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Specificity of peripheral nerve regeneration: Interactions at the axon level

Ilary Allodi, Esther Udina, Xavier Navarro *

Group of Neuroplasticity and Regeneration, Institute of Neurosciences and Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Barcelona, Spain

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ABSTRACT

Peripheral nerves injuries result in paralysis, anesthesia and lack of autonomic control of the affected body areas. After injury, axons distal to the lesion are disconnected from the neuronal body and degenerate, leading to denervation of the peripheral organs. Wallerian degeneration creates a microenvironment distal to the injury site that supports axonal regrowth, while the neuron body changes in phenotype to promote axonal regeneration. The significance of axonal regeneration is to replace the degenerated distal nerve segment, and achieve reinnervation of target organs and restitution of their functions. However, axonal regeneration does not always allows for adequate functional recovery, so that after a peripheral nerve injury, patients do not recover normal motor control and fine sensibility. The lack of specificity of nerve regeneration, in terms of motor and sensory axons regrowth, pathfinding and target reinnervation, is one the main shortcomings for recovery. Key factors for successful axonal regeneration include the intrinsic changes that neurons suffer to switch their transmitter state to a pro-regenerative state and the environment that the axons find distal to the lesion site. The molecular mechanisms implicated in axonal regeneration and pathfinding after injury are complex, and take into account the cross-talk between axons and glial cells, neurotrophic factors, extracellular matrix molecules and their receptors. The aim of this review is to look at those interactions, trying to understand if some of these molecular factors are specific for motor and sensory neuron growth, and provide the basic knowledge for potential strategies to enhance and guide axonal regeneration and reinnervation of adequate target organs.

Contents

Abbreviations: AKT/PKB, protein kinase B; BDNF, brain derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CAMs, cell adhesion molecules; Cdc42, cell division control protein 42 homolog; cGMP, cyclic guanosine monophosphate; ChAT, choline acetyltransferase; CGRP, calcitonin gene-related peptide; CNTF, ciliary neurotrophic factor; CSPG, chondroitin sulfate proteoglycan; DRG, dorsal root ganglia; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GAP, growth associated protein; GDNF, glial cell-derived neurotrophic factor; GFR, glial cell derived neurotrophic factor family receptor; GGF, glial growth factor; GSK3β, glycogen synthase kinase 3 beta; HGF/SF, hepatocyte growth factor/scatter factor; HNK1, human natural killer 1; HSPG, heparan sulfate protoglycan; IB4, isolectin B4; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; JNK, c-Jun N-terminal kinase; LIF, leukemia inhibitory factor; mTOR, mammalian target of rapamycin; MAP, microtubule-associated protein; MAPK, Mitogen-activated protein (MAP) kinase; NCAM, neuronal cell adhesion molecule; NGF, nerve growth factor; NRG1, neuregulin 1; NT-3, neurotrophin 3; OPN, osteopontin; P38, mitogen-activated protein kinase 38; P75, low-affinity nerve growth factor receptor/P75 neurotrophin receptor; PKA, protein kinase A; PMR, preferential motor reinnervation; PNS, peripheral nervous system; PTEN, phosphatase and tensin homolog; PTN, pleiotrophin; RET, proto-oncogene-receptor tyrosine kinase; Rho, ras homolog gene family; Sema 3A, semaphoring 3A; SP, substance P; STAT3, signal transducer and activator of transcription 3; TGFα-1, transforming growth factor alpha 1; Thy-1/CD90, cluster of differentiation 90; TrK, receptor tyrosine kinase; TSC, tuberous sclerosis protein; VEGF, vascular endothelial growth factor.

* Corresponding author at: Facultat de Medicina, Universitat Autònoma de Barcelona, E-08193 Bellaterra, Spain. Tel.: +34 935811966; fax: +34 935812986.
E-mail address: xavier.navarro@uab.cat (X. Navarro).

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1. Introduction

Injuries to the peripheral nerves result in loss of motor, sensory and autonomic functions conveyed by the involved nerves. After a nerve injury, transected fibers distal to the lesion are disconnected from the neuronal body and undergo Wallerian degeneration, thus, leaving the peripheral organs denervated. In parallel, a series of molecular and cellular changes known as retrograde reaction and chromatolysis occur at the soma of axotomized neurons. Wallerian degeneration serves to create a microenvironment distal to the injury site that favors axonal regrowth, while retrograde reaction leads to metabolic changes necessary for regeneration and axonal elongation. The functional significance of axonal regeneration is to replace the distal nerve segment lost during degeneration, allowing reinnervation of target organs and restitution of their corresponding functions. Through this sequence of events, injured axons of the peripheral nervous system are able to regenerate and reinnervate their target organs.

