REVIEW ARTICLE

Advances in Experimental and Clinical Studies of Chemotaxis

Aikeremujiang Muheremu, Yu Wang, Jiang Peng

ABSTRACT: The theory of chemotaxis has been widely accepted, but its mechanisms are disputed. Chemotactic growth of peripheral nerves may be tissue, topographic and end-organ specific. Recent studies indicated that peripheral nerve regeneration lacks topographic specificity, but whether it has end-organ specificity is disputed. Chemotaxis in nerve regeneration is affected by the distance between stumps, volume, and neurotrophic support, as well as the structure of distal nerve stumps. It can be applied to achieve precise repair of nerves and complete recovery of end organ function. Small gap sleeve bridging technique, which is based on this theory shows promising effects but it is still challenging to find the perfect combination of nerve conduits, cells and neurotrophic factors to put it into its best use. In this paper, we made a comprehensive review of mechanisms, effect factors and applications of chemotaxis.

RÉSUMÉ: Progrès dans les études expérimentales et cliniques de la chimiotaxie. La théorie de la chimiotaxie est couramment acceptée, mais ses mécanismes demeurent controversés. La croissance chimiotaxique des nerfs périphériques pourrait être spécifique selon les tissus, la topographie et l'organe-cible. Des études récentes indiquent une absence de spécificité topographique dans la régénérescence des nerfs périphériques. Cependant la spécificité concernant les organes-cibles demeure controversée. La chimiotaxie dans la régénérescence nerveuse est influencée par la distance entre les extrémités du nerf, le volume et le support neurotrope ainsi que la structure des extrémités nerveuses distales. La chimiotaxie peut être utilisée pour réaliser une réparation précise de nerfs et pour obtenir une récupération de la fonction de l'organe-cible. Une technique de relais par manchon de petits écarts basée sur cette théorie a semblé avoir des effets prometteurs, mais trouver la combinaison parfaite de conduits nerveux, de facteurs cellulaires et neurotropes pour optimiser son utilisation constitue encore un défi. Dans cet article, nous faisons un examen approfondi des mécanismes de la chimiotaxie, des facteurs qui l'influencent et de ses applications.

Can J Neurol Sci. 2013; 40: 292-298

Peripheral nerve injuries affect up to 5% of patients admitted to trauma centres[1,2]. These injuries represent an important issue in medicine because patients with peripheral nerve trauma are often at the peak of their employment productivity and any loss or decrease of function is particularly devastating.[3] Injuries to peripheral nerves are challenging surgically. Despite advancements in microsurgical techniques, complete recovery of nerve function after repair is almost never achieved.[4] Peripheral nerve repair has reached a plateau today, with functional recovery still unsatisfactory and surgical techniques can not be further refined. Despite early diagnosis and modern surgical techniques, functional recovery of end organs never reaches the pre-injury level. Poor outcome may be explained by factors both intrinsic and extrinsic to the nervous system, such as the type and level of injury, associated injuries, timing of the surgery, and changes in spinal cord neurons and end organs.[5-7] Misdirection of regenerated axons at the injury site is still a major problem, resulting in an increased interest in the role of micro-environmental factors in regulating axonal growth and direction. Unlike the central nervous system, the peripheral nervous system has strong potential for regeneration. With an appropriate microenvironment, the regenerating axons can extend their processes into the distal Bungner bands to regain normal function. Traditional epineurium neurorrhaphy induces regeneration by direct nerve contact, which leads to enforced inosculation and inappropriate nerve fascicle coaptation and may result in neuroma. The theory of chemotaxis provides new methodsdistinct from epineurium neurorrhaphy, thus reducing the likelihood of neuroma while gaining appropriate and concise axon regeneration.

1. Theories related to chemotaxis

Forssman's 1898 theory of selective peripheral nerve regeneration involved assuming that regenerated axons after nerve injury could recognize the distal stumps of the nerves and

From the Institute Of Orthopaedics, Chinese PLA General Hospital, Fifth Affiliated Hospital of Xinjiang Medical University, Beijing, China.

Received November 24, 2011. Final Revisions Submitted November 1, 2012.

Correspondence to: Jiang Peng, Institute of Orthopaedics, Chinese PLA General Hospital, NO28, Fuxing Rd, Haidian District, Beijing, China. Postal Code: 0086-100853. Email: pengjdxx@126.com.

