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Sensory Nerve Regeneration at the CNS-PNS Interface

Xiaoqing Tang, Andrew Skuba, Seung-Baek Han, Hyukmin Kim, Toby Ferguson and Young-Jin Son
Shriners Hospitals Pediatric Research Center and Center for Neural Repair and Rehabilitation, Temple University School of Medicine, Philadelphia USA

1. Introduction

Over a century ago, Ramon y Cajal, using the Golgi staining technique to label a subset of dorsal root ganglion (DRG) axons, showed that injured DR axons regenerate within the root but fail to re-enter the adult spinal cord. As shown in his drawing (Fig. 1), DR axons grow away from (arrow), or stop at (arrowheads), the junction between the CNS and PNS, termed the dorsal root entry zone (DREZ). Regeneration of dorsal root (DR) axons into spinal cord is prevented at the dorsal root entry zone (DREZ), the transitional zone between the CNS and PNS. Why regeneration fails at DREZ has remained an interesting issue both because dorsal root injuries are common and because DREZ serves as an excellent model system for studying the reasons for the failure of CNS regeneration.

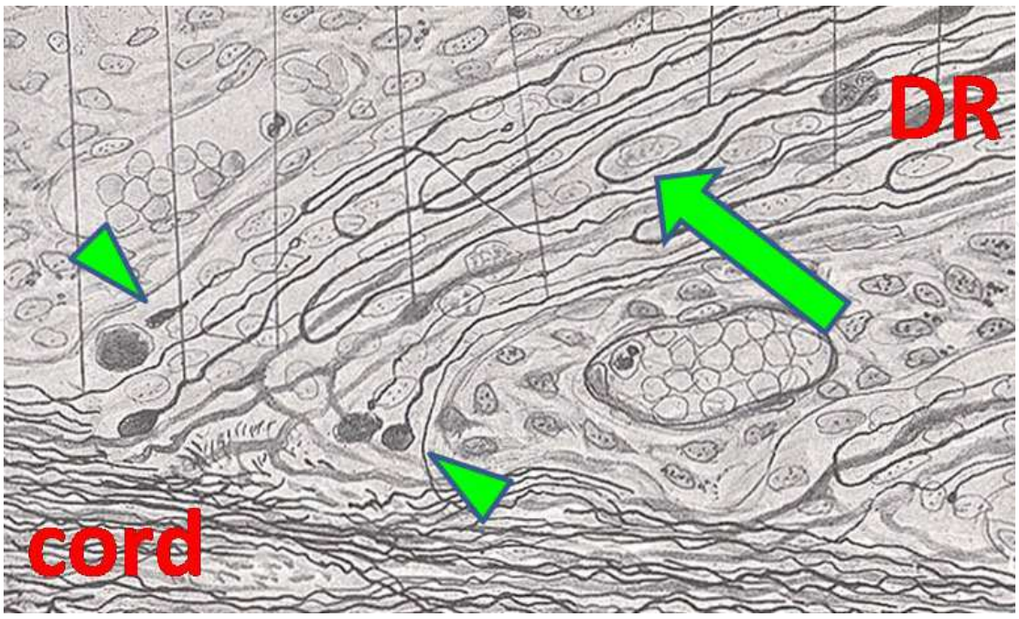

Fig. 1. Cajal's drawing illustrating DR axons growing away from (arrow) or arrested (arrowheads) at the entrance into adult spinal cord.

Spinal root injuries, e.g., brachial plexus, lumbosacral plexus and cauda equina injuries, have profound effects on the spinal cord and evoke chronic, often agonizing, pain and permanent sensory loss. Brachial plexus injury (BPI), the most common form of dorsal root injury, generally results from high-energy traction injuries in which the head and neck are forced away from the shoulder. Obstetrical BPI is a complication in 3/1000 births; in adults, BPI occurs most commonly in high-velocity motor vehicle accidents, particularly involving motorcycles, and in contact sports and falls. Overall, BPI is 10-20 times more common than spinal cord injury (SCI) (Ramer, McMahon, and Priestley 2001; Malessy and Pondaag 2009), and, similar to SCI, produces devastating consequences that include severe, often intractable, pain, and persistent loss of sensation and motor function. There is an urgent need for effective therapies that can reduce the extent of the initial injury acutely or, at a later stage, enhance repair. The need for effective treatment of BPI is increasing due to higher survival rates following severe traumatic injuries and the increasing number of elderly individuals susceptible to BPI because of falls.

