Injury, Int. J. Care Injured (2005) **36S**, S24—S29

INJURY
INTERNATIONAL JOURNAL OF THE CARE OF THE INJURED

www.elsevier.com/locate/injury

Regeneration and repair of peripheral nerves

Elizabeth O. Johnson [a,*], Aristides B. Zoubos [b], Panayotis N. Soucacos [b]

[a] *Department of Anatomy, Histology & Embryology, University of Ioannina, School of Medicine, 45110 Ioannina, Greece*
[b] *Department of Orthopaedic Surgery, University of Athens, School of Medicine, Athens, Greece*

KEYWORDS
Axon;
Peripheral nerve;
Conduits;
Degeneration;
IGF-I;
Myelin;
Schwann cells;
Nerve repair;
Tissue regeneration;
Growth factors

Summary Posttraumatic nerve repair continues to be a major challenge in restorative medicine and microsurgery. Although progress has been made in surgical techniques over the last 30 years, functional recovery after a severe lesion of a major nerve trunk is often incomplete and often unsatisfactory. Functional recovery after surgical repair of mixed nerves is even more disappointing. Functional recovery after peripheral nerve lesion is dependent upon accurate regeneration of axons to their original target tissues. Thus, in order to enhance regeneration, a better understanding of the cellular and molecular biology of selective nerve regeneration is required. Schwann cells and their endoneurial extracellular matrix play pivotal roles in the selective promotion of motor and sensory axon regeneration. Knowledge of these mechanisms allows for the better development of biocompatible nerve grafting material.

Introduction

Injury to a peripheral nerve is a common injury. Despite over 150 years of experience in modern surgical management of the peripheral nerve, repair of a nerve gap remains a problem in microsurgery. Widely accepted method by most surgeons is bridging the defect with an autologous donor nerve. This is associated with several disadvantages, including an extra incision for removal of a healthy sensory nerve ultimately resulting in a sensory deficit. Finally, donor graft material is limited, particularly for managing extensive lesions (e.g. brachial plexus), which require several lengths of nerve graft. As a result, increasing efforts have been made in the last decade to understand nerve regeneration and find alternatives to the autogenous nerve graft. Studies on nerve conduits for nerve regeneration have focused on the application of various conduit materials in order to avoid sacrifice of a donor nerve (Fig. 1).

Nerve allografts or xenografts are considered a good alternative for nerve conduits, if immunosuppressant is found safe and efficacious. Nerve allotransplantation has already been performed in patients with adequate sensory reinnervation.[24] Neurotrophic factors play an important role in nerve regeneration and as a result, there is great clinical interest in addressing whether they can

* Corresponding author. Tel.: +30 26510 97584; fax: +30 26510 97860.
E-mail addresses: ejohnson@cc.uoi.gr, soukakos@panofonet.gr (E.O. Johnson).

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doi:10.1016/j.injury.2005.10.012

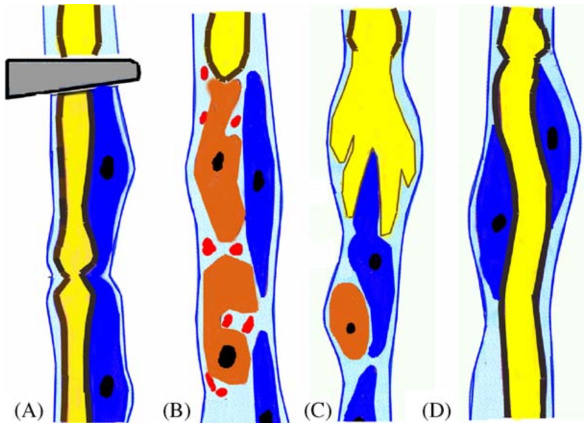

Figure 1 Process of degeneration and regeneration of a peripheral nerve fiber. (A) An intact nerve fiber is cut peripherally. (B) Macrophages that have entered the endoneurial tube from nearby capillaries, engulf myelin pieces which have broken off from the degenerating myelin sheath. (C) Regeneration is noted with an axonal sprout entering into the distal stump. The surface of the Schwann cells guide the growth cone. (D) Myelination of the new regenerated axon begins proximally.

supplement damaged nerve and nerve repairs in order to enhance sensory or motor recovery, or alternatively to avoid excessive tissue inflammation and scarring.

Current issues in peripheral nerve surgery include improvement of regeneration and creation of alternative sources of donor nerves. Several advances have been made in the surgical technique, including introduction of the end-to-side neurorrhaphy and baby-sitter nerve anastomoses.[38] Biotechnological advances include allotransplantation of nerves, growth factors and artificial nerve conduits.[25]

Nervous tissue

Neurons are specialized cells that receive and send signals to other cells through their numerous extensions, axons and dendrites. Most neurons give rise to a single axon and many dendrites. Dendrites receive and transmit incoming synaptic information to the nerve cell body, whereas axons convey impulses from the neuron to its synaptic terminal.

A peripheral nerve contains both dendrites and axons; fibers which conduct information to (afferent) or from (efferent) the CNS, respectively. Efferent fibers, for the most part axons, relay impulses related to motor function from the brain and spinal cord to muscles, glands, etc. in the periphery. On the other hand, afferent fibers, mostly dendrites, usually convey sensory stimuli to the CNS via their nerve cell bodies in the spinal ganglia.

Axons consist of a cylindrical tube of cytoplasm covered by membrane, the axolemma. Neurofilaments and microtubules that run through the axon, comprise the cytoskeleton and provide the framework for fast axonal transport. Although the smallest axons are unmyelinated, most axons in a peripheral nerve are myelinated with the multiple concentric layers of lipid-rich, biochemically modifying plasma membrane produced by Schwann cells. As glycoproteins are prominent components of the Schwann cell plasma membrane, they play important roles in the formation, maintenance and degeneration of the myelin sheath following injury.[28] The functional and anatomical integrity of an axon is maintained by the nerve cell body.

Reaction of neurons to physical trauma: degeneration and regeneration

Following focal lesion of the axon, Wallerian anterograde, involving both the axon, its terminals, and myelin sheath, occurs distal to the lesion. In addition, Schwann cells dedifferentiate and divide, distal to the level of transection and along with macrophages phagocytize remnants of the myelin sheaths which lose their integrity during Wallerian degeneration. These changes cascade distally from the lesion, spreading out across the distal transected segment. Although when using Marchi's stain the proximal part of the fiber often does not show any changes, Cajal described a process of retrograde degeneration of Wallerian type which extended backwards along the fiber as far as the first node of Ranvier proximal to the site of damage. It has now been established that more extensive changes sometimes do occur in the fiber proximal to the injury, such as retrograde atrophy of the nerve cell body that is accompanied by degeneration of all its neurites. Thus, although the degenerative changes in the nerve fibers are termed in this case, as retrograde (as they occur proximal to the lesion), they proceed in a centrifugal direction (from the nerve cell soma towards the lesion).[15,28]

Reaction of neurons to physical trauma has been studied most extensively in motor neurons with peripheral axons, and centrally where their axons form well-defined tracts. When an axon is crushed or severed, changes occur on both sides of the lesion.[27] Distally the axon initially swells and subsequently breaks up into a series of membrane-bound spheres, the process begins near the point of damage and progresses distally. These anterograde changes which also involve the axon terminal