selectively grow toward their counterparts because of concentration gradients of specific matter produced by the target organs. In 1928, Cajal[8] reported the phenomenon of elective axonal growth toward the peripheral nerve's counterpart, the result of concentration gradients produced by the end-organ, a phenomenon defined as chemotaxis. However, in 1943, Weiss and Tailor[9] did not find chemotactic nerve regeneration when they repaired rat sciatic nerve by an isogenic- artery Y-conduit. By the end of the 1980s, Lundborg[10] et al performed the Y conduit experiment again and found regenerated axons preferentially grew toward the distal nerves. This discrepancy between Weiss and Lundborg may have resulted from different experimental conditions, as Lundborg et al used a synthetic Y conduit that was not yet invented in the 1940s. Lundborg revealed that chemotaxis had nerve tissue, topographic and target tissue specificity. The tissue specificity has been verified with a Y-conduit tibial and fibular nerve regeneration model: Politis[11] found that the proximal ends of tibial and fibular nerves correspondingly grew towards their respective distal stumps. The author assumed that this situation resulted from specific factors produced by the distal nerve stumps. Lee et al[12] redid the tibial and fibular nerve experiment and found that proximal stumps of tibial and fibular nerves grew more toward the tibial site than the fibular site, which suggested that nerve chemotaxis lacked topographic specificity. Brushart et al[13] inserted the proximal stump of the rat femoral nerve into the proximal end of the Y conduit and the distal stump of the nerves into the quadriceps femoris nerve and saphenous nerve. After two, three, and eight weeks, only the motor axons that grew into the endoneurium of motor nerves had survived (pruning syndrome). However, sensory nerves did not show a pruning phenomenon, suggesting sensory nerves may not have the specificity of selective growth. Maki et al[14] assessed the selectivity of motor and sensory axon regeneration towards the distal motor and sensory nerve segments that were disconnected from end organs in a rat silicone Y chamber model. Motor axons showed no selective regeneration, but sensory axons did (Figure 1). Whether nerve chemotaxis has target organ specificity still needs further evaluation.

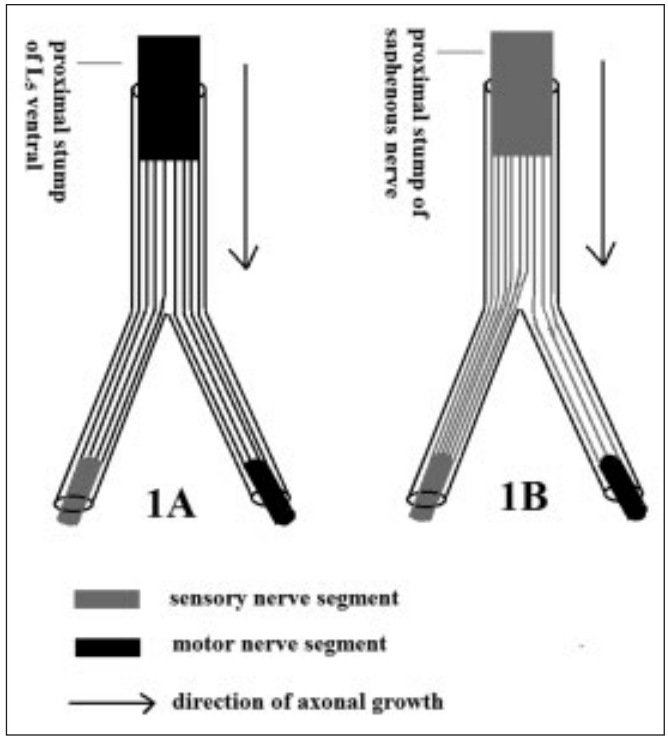

Figure 1: *The L5 ventral root was used as a pure motor nerve, and the saphenous nerve was used as a sensory nerve. In experiment 1 (1A), the proximal stump of the L5 ventral root, a 1-cm-long L5 ventral root segment and a saphenous nerve segment were inserted into a silicone Y chamber. In experiment 2 (1B), the proximal stump of the saphenous nerve, a L5 ventral root segment and a saphenous nerve segment were inserted into a Y chamber. The distance between the nerve stumps was 5 mm. Six weeks later, the number of regenerated myelinated motor and sensory axons was measured and compared in the distal two channels. Motor axons showed no selective regeneration, but sensory axons did.*

2. Mechanisms of chemotaxis

The theory of chemotaxis has been widely accepted, however, its mechanism is still unclear. Hari et al[15] found that the interaction among neurotrophic factors, basal extra-cellular protein and fibronectin can regulate chemotactic regrowth. The authors assumed that recognition particles (neural cell adhesion molecule, L1 family) are the basis of nerve chemotaxis. Hoke et al[16] assumed that chemotaxis of peripheral nerves contributes in part to the SC phenotype. Both myelin-forming and non-myelin-forming SCs of motor and sensory neurons have different phenotypes. The neurotrophic factors they secrete are not all the same, and thus they have different moderating effects on the chemotaxis of neurons. Studies have indicated that the direction of regenerating axons is regulated by different concentrations of neurotrophic factors secreted by distal-end nerve stumps. Mechanisms of nerve chemotaxis still need to be explored.

3. Factors that effect chemotaxis

Multiple factors can affect chemotactic regrowth in peripheral nerve repair, including the distance between the nerve stumps, volume of the distal nerve stump, neurotrophic support and structure of the nerve.

3.1 Distance between the nerve stumps

The theory of chemotaxis suggests that, after nerve injury, distal nerves and target organs have a chemotrophic and chemotactic influence on the proximal end of the regenerating nerves. However, the distance between the nerve stumps is also a factor. If the distance is too large, neurotrophic factors cannot achieve sufficiently high concentrations, and if too small, regenerating axons will grow directly into the distal endoneurium. Lundborg et al[17] found that a gap of 6 to 10 mm between stumps of rat sciatic nerves showed chemotactic regrowth, but with gaps > 10 mm, growth of the proximal end nerve was prohibited. Politis et al,[18] studying chemotaxis in rat tibial-fibular nerves, chose a distance of 4 to 5 mm, because distances > 6.5 mm showed no significant chemotactic growth.

https://doi.org/10.1017/S0317167100014220 Published online by Cambridge University Press

