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Review Article

Surgical repair in humans after traumatic nerve injury provides limited functional neural regeneration in adults

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ABSTRACT

Traumatic nerve injuries result in devastating loss of neurologic function with unpredictable functional recovery despite optimal medical management. After traumatic nerve injury and denervation, regenerating axons must traverse a complex environment in which they encounter numerous barriers on the way to reinnervation of their target muscle. Outcomes of surgical intervention alone have unfortunately reached a plateau, resulting in often unsatisfactory functional recovery. Over the past few decades, many improvements were developed to supplement and boost the results of surgical repair. Biological optimization of Schwann cells, macrophages, and degradation enzymes have been studied due to the key roles of these components in axonal development, maintenance and response to injury. Moreover, surgical techniques such as nerve grafting, conduits, and growth factor supplementation are also employed to enhance the microenvironment and nerve regeneration. Yet, most of the roadblocks to recovery after nerve injury remain unsolved. These roadblocks include, but are not limited to: slow regeneration rates and specificity of target innervation, the presence of a segmental nerve defect, and degeneration of the target end-organ after prolonged periods of denervation. A recognition of these limitations is necessary so as to develop new strategies to improve functional regeneration for these life changing injuries.

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1. Introduction

Traumatic nerve injuries are severe injuries that occur in up to 2.8% of all polytrauma patients (Noble et al., 1998). These injuries have life-altering impact on patients, causing them to suffer months, or even years, of uncertainty while waiting for an often unpredictable, marginal level of recovery (Grinsell and Keating, 2014; Kang et al., 2011). Patients may be left with devastating and disabling sensory and motor deficits such as numbness of a limb, cold intolerance, dysesthesias, paralysis, and neuropathic pain. The management of traumatic nerve injuries is influenced by multiple factors including the location of the injury, the type of injury, the size of segmental nerve deficit, the timing of injury presentation, and accompanying soft tissue injury. Despite the permissive growth environment of the peripheral nervous system (PNS),

Abbreviations: MJ, neuromuscular junctions; AChRs, acetylcholine receptors; PNS, peripheral nervous system; SC, Schwann cells; ECM, extracellular matrix.

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major nerve injuries in humans have very limited potential for spontaneous recovery. On a molecular level, both physiological and histopathological changes to the nerve and its surrounding soft tissue occur, including demyelination, degeneration, remyelination and regeneration. Despite a significant amount of research addressing the molecular biology of nerve injury, and numerous surgical advances in peripheral nerve repair, these improvements have achieved only partial recovery of the affected limb, with plateauing of functional outcomes. In a recent meta-analysis of 2997 digital nerve repairs, good outcomes were seen with respect to sensory recovery in just 42% of repairs, with excellent outcomes seen in only 25% of repairs (Paprottka et al., 2013). The regenerating nerve encounters numerous unsolved obstacles that need to be overcome to allow for efficient and effective neural regeneration. Many unexplored barriers to regrowth remain unaddressed by current practice; these include the rate of regeneration, specificity of regeneration, segmental nerve defects and degeneration of the target-end organ.

2. Microanatomy

Peripheral nerves are heterogeneous composite structures that are comprised of neurons, Schwann cells, fibroblasts and macrophages, and are heavily dependent on a complex blood supply. The neuron itself is a polarized cell that forms the foundation of the nerve. It consists of dendrites, the cell body, and a single axon. The axon originates from a unique region of the cell body called the axon hillock, which is also responsible for initial generation of the action potential. Axons project towards their sites of innervation, where they form synapses with target end-organs. Schwann cells produce myelin to encapsulate the axon and aid in action potential transmission. If the axonal diameter is greater than or equal to 1 μm, each Schwann cell will wrap its plasma membrane around a single region of an axon, thereby forming myelin. Myelin acts as an insulator, allowing fast and efficient conduction and propagation of an action potential down an axon. The blood supply to the nerve is a complex vascular plexus formed from anastomoses of epineural, perineural and endoneurial plexis (Yegiyants et al., 2010) as well as a segmental blood supply derived from a number of nutrient arteries. The blood supply to the nerve is quite fragile, and may be disrupted due to trauma or to tension during nerve repair. In addition, peripheral nerves have connective tissue layers that provide strength and protection to the nerve: namely, the epineurium, perineurium, and endoneurium. It is crucial to recognize that all surgical interventions are strictly directed at these connective tissue layers, leaving the axon and Schwann cells to respond to injury and regenerate via their inherent biology.