2. Dorsal Root Entry Zone (DREZ)

The cell bodies of dorsal root ganglion (DRG) neurons, which relay sensory information into the spinal cord, are located in peripheral ganglia. These cells emit one process that bifurcates into both a peripheral axon branch and a central axon branch that projects into the spinal cord within the dorsal root. DRG neurons mount a robust regenerative response to injury of their peripheral processes, but react much less vigorously to injury of their central processes. Several features make the dorsal root/DREZ system attractive for regeneration studies. First, PNS Schwann cells, which promote regeneration, are immediately juxtaposed to CNS astrocytes, which impede regeneration (Fig. 2).

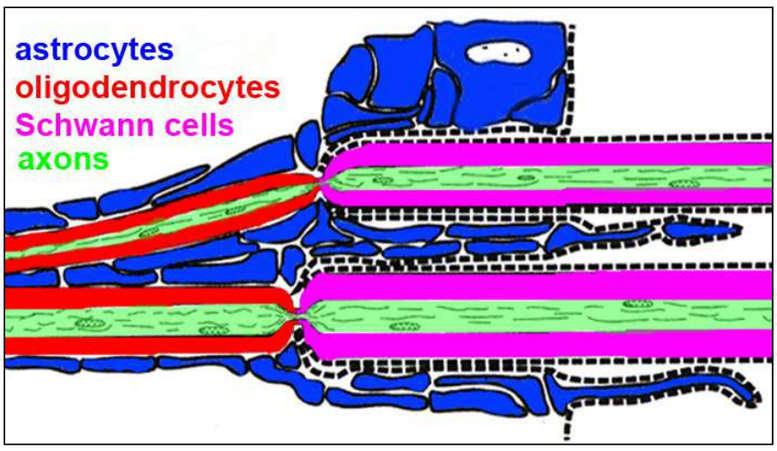

Fig. 2. Glial organization at dorsal root entry zone (DREZ), the interface between CNS and PNS where astrocytes, oligodendrocytes and Schwann cells are juxtaposed in association with DR axons. Central to the interface, myelin sheaths are formed by oligodendrocytes (Red) and the supporting tissue is astrocytic (Blue). Peripheral to it, sheaths are formed by Schwann cells (Pink) enveloped in endoneurial tubes. Adopted and modified from (Fraher 1999).

Because DRG axons must pass through the transitional DREZ to enter the spinal cord, regeneration can be directly contrasted in permissive and non-permissive environments.

Second, the reactions of glial cells at the DREZ closely resemble those within the spinal cord, allowing a major barrier to intraspinal regeneration to be studied without direct injury to spinal cord parenchyma. Lastly, DRG neurons are unique because the regeneration potential of their central processes can be enhanced by a prior injury to their peripheral processes ("conditioning lesion effect"). The model has therefore been extensively used to provide valuable insights into successful and failed CNS regeneration (Ramer, McMahon, and Priestley 2001; Tessler 2004).

3. DREZ after dorsal root injury

Dorsal root (DR) injury (i.e., rhizotomy) in adult mammals evokes complex molecular and cellular changes. On the PNS side, macrophages invade the DR and rapidly phagocytose myelin and degenerating axons (Avellino et al. 1995), while Schwann cells dedifferentiate and occupy axon-free endoneurial tubes, generating a growth-promoting environment. By contrast, on the CNS side, and especially at the DREZ, astrocytes rapidly undergo reactive changes, which include proliferation, hypertrophy and extension of their processes further distally into the DR (i.e., astrogliosis) (Bignami, Chi, and Dahl 1984; Fraher et al. 2002). Microglia/macrophages invade DREZ much more slowly than the PNS (Liu et al. 1998), resulting in markedly delayed elimination of central myelin and axon debris, which likely contributes to the regeneration failure (Ramer et al. 2001).

The extent to which the astrocytic reaction at the DREZ resembles the response to direct CNS lesions remains unclear. Nonetheless, DR axons do contact astrocytes when they have stopped regenerating (Carlstedt 1985; Dockery et al. 2002; Fraher 2000) and reactive astrocytes are thought to form the primary regenerative barrier at the DREZ. In support of this notion, axons grow through the DREZ that has been depleted of astrocytes by X-irradiation (Sims and Gilmore 1994), and, although permissive under some conditions (Golding et al. 1999; Carlstedt, Dalsgaard, and Molander 1987), reactive astrocytes generally inhibit neurite outgrowth (Fawcett and Asher 1999; Silver and Miller 2004). How astrocytes prevent regeneration at the DREZ is uncertain and the molecular basis for astrocytic inhibition is incompletely understood (see below).