3.2 Distal nerve stumps

Distal stumps of injured nerves go through a series of cellular and biomolecular changes, including elimination of axons, proliferation of SCs, and Wallerian degeneration. Proliferated but not yet differentiated SCs form a "band of Bungner" in the inner membrane conduits and produce various neurotrophic factors such as nerve growth factor (NGF) and brain derived neurotrophic factors (BDNF). These molecules promote nerve chemotaxis. After denaturation of the distal nerves, the distal end of the basic membrane conduit remains and can provide a channel and structural basis for the regeneration of nerve axons. Zhang et al[19] studied the influnce of volume of the distal nerves on chemotaxis. They divided 32 rats into 4 groups, proximal nerve stumps were inserted in a nerve tube, and different volumes of nerve grafts were inserted in the distal ends of tubes. After six weeks, the diameter, density, thickness and axonal transport rate of regenerated nerves in the tubes were measured. No significant statistical difference was found between groups, which suggested that the volume of distal nerves does not effect chemotaxis. Takahashi et al,[20] with two groups of rats (n=20 each), built rat sciatic-nerve Y-conduit regeneration models. Nerve grafts of different volumes were inserted in the distal ends. Axons were counted after six weeks. Regenerated axons in tubes with larger grafts demonstrated more nerve axons, the larger the volume of the graft, the greater the number of regenerated nerve axons. Madison et al[21] studied a nerve selective regeneration model of rat sciatic nerves and found that chemotactic regrowth of motor nerves is decided by neurotrophic support of distal nerves. Regenerated nerves grew preferentially into the side with rich neurotrophic factors, and the authors assumed that neurotrophic factors were produced by the interaction of distal organs and SCs. Robinson et al[22] used a rat femoral-nerve Y-conduit model to study the accuracy of motor-axon chemotactic regrowth. The authors found that when sensory and motor axons of similar volume were inserted into the distal end, regenerated nerves grew equally toward the two sides at the early stage but preferentially toward the motor nerve stumps at a later stage. With thick sensory nerves inserted in the far end, regenerated nerve axons grew preferentially towards the sensory nerve stumps. Therefore, regeneration of motor axons is affected by the volume of the disal nerve, which depends on neurotrophic factors secreted by SCs, which can induce the regrowth of proximal nerve stumps. Moradzadeh et al[23] proposed the theory of nerve architecture: the size of the basal membrane of the conduit of SCs has a strong effect on the regeneration of nerve axons. SCs of motor axons have larger basal conduit membranes than sensory nerve axons, which can facilitate more in-growth of nerves for further repair. Thus, it can be assumed that the chemotactic effect of motor nerves is superior to those of sensory nerve stumps.

3.3 Neurotrophic factors

Recent advances in the understanding of molecular pathways and their physiological role demonstrate that neurotrophic factors play an important role in the development, maintenance, and regeneration of the nervous system.[24-26] Such factors include NGF and the other recently identified members of the neurotrophin family, namely, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4/5. Other factors include the neurokines, ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF), as well as transforming growth factor (TGF)-β and its distant relative, glial cell line–derived neurotrophic factor (GDNF).

During peripheral nerve regeneration, the neurotrophins NGF, NT-3 and BDNF have a well-defined and selective beneficial effect on the survival and phenotypic expression of primary sensory neurons in spinal-cord dorsal root ganglia and motoneurons. Other neurotrophic factors such as CNTF, GDNF and ILGF[27] may also facilitate the chemotactic growth of neuronal cells.

Nerve growth factor maintains activity of neurons, induces and promotes the sprouting of axons, and provokes SCs to express neural-cell adhesion molecules. Utly et al[28] used BDNF and collagen matrix to repair defects in rat sciatic nerves and found that BDNF significantly accelerated the chemotactic regrowth of peripheral nerves.

To improve the nerve regeneration effect, neurotrophic factors have been added into conduits. Adding exogenous NGF locally has been adopted. This method seems useful in repairing long nerve defects and improving the nerve regeneration effect. HEK-293 cells can be genetically modified to release and regulate NGF *in vitro*. A 13-mm sciatic nerve gap was bridged with silastic conduits in 120 nude rats, and transfected HEK-293 cells were added and induced with ponasterone A to secrete bioactive NGF. The process increased bioactive NGF expression, enhanced macroscopic nerve growth, and improved functional recovery and regeneration seen on histology from seven days to four months.[29]

4. Use of nerve chemotaxis

The theory of chemotaxis has provided new ways to promote peripheral nerve regeneration[30]. The influencing factor in postoperative functional recovery is the correct matching of the proximal sensory or motor tracts with the corresponding tracts in the distal stumps. With a small gap between the ruptured mixed nerve, the proximal sensory and motor nerve fibers grow through the gap and selectively find their counterparts in the distal nerve stumps.[31] Small gaps can form a microenvironment suitable for chemotactic factors from the distal stumps to affect the proximal stumps. Preserving a cavity of a specific size between the proximal and distal stumps, called small-gap bridging, may be beneficial in regenerating mixed nerve fibers. The technique drives more regenerating nerve fibers into the distal stumps than with epineurium neurorrhaphy and provides a relatively close microenvironment to facilitate regeneration because cells are protected against invasion. As well, neurotrophic factors are enriched for the regenerating nerve, and as long as enforced coaptation of nerve stumps is avoided by use of the bridging technique, scar formation is minimized.[32,33]

Small-gap sleeve bridging based on the chemotaxis theory has had satisfactory results in both experimental and clinical studies. The technique might replace epineurium neurorrhaphy as the gold standard for repairing peripheral nerve injury. With tibial nerves of rats, Jiang et al[34] found small-gap sleeve bridging more effective than direct epineural suturing.

