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An assessment of current techniques for inducing axon regeneration and neurological recovery following peripheral nerve trauma

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ABSTRACT

Restoring neurological function to a damaged peripheral nerve separated by a gap requires axon regeneration (1) across the gap, no matter its length, and then (2) through the distal portion of the nerve, regardless of the time between the trauma and repair, and irrespective of animal or patient age. Sensory nerve grafts, the clinical "gold standard", and most alternative techniques for bridging nerve gaps, promote reliable axon regeneration only across nerve gaps <2 cm in length, and with few axons regenerating when nerve repairs are performed >2 months post-trauma or for patients >20 years of age. Three novel nerve repair techniques are discussed that induce axon regeneration and neurological recovery clinically under conditions where other techniques are ineffective: for nerve gaps up to cm long, repairs performed as late as 3.25 years post-trauma, and for patients up to 58 years old. The mechanisms by which these techniques may work are discussed. Although these techniques provide significant improvements in the extents of axon regeneration and neurological recovery, more extensive and reliable clinical recovery of neurological function is needed and will probably require the simultaneous application of multiple techniques.

Contents

Abbreviations: PRP, platelet-rich plasma; PDGF, platelet-derived growth factor; IGF-1, insulin-like growth factor-1; MMPs, matrix metalloproteinases; EGF, epidermal growth factor; FGF, fibroblast growth factor-2; VEGF, vascular endothelial growth factor; cAMP, cyclic adenosine monophosphate; TGF-beta, transforming growth factor-beta; MSCs, mesenchymal stem cells; DRG, dorsal root ganglion; RGC, mice retinal ganglion cell; CSPG, chondroitin sulfate proteoglycan; ECM, extracellular matrix.

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1. Introduction

The restoration of neurological function following a peripheral nerve trauma requires the injured axons to regenerate to their denervated targets on which they must form functional synapses. The axons of an acutely crushed nerve regenerate with high fidelity to their targets in association with the denervated Schwann cells and extracellular matrix of their distal pathway. However, when a nerve injury creates a gap in a nerve, the first step in attempting to restore neurological recovery is to bridge the gap with a material that is both permissive to and promotes axon regeneration entirely across the gap. Unfortunately, current nerve repair techniques promote the reliable regeneration of large numbers of axons only across nerve gaps <2 cm in length, while various obstacles prevent axons from regenerating through their distal pathway when nerve repairs are performed >2 months post-trauma, a delay often required before many clinical nerve repair surgeries can be performed, and when individuals are >20 years of age. Therefore, under typical clinical circumstances of peripheral nerve trauma, axons do not regenerate across the nerve gaps, or if they do, they do not regenerate through the distal portion of the nerve to their targets, and thus, these individuals suffer permanent neurological deficits.

The purpose of this review is to examine the current status of techniques applied to animal models and clinically that are designed to promote axon regeneration and neurological recovery while taking into consideration the three most important variables of peripheral nerve traumas: the length of the nerve gap length, the time between nerve trauma and repair, and animal/patient age. This review begins with a discussion of the basic requirements for promoting axon regeneration, and then discusses the influences of sensory nerve grafts, the current clinical "gold standard" technique for promoting axon regeneration across nerve gaps, and alternative techniques that have been tested, that generally induce axon regeneration only across relatively short nerve gaps. It then examines the questions of why neurological recovery is limited following delayed nerve repairs and for older patients. Finally, the paper discusses several novel clinically tested techniques that induce axon regeneration and neurological recovery under conditions where no other techniques are effective (for nerve gaps up to 16 cm, repairs performed >3 years post nerve trauma, and in patients up to 58 years of age), and the paper concludes with a discussion of the potential mechanisms by which these techniques may exert their influences.

2. Basic mechanisms for promoting axon regeneration

2.1. Substrate-bound and diffusible factors

Both substrate-bound and diffusible factors are critical to promoting the elongation of axons in vivo and in vitro. Some substrate-bound factors that promote growth cone adhesion and elongation include: laminin for embryonic chick dorsal root ganglion (DRG) neurons (Adams et al., 2005), chick spinal neurons (Hammarback et al., 1988), mice retinal ganglion cell (RGC) neurons in vitro (Snow et al., 1991), adult mouse DRG neurons in vitro (Plantman et al., 2008), chondroitin sulfate proteoglycan (CSPG) for rat mossy fibers (Butler et al., 2004), frog DRG neurons (Castro and Kuffler, 2006), brain-derived neurotrophic factor (BDNF) (Mai et al., 2009), and netrin for cultured rat hippocampal neurons (Mai et al., 2009), RGC neurons (de la Torre et al., 1997), and embryonic mouse RGC neurons (Deiner et al., 1997). Some of the diffusible factors that promote and direct axon regeneration, often up concentration gradients of neurotrophic and other factors include: acetylcholine delivered from a pipette onto adult frog DRG neuron growth cones (Kuffler, 1996; Song et al., 1997) and embryonic Xenopus neurons in vitro (Zheng et al., 1994), BDNF onto Xenopus embryonic spinal (Joanne Wang et al., 2008; Song et al., 1997) and rat hippocampal neurons in vitro (Mai et al., 2009), denervated muscle fiber-released factors in frogs in vivo (Kuffler, 1986a, 1987, 1989, 1996; McMahan et al., 1980), and Schwann cell-released neurotrophic factors in frogs in vivo (Kuffler, 1986a,b, 1987, 1989, 1996; McMahan et al., 1980; Zheng and Kuffler, 2000), which are effective over distances of several centimeters (Kuffler, 1986b, 1987, 1989, 1996). Physiologically, substrate-bound and diffusible factors act singly and simultaneously to induce both axon regeneration and branching in vivo in adult frogs (Kuffler, 1986a, b, 1987, 1989, 1996; Marshall et al., 1977; Sanes et al., 1978).

2.2. Platelet rich plasma clots

The physiological method by which axons are supported and promoted to regenerate across short nerve gaps (<3 mm) is by the gap becoming filled with a platelet-rich plasma (PRP) clot (Anitua et al., 2004). However, when nerve gaps >3 mm in length, axons cannot regenerate across the gap to the distal nerve stump because the fibrin flows away and does not have the opportunity to polymerize into a clot between the nerve stumps. Therefore, to restore neurological function when the nerve stumps cannot be