3. Nerve response to injury

In contrast to chronic nerve injuries which are Schwann cell driven, acute nerve injuries are axonally mediated. In the initial stages of injury, Wallerian degeneration begins with granular disintegration of the axonal cytoskeleton. Within 48 h of injury, Schwann cells (SC) break down myelin and phagocytose axonal debris from the distal stump. Macrophages are then recruited to the area, which release growth factors that in turn encourage SC and fibroblast proliferation. SCs begin the reparative process by forming longitudinal bands of Bungner, which are essentially growth-promoting conduits for regenerating axons. Injection of pre-differentiated SCs near injured nerves has been shown to aid remyelination in regenerating axons and reduce the amount of myelin debris, thereby improving functional recovery in rodents (Khuong et al., 2014). At the tip of the regenerating axon is the growth cone, which is composed of cellular matrix from which fingerlike projections called filopodia extrude to explore the microenvironment. Proteases, under the influence of various factors, are released from the growth cone to clear a path towards a target organ. Simultaneously, SCs upregulate neurotrophic factors including nerve growth factor (NGF) and brain-derived growth factor (BDNF), as well as their corresponding receptors in the distal stumps (Flores et al., 2000; Stoll and Müller, 1999). This increase in expression of NGF and its low density receptors is believed to promote extensive proliferation and migration of SCs (Anton et al., 1994) and mainly affects properties of sensory neurons. BDNF levels are also increased and are postulated to act as an anterograde trophic messenger under the influence of NGF. Interestingly, the neurotrophic factor ciliary neurotrophic factor (CNTF) which is believed to affect survival and regeneration of motor neurons, is found to be reduced significantly in the SCs of the distal stump, with the reduction in CNTF levels extending to the neuromuscular junction (Hiruma et al., 1997). Furthermore, there is increased retrograde axonal transport of CNTF after nerve injury (Curtis et al., 1993). Neurite-promoting factors such as laminin and fibronectin, and matrix-forming precursors such as fibrinogen, are all synthesized in response to nerve injury (Yegiyants et al., 2010).

In addition to this complex milieu of pro- and anti-neurotrophic factors, microtubulin is another molecule that plays a crucial role with respect to axonal integrity and regeneration. Following traumatic nerve injury, calcium-dependent activation of the histone deacetylases HDAC5 and HDAC6, in particular, leads to tubulin degeneration that likely serves to inhibit axonal regeneration (Cho and Cavalli, 2012; Rivieccio et al., 2009). Interaction between axons and SCs has also emerged as an important regulator of peripheral nervous system development and regeneration. Fleming et al. identified that the receptor tyrosine kinase *Ret* genetically interacts with *Er81* to control *Nrg1-Ig* in promoting the formation of Pacinian corpuscles (Fleming et al., 2016). Taken together, these factors have the potential to promote regeneration and to provide signaling for cell survival, neuronal differentiation and proliferation, as well as to influence synaptic function (Rummler and Gupta, 2004).

Neurons in the peripheral nervous system also upregulate a number of regeneration-associated genes (RAGs) that may have direct role in neurite outgrowth following peripheral nerve injury. For example, the overexpression of transcription factor ATF-3 has been shown to promote neurite outgrowth after peripheral nerve injury (Seijffers et al., 2006). In their animal study, Bomze et al. concluded that growth-associated protein 43 (GAP-43) and cytoskeleton-associated protein 23 (CAP 23) were expressed after nerve injury, and together, were able to induce a dramatic increase in the number of regenerated axons (Bomze et al., 2001). Pathways associated with optimization of regeneration after nerve injury have also been identified. The ERK pathway was shown to mediate axonal elongation, with the kinases ERK and Akt promoting regeneration after axonal injury (Chierzi et al., 2005). Additionally, the cytokine interleukin-6 has been shown to work through the JAK-STAT3 pathway to overcome some of the inhibitory molecules that inhibit axonal regeneration (Cao et al., 2006). In addition to pathways that are involved in axonal regeneration, there are also pathways that have been associated with inhibition of axonal regeneration. The small GTPase Rho signaling pathway, for instance, has a role in cytoskeletal reorganization and cell motility. Studies have shown that activation of Rho results to collapse of growth cones, and inhibiting Rho pathway allows for contractility and promotes neurite outgrowth (Jalink et al., 1994; Wahl et al., 2000).

4. Surgical repair

The current mainstay of treatment for traumatic peripheral nerve injury involves surgical intervention. The primary goal of nerve repair is to correctly align and approximate severed nerve segments to allow reinnervation of the target organs with hopes of achieving functional recovery. Historically, it was thought best to wait 3 weeks for the completion of the Wallerian degeneration process before nerve repair. However, studies by Fu and Gordon (1995) and Mackinnon (1989) suggested that immediate repair produced better outcomes. Major prerequisites to nerve repair include a clean wound, viable blood supply, no crush component to the injured nerve, adequate soft tissue coverage, skeletal stability, and minimal tension on the nerve repair.