Myelin-associated molecules, including Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein, are thought to account for the contribution of oligodendrocytes to regeneration failure at the DREZ (Ramer et al. 2001). If so, their actions seem to be exerted only transiently and during the initial phase of inhibition, because myelin-associated molecules are eventually, although slowly, cleared, while axons that have failed to regenerate remain associated with astrocytes long after injury (Carlstedt 1985; Chong et al. 1999; Fraher et al. 2002). Macrophages are unlikely to directly impede growth at DREZ, because axons grow well in peripheral nerves where macrophages are abundant (Bruck 1997). These considerations highlight our current lack of understanding of the molecular and cellular mechanisms that account for regeneration failure at the DREZ.

Here, we focus our review on intrinsic factors that have been suggested to play a role in preventing axons from regenerating into the DREZ. We then briefly discuss extrinsic factors and treatments reported to promote regeneration at this site. Lastly, we discuss the first *in vivo* imaging study of regenerating dorsal root axons, which was carried out in our laboratory and provides a novel explanation for axon growth cessation at the DREZ.

4. Intrinsic factors preventing regeneration

4.1 Tenascins

Tenascins are a family of extracellular matrix glycoproteins which displays highly dynamic patterns of expression during development and after nervous system injury (Jones and Jones 2000). Members of the tenascin family have been implicated in axon growth and pathfinding during central nervous system development and regeneration. Several reports, however, suggest a role for tenascins as inhibitory molecules preventing axons regenerating into the DREZ. For example, tenascin-C and tenascin-R have been observed within the CNS territory of the DREZ (Golding et al. 1999; Pesheva and Probstmeier 2000). In addition, tenascin-Y, the avian homologue of mammalian tenascin-X, caused rapid collapse of sensory growth cones cultured on fibronectin, and was avoided by growing sensory neurites in microstripe assays (Tucker et al. 2001). It is noteworthy, however, that tenascin-C was highly upregulated along injured dorsal roots, where sensory axons regenerate well, whereas it was only weakly expressed at the DREZ (Zhang et al. 2001). This observation indicates that tenascin-C is unlikely to be the determining factor for regeneration failure at the DREZ.

4.2 Semaphorin3A

Semaphorin3A is a repulsive guidance molecule important for axon pathfinding and targeting during development (Kolodkin et al. 1997; Kolodkin, Matthes, and Goodman 1993; Behar et al. 1996; He and Tessier-Lavigne 1997), and has been implicated as a potential barrier molecule at the DREZ. Semaphorin3A and its receptors, neuropilin-1 and plexin-A1, continue to be expressed in adults (Tanelian et al. 1997; Giger et al. 1998). Injury to the dorsal columns of the spinal cord induced strong expression of semaphorin3A mRNA in fibroblasts associated with the glial scar, and semaphorin3A receptors were present on injured dorsal column axons; dorsal column axons fail to penetrate the semaphorin3A-expressing scar tissue (Pasterkamp, Anderson, and Verhaagen 2001). Increased sensory axon growth was also observed in semaphorin3A knockout mice (Taniguchi et al. 1997). On the other hand, semaphorin3A was absent or greatly downregulated in response to dorsal root injury (Pasterkamp, Anderson, and Verhaagen 2001; Pasterkamp et al. 1999; Pasterkamp, Giger, and Verhaagen 1998). More studies are required to determine the role of Semaphorin3A at the DREZ.

4.3 CSPGs

Several CSPGs in the extracellular matrix are thought to be involved in instructively collapsing or repelling neurite outgrowth (Grimpe et al. 2005; Busch and Silver 2007). CSPGs are also the most prominent growth inhibitory molecules associated with the glial scar, which plays a major role in the regenerative failure after CNS injury (Davies et al. 1999; Rolls, Shechter, and Schwartz 2009). Members of the CSPG family of extracellular matrix (ECM) molecules include neuroglycan 2 (NG2), aggrecan, brevican, neurocan, vesican and phosphacan (Fawcett and Asher 1999). These molecules are expressed by astrocytes and found at the DREZ both during development and after dorsal root injury (Pindzola, Doller, and Silver 1993). The inhibitory properties of CSPGs are primarily due to glycosaminoglycan (GAG) side chains; enzymatic removal of GAG chains by chondroitinase

ABC (ChABC) promotes intraspinal axon regeneration (Bradbury et al. 2002; Grimpe et al. 2005). The differential expression and contribution of individual members of the CSPG family have also been studied. NG2, the most important component, was found to be a major inhibitory proteoglycan for sensory axons (Fidler et al. 1999). NG2 is expressed by oligodendrocyte progenitor cells, which react rapidly following CNS injury, and by some reactive astrocytes. Virus-mediated knockdown or antibody blocking of NG2 has been shown to promote intraspinal sensory axon regeneration (Donnelly et al. 2010). Recently, a transmembrane protein tyrosine phosphatase, PTPσ, was identified as a high affinity receptor of CSPG that mediates its inhibitory effect (Shen et al. 2009). Disruption of the PTPσ gene reduced inhibition by CSPG.

