles were written by institutes in the USA. These articles on peripheral nerve injury play an important role in guiding future research.

(4) Researchers in China mainly focus their attention on surgical treatment, and the articles are of a high academic level. However, Chinese studies do not often use drug therapy, cell transplantation, nerve factors or gene therapy.

(5) Approaches using biomaterials in the repair of peripheral nerve injury have developed rapidly, but the use of biomaterials is still mainly limited to scaffolds for nerve autografts. Composite bioengineered materials containing an acellular nerve matrix and synthetic biodegradable substances may be ideal scaffolds for the repair of peripheral nerve injuries and defects. Seed cells and neurotrophic factors are needed to obtain good nerve regeneration.

(6) Gene therapy has broad application prospects for peripheral nerve repair. Nevertheless, gene therapy has some shortcomings at present, such as the lack of efficient and sustainable exogenous gene expression and the biological risk associated with viral vectors. However, in the near future, this technology will become an important method for the clinical repair of peripheral nerve injury.

(7) Combining increasingly sophisticated microsurgical techniques with tissue and genetic engineering will help to improve the efficiency of peripheral nerve repair.

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Conflicts of interest: *None declared.*

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