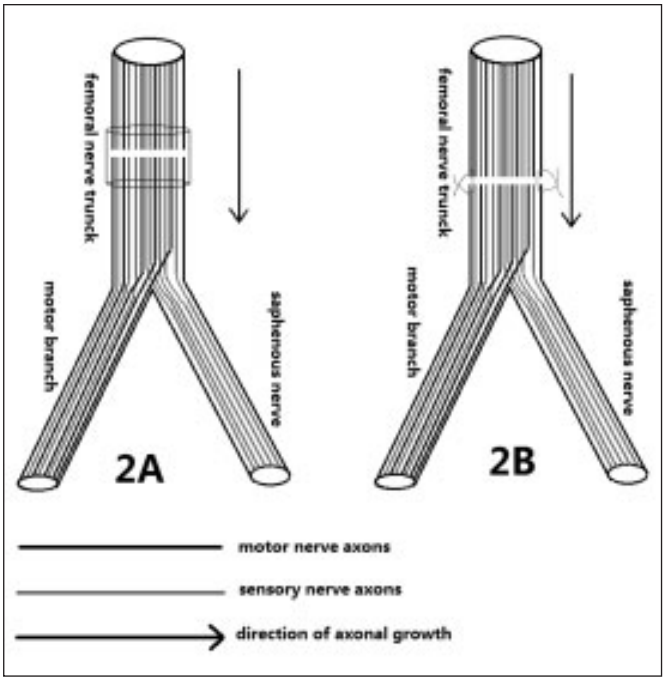

Figure 2: *Small gap bridging technique (2A) prevents enforced coagulation and creates a favorable microenvironment that enhances accurate nerve coaptation, while direct epineural suturing (2B) may result in enforced coagulation and inaccurate nerve coaptation.*

4.1 Nerve conduits

Autologous nerve grafting is the golden standard for treating peripheral nerve injury. However, autograft harvesting requires a second operative site with the sacrifice of a functional nerve, which results in donor sensory loss, potential formation of neuroma and neuropathic pain.[35]

The theory of nerve chemotaxis has provided the method of nerve conduit bridging to treat large-fragment nerve injury. With such bridging, an appropriate microenvironment is provided to promote the chemotactic regrowth of nerve axons. The conduit provides both stumps with trophic support and prevents the invasion of surrounding tissues. The regenerating stumps are prevented from growing randomly in different directions but not toward their original pathways, which may have developed neuroma. Moreover, nerve conduits enrich the neurotrophic factors secreted from the distal stumps, which influences proximal stumps in building a microenvironment beneficial for the regeneration of nerves (Figure 2).

Brushart et al[13] found, using rat sciatic nerves, that the microenvironment produced by nerve conduit bridging is beneficial for autoslection and functional regeneration. Nakamura et al[36] reported better results using PGA tubes filled with collagen sponge than autografts on 15-mm gap in the peroneal nerve of beagle dogs. Weber et al[37] compared polyglycolic acid conduit (PGA) bridging and direct suturing in a randomized controlled study of 136 patients with peripheral nerve injury in five US medical centers. The authors found 91% satisfactory healing with PGA bridging and 49% with direct suturing. They suggested that conduit bridging is more effective with defects > 8 mm. Taras et al[38] performed peripheral nerve conduit repair on 73 patients. Except for two patients with scar formation, all other patients achieved satisfactory recovery. Lohmeyer et al[39] used nerve conduits to repair nerve defects of the forearms in 14 patients: four patients achieved excellent recovery, five satisfactory recovery, one unsatisfactory improvement and two no improvement. Therefore, small-gap sleeve conduit bridging is effective in treating nerve defects, but excellent microscopic surgical skill is vital. To evaluate the clinical application of nerve conduits, Meek et al[40] compared nerve tubes approved by the EU and US Food and Drug Administration, favoring the PGA nerve conduit for repair of peripheral and cranial nerve defects because of its advantages in length, price, and availability of clinical data.

Nerve conduit bridging creates nerve regeneration chambers, which are beneficial for tissue engineering. Bioabsorbable conduits[41] and compound conduits (consisting of neurotrophic factors, nerve supporters, SCs42 and nerve stem cells) have promoted chemotactic growth of peripheral nerves and enhanced nerve repair.

Various non-neural conduits have been studied, both synthetic and biological, including silicone tubes,[43] fibronectin mats,[44] denatured skeletal muscle or muscle basal lamina,[45,46] human amniotic membrane,[47] veins,[48] and polyglycolic acid-collagen tubes.[49,50] Some of these have been more potent in promoting peripheral nerve regeneration with the introduction of SCs.[51] The silica gel canal was the earliest artificial conduit. Its use avoided the harvesting of autologous tissue, which resulted in a positive regeneration effect but was verified to be inferior to the use of veins and needed secondary removal surgery to avoid chronic nerve compression syndrome or inflammatory reaction.[52] Hence, a biodegradable and bioabsorbable artificial conduit is required. Many scholars have used autogeneic epineurium[53,54] or normal nerve-trunk[55] autogeneic veins, small arteries and even muscle fibers[56,57] to promote peripheral nerve selective regeneration[58,59].