Notably, however, the same CSPG molecules are expressed equally or even more abundantly along the injured dorsal root as at the DREZ or within the spinal cord (Zhang et al. 2001) and degradation of CSPGs by chondroitinase ABC or Pi-PLC, which enhances regeneration after CNS injuries (McKeon, Hoke, and Silver 1995), does not promote regeneration across DREZ (Steinmetz et al. 2005; but see Cafferty et al., 2007).

4.4 Myelin-associated inhibitors

Another group of inhibitory molecules of axon regeneration in the CNS is associated with myelin and includes myelin-associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMgp), and Nogo (Mukhopadhyay et al. 1994; McKerracher et al. 1994; Kottis et al. 2002; Wang et al. 2002; GrandPre et al. 2000). These molecules are synthesized by oligodendrocytes and distributed in the myelin that ensheathes CNS axons. Their inhibitory role has been demonstrated in tissue culture and *in vivo*. All three myelin inhibitors bind to the glycosylphosphatidylinositol-anchored Nogo-66 receptor (NgR1), which is expressed by many CNS neurons (Hunt, Coffin, and Anderson 2002; Hunt et al. 2002). Treatment with an NgR1 antagonist enhanced neurite outgrowth from DRG neurons in a co-culture model (Hou et al. 2006) but other receptors have also been implicated in the inhibitory effect, including NgR2 and the paired immunoglobulin-like receptor B (PirB) (Venkatesh et al. 2005; Atwal et al. 2008). Blocking both PirB and NgR receptors led to near-complete reversal of myelin inhibition. Harvey et al. reported that a soluble peptide fragment of the NgR (sNgR) which binds and blocks all three inhibitor ligands, elicited extensive ingrowth of myelinated, but not unmyelinated, sensory axons after dorsal root crush (Harvey et al. 2009). Microelectrode recordings from peripheral nerve confirmed that ingrowth was accompanied by gradual restoration of synaptic activities, and paw preference, paw withdrawal and grasping improved in the denervated forelimb.

4.5 Synaptogenic activity

The available evidence suggests that growth inhibitory molecules associated either with astrocytes or oligodendrocytes could account for the turning but not the arrest of DR axons at the DREZ. For example, repellent cues, including CSPGs, Nogo, MAG and OMgp, cause brief growth cone or filopodial collapse and allow axons to turn and grow away without a significant pause or long-term immobilization (Snow et al. 1990; Li et al. 1996; Raper and Kapfhammer 1990; Drescher et al. 1995). Moreover, DRG axons grow despite growth cone collapse (Marsh and Letourneau 1984; Jones, Selzer, and Gallo 2006; Jin et al. 2009) and

axons entering the DREZ *in vivo* are accompanied by Schwann cells, which would provide an alternative growth pathway by causing axons to turn around, rather than to stop. These considerations led us to suspect that a novel mechanism plays a more decisive role in preventing regeneration across the DREZ.

Previous studies based on static analyses have provided evidence that is often conflicting or inconclusive. The combination of *in vivo* imaging and fluorescent mouse transgenic technology now allows dynamic processes such as axon regeneration to be studied directly in living spinal cords, providing an unprecedented opportunity to resolve issues that conventional static analyses cannot decipher (Lichtman and Sanes 2003; Bishop et al. 2004; Balice-Gordon and Lichtman 1990; Trachtenberg et al. 2002; Pan and Gan 2008; Grutzendler and Gan 2006; Kerschensteiner et al. 2005; Misgeld, Nikic, and Kerschensteiner 2007). Over the last few years, our laboratory has pioneered in applying *in vivo* imaging to monitor regeneration of DR axons using wide-field microscopy and a line of thy1-YFP mice. Unexpectedly, we observed that > 95% YFP+ axons are immobilized or stabilized surprisingly quickly as they enter the DREZ, even after conditioning lesions that enhanced intrinsic growth potential. Moreover, we have obtained novel evidence that these axons form presynaptic terminals on non-neuronal cells that do not appear to be either astrocytes or oligodendrocytes (Fig. 3; Di Maio et al. 2011).

