Nerve Regeneration
Understanding Biology and Its Influence on Return of Function After Nerve Transfers

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KEYWORDS

• Peripheral nerve injury • Peripheral nerve regeneration • Skeletal muscle reinnervation
• Motor nerve sprouting • Perisynaptic Schwann cells • Chronic Schwann cell denervation • Axotomy

KEY POINTS

- Schwann cells support regeneration in the peripheral nervous system after nerve injuries, but functional outcomes are frequently disappointing.
- Strategies, including brief electrical stimulation at the time of surgical repair, are effective in significantly improving outcomes of peripheral nerve injury.
- Autologous nerve cross-bridges placed between a donor intact nerve and a recipient denervated nerve stump improve nerve regeneration through chronically denervated Schwann cells.
- Axonal sprouting in partially denervated muscles and skin is effective, but to a limit, in compensating for loss of innervation.
- Motor control may be compromised by a few nerves to partially denervate and partially reinnervate muscles after sprouting and/or nerve transfers.

INTRODUCTION

Poor functional outcomes are frequent after peripheral nerve injuries despite the well-recognized capacity for the Schwann cells (SCs) of the peripheral nervous system to support axon regeneration. The poor outcomes are particularly frequent for injuries that are sustained at short distances from motoneuron cell bodies in the spinal cord and lower brainstem as well as from the sensory nerves whose cell bodies lie in the dorsal root ganglia alongside the spinal cord. This review considers the biology of peripheral nerve injury, nerve regeneration, and axonal sprouting. Nerve regeneration is the growth of lost axons from the stump of the remaining crushed or transected nerve: regenerating axons grow into the denervated nerve stumps where the axons undergo Wallerian degeneration and the remaining SCs in the empty endoneurial sheaths support axon regeneration. Sprouting describes axonal outgrowth under a variety of pathologic conditions. These conditions include: first, the axonal outgrowth from the proximal stump of an injured nerve, and second, the motor and sensory axon sprouts from intact intramuscular nerve sheaths to reinnervate partially denervated muscles and skin, respectively. The review concludes with the consideration of surgical procedures that include nerve transfers to promote functional return in the context of the limits of sprouting and the reduced capacity for smooth gradation of contractile forces by fewer motoneurons.

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PERIPHERAL NERVE INJURY

Neuronal Response to Axotomy

Nerves in the peripheral nervous system are subjected to injuries that damage the nerves to varying degrees.[1–3] Under circumstances where the injury results in disruption of the axonal continuity, as may be the case for crush and transection injuries, the injuries are referred to as axonotmesis and neurotmesis, respectively, using the Seddon classification scheme,[4] and second-degree and fifth-degree injuries, using the Sunderland criteria.[3]

In adults, no motoneurons are lost unless the nerve injuries are sustained close to the cell body,[5–7] but morphologic criteria of cell death indicate a loss of up to 35% of the sensory neurons.[8–10] The injured neurons undergo morphologic changes known as chromatolysis[11,12] (**Fig. 1**A). These changes include the movement of the nucleus from a central to an asymmetric position in the neuronal soma and the disruption of Nissl bodies that comprise the rough endoplasmic reticulum; the morphologic changes reflect the molecular response of the neuron of changed expression of hundreds of genes, including a large number of immediate early genes, transcription factors, and many novel genes.[13–15] These genes are frequently referred to as growth or regeneration associated genes (RAGs), and they include those that transcribe neurotrophic factors and their receptors, such as brain-derived neurotrophic factor (BDNF) and its neurotrophin trkB receptor and glial derived neurotrophic factor (GDNF) and its receptors GFRα1 and ret. They also include the cytoskeletal proteins, tubulin and actin,[16–21] that are transported down the axons and are essential for the extension of the growth cones from the proximal nerve stump.[22] The transcriptional upregulation of the growth-associated proteins of GAP-43, CAP-23, and SCG10 is directly correlated with the regenerative capacity of the injured neurons[23] (see **Fig. 1**A).

RAG expression after nerve injury is transient, the expression declining in neurons without target contact (axotomy), but the genes are upregulated a second time by the refreshment cut axotomy that is frequently performed before nerve repair in humans and in animal models.[24,25] The significance of the second upregulation is that the injured neurons respond to positive signals emanating from the injury site rather than to negative signals resulting from the isolation of the axotomized neurons from target derived neurotrophic

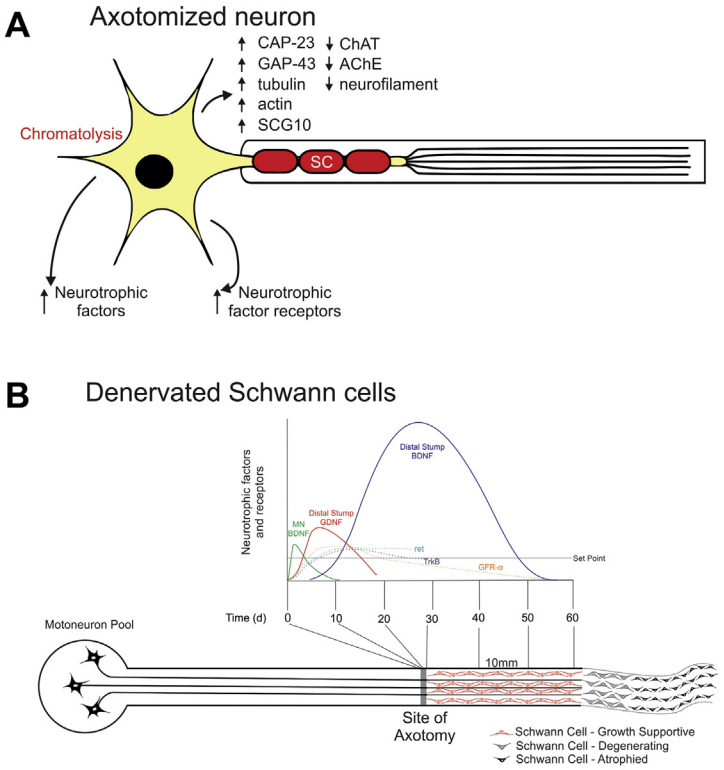

Fig. 1. Schematic illustrations of an axotomized motoneuron and denervated Schwann cells (SCs) after peripheral nerve injury. (*A*) The neuronal cell body that is isolated from its target (axotomy) undergoes morphologic changes known as chromatolysis. These changes reflect altered gene expression in which several RAGs are upregulated, and others, including choline-acetyltransferase (ChAT) and acetylcholine esterase (AChE), are downregulated. (*B*) Denervated SCs in the nerve stump distal to the site of injury (axotomy) lose their myelin, proliferate, and convert to a growth-supportive state. They express several growth factors, including glial and brain-derived neurotrophic factors (GDNF and BDNF, respectively). BDNF is also expressed in motoneurons as are the receptors for both factors, TrkB for BDNF, and GFR-α and ret for GDNF. The transient expression of the growth factors and receptors in both the axotomized neurons and denervated SCs is responsible, at least in part, for the progressive failure of neurons to regenerate after delayed nerve surgery or when injured nerves regenerate over long distances to reach denervated targets. ([*B*] *Adapted from* Furey MJ, Midha R, Xu Q-G, et al. Prolonged target deprivation reduces the capacity of injured motoneurons to regenerate. Neurosurgery 2007;60(4):730; with permission.)