Common biodegradable materials include collagen, chitin, polylactic acid (PLA), polyglycolic acid (PGA), poly (lactide-co-glycolide) (PLGA), poly(caprolactone) (PCL/ PCA). These materials can provide initial support for the nerve, and degrade to an innocuous product after the nerve completes the regeneration. (Table 1)

4.2 Schwann cells

SCs are one of the key elements in peripheral nerve regeneration[60]. After nerve injury, SCs in the distal stump undergo proliferation and phenotypical changes to prepare the local environment for axonal regeneration. SCs direct peripheral nerve regeneration by Netrin-1 receptors and Unc5H2. SCs in the peripheral nerve trunk exist in two forms: myelin and nonmyelin forming cells, both differentiating from a common pool of immature SCs derived from the neural crest via intermediate cells called SC precursors.[61]

Modifying nerve conduits by implanting SCs has become a hot topic in research of the nerve gap bridging technique. Siemionow et al[62] transplanted 24 epineural tubes as a conduit to bridge 20-mm nerve-gap defects in two experimental groups. For group 1, the tube was filled with saline and for group 2, with

https://doi.org/10.1017/S0317167100014220 Published online by Cambridge University Press

Table: Some of the studies on the application of conduits for peripheral nerve injury

Author reference NO	Year	Subject	Nerve	Length	Conduit Material	Results
Zhang [41]	2010	SD Rats	sciatic	1cm	acellular nerve matrix with stem cells	Stem cells promote nerve regeneration.
Nakamura [42]	2004	beagle dogs	peroneal nerve	1.5cm	PGA with collagen sponge	The mylinated axons in the PGA side are larger in diameter than the autograft side.
Weber [43]	2000	clinical trial	digital nerve		PGA conduit	Excellent results were obtained in 43 percent of repairs, good results in 43 percent, and poor results in 14 percent.
Xu [47]	2011	SD rat ,	sciatic	1cm	PDLLA/Chondroitin sulfate/Chitosan	Rapid functional recovery achieved in the experimental group.
Williams [49]	1984	rat	sciatic nerves	1cm	silicone chamber	Nerve regeneration promoted in the conduit group.
Whitworth [50]	1995	inbred Lew rats	sciatic nerve	1cm	orientated strands of the cell adhesive fibronectin,	Fibronectin supported a significantly faster rate of growth and amount of axons than the freeze-thawed muscle grafts.
Glasby [51]	1986	marmosets	ulnar nerve		autogenous skeletal muscle	normal hand function had returned and the grafts were shown to transmit normal compound extracellular action potentials in both directions by six months,
Fawcett [52]	1986	rat ,rabbit	sciatic nerves	Rat: 0.5cm Rabbit: 4cm	muscle basal lamina grafts	Satisfactory results achieved functionally, electrophysiologically, and anatomically
Tang [54]	1993	clinical trial	digital nerve defects	0.5~ 5.8cm	autogenous vein graft taken from forearm	Follow-up revealed excellent recovery in two digital nerves, good in nine, fair in five and poor in two
Ashley [55]	2006	New born infants	brachial plexus		collagen matrix tubes	Most patients achieved good recovery
Kiyotani [56]	1996	cats	sciatic nerves	2.5cm	PGA mesh coated with collagen	16 months after implantation of the tube revealed regeneration of well vascularized nerve tissue.
Brown [57]	1996	rabbit	hind-limb nerve	3cm	polyglycolic acid filled with gelatin/Schwann-cell suspension	No significant difference between experimental and a control grou in which the nerve gap was reconstructed by using a PGA conduit filled with gelatin only
Ayhan [59]	2000	Wistar rats	sciatic nerves	1cm	epineurial sheath tube	Sciatic functional indices and histomorphometric analyses revealed statistically significant improvement in experimental group
Karacaoglu[60]	2001	rat	sciatic nerves	1cm	epineurial tubes	Morphometric analysis showed significant improvement in experimental group
Geuna[62]	2004	Inbred Lew rats	sciatic nerve	1cm	muscle-vein combined conduits	Experimental group showed significant improvement by total number, mean density and mean size of myelinated nerve fibers,
Varejao [63]	2003,	rat	sciatic nerve	1cm	Poly (DLLA-epsilon-CL) conduit enriched with fresh skeletal muscle	a-GFAP (glial fibrillar acid protein) immuno-labelling of Schwann cells showed progression inside muscle-enriched tubes
Barcelos [65]	2003	Wistar rats	sciatic nerves	1cm	inside-out vein grafts(IOVG) and inside-out artery grafts (IOAG)	IOVG presented a closer-to-normal nerve organization than IOAG

isogenic bone-marrow stromal cells (BMSCs) prestained with PKH-dye. Twelve autograft sciatic nerve repairs served as a control. After 12 weeks, the epineural tube/BMSC construct was comparable to autograft repair in sensory and motor recovery. For repair of a long-gap (15-mm) rat sciatic nerve defect model, Lin et al[63] divided 30 rats into four groups for treatment with silk conduits with empty silk microspheres, silk microspheres with GDNF uniformly distributed in the conduit wall, silk microspheres with the highest GDNF concentration at the distal end, and isografting. At six weeks, histological analysis revealed that porous-silk fibroin–based nerve conduits with controlled GDNF infusion had the best curative effect. di Summa et al[64] compared the efficacy of fibrin conduits implanted with primary SCs, SC-like differentiated bone marrow-derived mesenchymal stem cells (dMSCs), and SC-like differentiated adipose-derived stem cells (dASCs) to bridge a 1-cm rat sciatic nerve gap in a

https://doi.org/10.1017/S0317167100014220 Published online by Cambridge University Press

long-term experiment (16 weeks). Control groups were fibrin conduits without cells and autografts. Conduits with SCs, dMSCs, and dASCs demonstrated better regenerative qualities in terms of functional and morphological properties of regenerated nerves than did conduits without cells.