After axonotmesis, where the connective sheaths of the nerve are preserved and only the axons are injured, functional recovery is usually good. In contrast, after neurotmesis (nerve transection), when the endoneurial tubes loss their continuity, axons are often misdirected and reinnervate incorrect target organs even if refined repair is applied (Bodine-Fowler et al., 1997; Molander and Aldskogius, 1992; Valero-Cabre and Navarro, 2002). Thus, although the amount of axonal regeneration can be considerably high, the lack of selectivity of axon-target reconnection leads to a poor functional recovery. Indeed, only a low percentage of adult patients regain normal function after complete transection and surgical repair of a major peripheral nerve. Appropriate and inappropriate targets can be reinnervated by axotomized neurons. For example, efferent motor axons may be misdirected to sensory end organs, and cutaneous afferents to motor endplates or sensory end organs of inappropriate modality or location. Thus, function will be degraded or permanently lost, depending on the severity of mismatch. As surgical nerve repair techniques cannot be further refined, there is a need for new and improved strategies to enhance specific axon regeneration following nerve injuries (Lundborg, 2003). Tissue specificity, i.e. preferential growth of axons towards a distal nerve stump rather than to other tissues, has been documented (Politis et al., 1982). Fascicular specificity, the preferential regeneration through the original nerve fascicle, was suggested in early studies but not confirmed by further investigations. Target organ specificity, or adequate reinnervation of each type of end organ (muscle, sensory receptor, ...) by axons that originally served that organ, is less than perfect, although preferential reinnervation has been observed (Fig. 1). However, the mechanisms through which motor and sensory axons specifically reinnervate their corresponding targets are still poorly understood. Some authors defend a preferential muscle reinnervation by motor axons, the so-called preferential motor reinnervation (Brushart, 1988, 1993; Brushart et al., 1998). Pruning of the axons that reinnervated an erroneous target may contribute to improve the specificity of regeneration (Madison et al., 1996). Expression of the peptide L2/HNK1 (Martini et al., 1992) in motor but not sensory Schwann cells, or the presence of NCAM and polysialic acid in the regenerative motor axons (Franz et al., 2005) can also mediate this preferential motor reinnervation, although other authors argue that the key point for preferential attraction of axons to their targets is the expression of trophic factors by the own target organ and the distal stump (Madison et al., 2007).

Since the mechanisms that control axon regeneration are diverse and complex, it is important to take all of them into account before designing new strategies that may improve specific reinnervation. After the lesion, the injured neurons suffer important changes to switch their neuro-transmitter state to a pro-regenerative state (Plunet et al., 2002). The environment that the axons find distal to the lesion site is also a determinant for successful regeneration. Neurotrophic factors secreted by Schwann cells or target organs modulate axonal attraction, and the creation of a favorable pathway in the distal nerve stump allows the growing axons to adhere and elongate. The cross-talk between axons and their immediate environment is thus essential in determining the intrinsic capacities for regeneration and reinnervation. Therefore, it is important to deeper understand the molecular interactions between neurotrophic factors, their receptors, adhesion molecules and extracellular matrix elements in the regenerative process. These clues are involved in cell chemotaxis, migration and axonal elongation, and their signaling pathways can promote cell survival or apoptosis. The focus of this work is to review those interactions, trying to understand whether any factors can be specific for motor and sensory axons, and how can they help to induce specific reinnervation of target organs.

2. Neuronal changes triggered by axonal injury

Neurons have an intrinsic growth capacity during the embryonic stage, which is repressed upon the adult transition to allow proper synaptic development. However, after axotomy, neurons switch again from a transmission state to a growth state, with changes in the expression of genes that encode for transcription factors (Herdegen et al., 1991; Leah et al., 1991; Schwaiger et al., 2000), which in turn regulate the expression of genes involved in cell survival and neurite outgrowth (for reviews see Navarro et al., 2007; Raivich and Makwana, 2007). This switch is essential in the capacity of neurons to regenerate; therefore the