MSCs are abundant and can be easily collected, which solves the problem of the SC source and allows for wide clinical application of SCs.[65] Furthermore, small-gap bridging of rat nerves with conduits including MSCs conferred a better effect than with simple conduits.[66] Matsuse et al[67] induced human umbilical cord Y-derived mesenchymal stromal cells (UC-MSCs) to differentiate into cells with SC properties by treatment with A-mercaptoethanol then retinoic acid and a set of specific cytokines and used them in nerve conduits as neurotrophic factors: functional recovery of injured nerves was significantly promoted, which indicates that cells with SC properties and the ability to support axonal regeneration and reconstruct myelin can be successfully induced from UC-MSCs to promote functional recovery after peripheral nerve injury.

Conclusions

Studies have shown that nerve regeneration has target tissue specificity. However, whether such regeneration has topographic or target organ specificity is not clear. The mechanism of chemotactic regeneration still needs further study. The use of small-gap conduit bridging creates a beneficial micro-environment for chemotactic nerve growth and is important in the functional recovery of end organs. Although the theory of chemotaxis and small gap bridging technique seemingly has promising effects, there are still huge challenges to overcome to find a perfect combination of nerve tubes, cells, cellular matrix, neurotrophic factors as well as appropriate distance between stumps to create a favorable microenvironment for chemotactic nerve regeneration to achieve full and precise nerve repair.

References

1. Belkas JS, Shoichet MS, Midha R. Peripheral nerve regeneration through guidance tubes. Neurol Res. 2004;26(2):151-60.
2. Taylor CA, Braza D, Rice JB, Dillingham T. The incidence of peripheral nerve injury in extremity trauma. Am J Phys Med Rehabil. 2008;87(5):381-5.
3. Whitlock EL, Tuffaha SH, Luciano JP, et al. Processed allografts and type I collagen conduits for repair of peripheral nerve gaps. Muscle Nerve. 2009;39(6): 787-99.
4. Eser F, Aktekin LA, Bodur H, Cigdem A. Etiological factors of traumatic peripheral nerve injuries. Neurol India. 2009;57: 434-7.
5. Shieh SJ, Lee JW, Chiu HY. Long-term functional results of primary reconstruction of severe forearm injuries. J Plast Reconstr Aesthet Surg 2007;60:339-48.
6. Herscovici D, Jr., Fiennes AG, Allgower M, Ruedi TP. The floating shoulder: ipsilateral clavicle and scapular neck fractures. J Bone Joint Surg BR. 1992;74(3):362-4.
7. Goss TP. Double disruptions of the superior shoulder suspensory complex. J Orthop Trauma. 1993;7(2):99-106.
8. Cajal RS. Degeneration and Regeneration of the Nervous System, Oxford University Press. 1928.
9. Weiss P, AC Taylor, 1944, Further experimental evidence against neurotropism in nerve regeneration. J Exp Zool. 1944;95: 233-57.
10. Lundborg G, Dahlin LB, Danielsen N, Nachemson AK. Tissue specificity in nerve regeneration. Scand J Plast Reconstr Surg. 1986;20(3):279-83.
11. Politis MJ. Specificity in mammalian peripheral nerve regeneration at the level of the nerve trunk. Brain Res. 1985;328(2):271-6.
12. Lee JM, Tos P , Raimondo S, Fornaro M, Papalia I, Geuna S. Lack of topographic specificity in nerve fiber regeneration of rat forelimb mixed nerves. J Neurosci. 2007;144(3):985-90.
13. Brushart TM, Gerber J, Kessens P, Chen YG, Royall RM. Contributions of pathway and neuron to preferential motor reinnervation. J Neurosci. 1998;18(21):8674-81.
14. Maki Y, Yoshizu T, Tsubokawa N. Selective regeneration of motor and sensory axons in an experimental peripheral nerve model without endorgans. Scand J Plast Reconstr Surg Hand Surg. 2005;39(5):257-60.
15. Hari A, Djohar B, Skutella T. Neurotrophins and extracellular matrix molecules modulate sensory axon outgrowth. Int J Dev Neurosci. 2004;22(2):113-7.
16. Hoke A, Redett R, Hameed H, et al. Schwann cells express motor and sensory phenotypes that regulate axon regeneration. J Neurosci. 2006;26(38):9646-55.
17. Lundborg G, Dahlin LB, Danielsen N, et al. Nerve regeneration in silicone chambers: influence of gap length and of distal stump components. Exp Neurol. 1982;76(2):361-75.
18. Politis MJ, Ederle K, Spencer PS. Tropism in nerve regeneration in vivo. Attraction of regenerating axons by diffusible factors derived from cells in distal nerve stumps of transected peripheral nerves. Brain Res. 1982;235(1-2):1-12.
19. Zhang W, Ochi M, Takata H, Icuta Y. Influence of distal nerve segment volume on nerve regeneration in silicone tubes. Exp Neurol. 1997;146(2): 600-3.
20. Takahashi Y, Maki Y, Yoshizu T, Tajima T. Both stump area and volume of distal sensory nerve segments influence the regeneration of sensory axons in rats. Scand J Plast Reconstr Surg Hand Surg. 1999;33(2):177-80.
21. Madison RD, Robinson GA, Chadaram SR. The specificity of motor neurone regeneration (preferential reinnervation). Acta physiologica (Oxford, England). 2007;189(2):201-6.
22. Robinson GA, Madison RD. Influence of terminal nerve branch size on motor neuron regeneration accuracy. Exp Neurol. 2009; 215(2):228-35.
23. Moradzadeh A, Borschel GH, Luciano JP, et al. The impact of motor and sensory nerve architecture on nerve regeneration. Exp Neurol. 2008;212(2):370-6.
24. Gravvanis AI, Tsoutsos DA, Tagaris GA, et al. Beneficial effect of nerve growth factor-7S on peripheral nerve regeneration through inside-out vein grafts: an experimental study. Microsurg. 2004; 24(5):408-15.
25. Zhang J, Lineaweaver WC, Oswald T, Chen Z, Chen Z, Zhang F. Ciliary neurotrophic factor for acceleration of peripheral nerve regeneration: an experimental study. J Reconstr Microsurg. 2004;20(4):323-7.
26. Lykissas MG, Batistatou AK, Charalabopoulos KA, Beris AE. The role of neurotrophins in axonal growth, guidance, and regeneration. Curr Neurovas Res. 2007;4(2):143-51.
27. Emel E, Ergun SS, Kotan D, et al. Effects of insulin-like growth factor-I and platelet-rich plasma on sciatic nerve crush injury in a rat model. J Neurosurg. 2011;114(2):522-8.
28. Utley DS, Lewin SL, Cheng ET, Verity AN, Sierra D, Terris DJ. Brain-derived neurotrophic factor and collagen tubulization enhance functional recovery after peripheral nerve transection and repair. Arch Otolaryngol Head Neck Surg. 1996;122(4): 407-13.
29. Scholz T, Rogers JM, Krichevsky A, Dhar S, Evans GR. Inducible nerve growth factor delivery for peripheral nerve regeneration in vivo. Plast Reconstr Surg. 2010;126(6):1874-89.
30. Chiu DT, Smahel J, Chen L, Meyer V. Neurotropism revisited. Neurol Res. 2004;26(4):381-7.
31. Jian Li, Jiang B, Zhang D. Using biological tube for bridging the peripheral nerve defect with a small gap: an experimental study. Chn J Hand Surg. 2003;19:118-20.
32. Pfister LA, Papaloizos M, Merkle HP, Gander B. Nerve conduits and growth factor delivery in peripheral nerve repair. J Peripher Nerv Syst. 2007;12(2):65-82.

33. Zhao FQ, Zhang PX, Jiang BG. Magnifying effect of conduit bridging in number of nerve fibers of broken peripheral nerves: experiment with rats. Zhonghua Yi Xue Za Zhi. 2007 Apr 17;87 (15):1043-7.
34. Jiang B, Zhang P, Zhang D, Fu Z, Yin X, Zhang H. Study on small gap sleeve bridging peripheral nerve injury. Artif Cells Blood Substit Immobil Biotechnol. 2006;34(1):55-74.
35. Zhang Y, Luo H, Zhang Z, et al. A nerve graft constructed with xenogeneic acellular nerve matrix and autologous adipose-derived mesenchymal stem cells. Biomaterials. 2010;31(20): 5312-24.
36. Nakamura T, Inada Y, Fukuda S, et al. Experimental study on the regeneration of peripheral nerve gaps through a polyglycolic acid-collagen (PGA-collagen) tube. Brain Res. 2004;1027(1-2): 18-29.
37. Weber RA, Breidenbach WC, Brown RE, Jabaley ME, Mass DP. A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. Plast Reconstr Surg. 2000;106(5):1036-45.
38. Taras JS, Nanavati V, Steelman P, Nerve conduits. J Hand Ther. 2005; 18(2): 191-7.
39. Lohmeyer JA, Siemers F, Machens HG. The clinical use of artificial nerve conduits for digital nerve repair: a prospective cohort study and literature review. J Reconstr Microsurg. 2009;25(1): 55-61.
40. Meek MF, Coert GH. US Food and Drug Administration/Conformit Europe-approved absorbable nerve conduits for clinical repair of peripheral and cranial nerves. Ann Plast Surg. 2008;60(4): 466-72.
41. Xu H, Yan Y, Li S. PDLLA/chondroitin sulfate/chitosan/NGF conduits for peripheral nerve regeneration. Biomaterials. 2011; 32(20):4506-16.
42. Bozkurt A, Deumens R, Beckmann C, et al. In vitro cell alignment obtained with a Schwann cell enriched microstructured nerve guide with longitudinal guidance channels. Biomaterials. 2009; 30(2):169-79.
43. Williams LR, Powell HC, Lundborg G, Varon S. Competence of nerve tissue as distal insert promoting nerve regeneration in a silicone chamber. Brain res. 1984;293(2):201-11.
44. Whitworth IH, Brown RA, Dore C, Green CJ, Terenghi G. Orientated mats of fibronectin as a conduit material for use in peripheral nerve repair. J Hand Surg (Br). 1995;20(4):429-36.
45. Glasby MA, Gschmeissner SE, Huang CL, De Souza BA. Degenerated muscle graft used for peripheral nerve repair in primates. J Hand Surg (Br). 1986;11:347-51.
46. Fawcett JW, Keynes RJ. Muscle basal lamina: a new graft material for peripheral nerve repair. J Neurosurg. 1986;65(3):354-63.
47. Davis GE, Engvall E, Varon S, Manthorpe M. Human amnion membrane as a substratum for cultured peripheral and central nervous system neurons. Brain Res. 1987;430(1):1-10.
48. Tang JB, Gu YQ, Song YS. Repair of digital nerve defect with autogenous vein graft during flexor tendon surgery in zone 2. J Hand Surg Br. 1993;18(4):449-53.
49. Ashley WW Jr, Weatherly T, Park TS. Collagen nerve guides for surgical repair of brachial plexus birth injury. J Neurosurg (6 Suppl Pediatrics). 2006;(105):452-6.
50. Kiyotani T, Teramachi M, Takimoto Y, Nakamura T, Shimizu Y, Endo K. Nerve regeneration across a 25-mm gap bridged by a polyglycolic acid-collagen tube: a histological and electro-physiological evaluation of regenerated nerve. Brain Res. 1996; 740:66–74.
51. Brown RE, Erdmann D, Lyons SF, Suchy H. The use of cultured Schwann cells in nerve repair in a rabbit hind-limb model. J Reconstr Microsurg. 1996;12(3):149-52.
52. Wei G, Zhu K. Advances of peripheral nerve regeneration using nerve guidance channel. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2001 Dec;18(4):653-7. (Chinese journal of biomedical engineering)
53. Ayhan S, Yavuzer R, Latifoglu O, Atabay K. Use of the turnover epineurial sheath tube for repair of peripheral nerve gaps. J Reconstr Microsurg. 2000;16(5):371-8.
54. Karacaoglu E, Yuksel F, Peker F, Guler MM. Nerve regeneration through an epineurial sheath: Its functional aspect compared with nerve and vein grafts. Microsurg. 2001;21(5):196-201.
55. Yuksel F, Ulkur E, Baloglu H, Celikoz B. Nerve regeneration through a healthy peripheral nerve trunk as a nerve conduit: a preliminary study of a new concept in peripheral nerve surgery. Microsurg. 2002;22(4):138-43.
56. Geuna S, Tos P, Battiston B, Giacobini-Robecchi MG. Bridging peripheral nerve defects with muscle-vein combined guides. Neurol Res. 2004;26(2):139-44.
57. Varejao AS, Cabrita AM, Meek MF, Fornaro M, Geuna S. Nerve regeneration inside fresh skeletal muscle-enriched synthetic tubes: A laser confocal microscope study in the rat sciatic nerve model. Ital J Anat Embryol. 2003;108(2):77-82.
58. Jiang B, Wang S, Feng CH. The comparison of small gap autogenic artery and epineurium anastomosis bridging peripheral nerve. Journal of Beijing Medical University. 1994;26:249-50.
59. Barcelos AS, Rodrigues AC, Silva MDP, Padovani CR. Inside-out vein graft and inside-out artery graft in rat sciatic nerve repair. Microsurg. 2003;23(1):66-71.
60. Hall S. The response to injury in the peripheral nervous system. J Bone Joint Surg Br. 2005;87(10):1309-19.
61. Mirsky R, Jessen KR. Schwann cell development, differentiation and myelination. Curr Opin Neurobiol. 1996;6(1):89-96.
62. Siemionow M, Duggan W, Brzezicki G, et al. Peripheral nerve defect repair with epineural tubes supported with bone marrow stromal cells: a preliminary report. Ann Plast Surg. 2011;67(1): 73-84.
63. Lin YC, Ramadan M, Hronik-Tupaj M et al. Spatially controlled delivery of neurotrophic factors in silk fibroin–based nerve conduits for peripheral nerve repair. Ann Plast Surg. 2011;67(2): 147-55.
64. di Summa PG, Kalbermatten DF, Pralong E, Raffoul W, Kingham PJ, Terenghi G. Long-term in vivo regeneration of peripheral nerves through bioengineered nerve grafts. Neurosci. 2011;181: 278-91.
65. Zhao FQ, Zhang PX, He XJ, et al. Study on the adoption of Schwann cell phenotype by bone marrow stromal cells in vitro and in vivo. Biomed Environ Sci. 2005;18(5):326-33.
66. Zhang P, He X, Zhao F, Zhang D, Fu Z, Jiang B. Bridging small-gap peripheral nerve defects using biodegradable chitin conduits with cultured Schwann and bone marrow stromal cells in rats. J Reconstr Microsurg. 2005;21(8):565-71.
67. Matsuse D, Kitada M, Kohama M, et al. Human umbilical cord-derived mesenchymal stromal cells differentiate into functional Schwann cells that sustain peripheral nerve regeneration. J Neuropathol Exp Neurol. 2010;69(9):973-85.