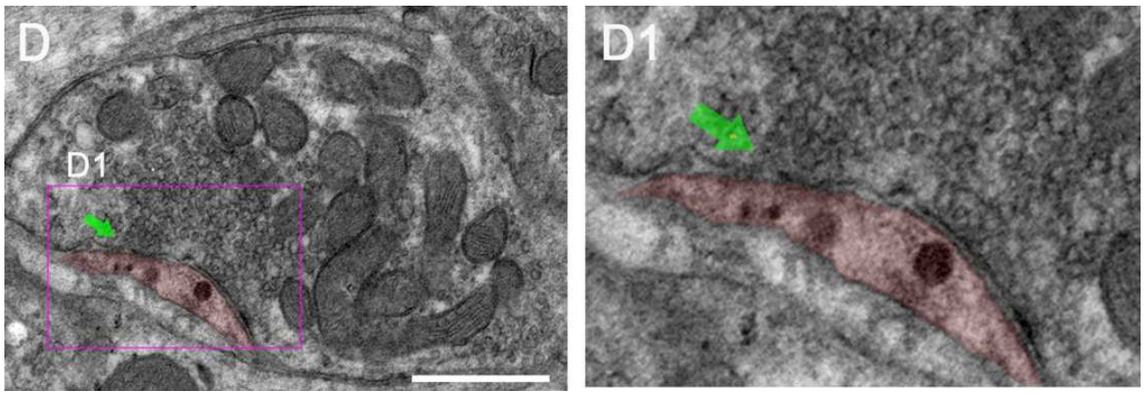

Fig. 3. An electron micrograph of the DREZ 13 days after crush injury showing a presynaptic axonal profile Vesicles are highly clustered and docked at an electron-dense membrane that resembles an active zone (green arrow). D1, an enlarged area of synaptic contact in D. No postsynaptic densities are present on the non-neuronal, postsynaptic cell process. Scale bar, 250nm

The unexpectedly rapid and persistent immobilization of axons entering the DREZ prompted us to determine whether they formed stable structures such as synapses when they arrived. We have found that almost all YFP+ axon tips are intensely immunolabeled with synapse markers such as SV2 and synaptophysin. Notably, in thy1-YFP16 mice, we also observed many additional synapses that did not colocalize with YFP+ axons, and which are presumably associated with YFP negative, small diameter axons. Our ultrastructural analysis of the DREZ demonstrated characteristic features of pre- but not postsynaptic profiles such as vesicles aggregated at the active zone (Fig. 3). Thus, almost all DR axons, including small diameter axons, appear to stop and form presynaptic terminals on non-neuronal cells at the DREZ. These findings thus suggest that axons are neither repelled nor continuously inhibited at the

DREZ by growth inhibitors but are rapidly stabilized after establishing presynaptic terminals on non-neuronal cells. Our findings are in line with an interesting idea raised many years ago and then virtually forgotten, which speculated that regenerating axons stop because they form synapses with non-neuronal cells (Carlstedt 1985; Liuzzi and Lasek 1987).

5. Exogenous factors promoting regeneration

5.1 Neurotrophic factors

During development, neurotrophic factors (NTFs) play a crucial role in axonal growth and pathfinding and neural circuit formation. Therefore, these growth-supportive molecules are excellent candidates to enhance growth-related responses and facilitate CNS regeneration in adults. Several NTFs have been reported to promote sensory axon regeneration across the DREZ and further into spinal cord with functional recovery. Members of the neurotrophin and glial cell line-derived neurotrophic factor (GDNF) families are among the most studied. The neutrophin family consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4). All neurotrophins bind to low affinity receptor p75, but their specific functions are mediated by distinct high affinity receptors: trkA for NGF, trkB for BDNF/NT-4 and trkC for NT-3. The GDNF family consists of GDNF, neurturin, artemin and persephin. Their function is mediated through a receptor complex, Ret and GFRα1-4, which may be expressed by nociceptive, mechanoreceptive and proprioceptive DRG neurons (Ramer, McMahon, and Priestley 2001).

Ramer et al. conducted a thorough study on the effect of NTFs on dorsal root regeneration (Ramer, Priestley, and McMahon 2000). After cervical dorsal root crushes, continuous intrathecal infusion of NGF, NT-3 or GDNF resulted in regeneration of different subtypes of dorsal root afferent axons, and re-innervation of dorsal horn neurons. Moreover, the trophic effect of these factors corresponded well to the known pattern of receptor distribution on subpopulations of DRG neurons, i.e. NGF led to ingrowth of small unmyelinated nociceptive fibers, NT-3 led to ingrowth of large myelinated fibers, GDNF induced growth of both small and large afferents. Rats treated with NGF and GDNF also showed restoration of nociceptive sensation. Long-term expression of NTFs in dorsal spinal cord by gene therapy techniques has also attracted damaged sensory axons (Romero et al. 2001). This strategy resulted in robust regeneration into both normal and ectopic locations within spinal cord. A combination of NGF and semaphorin3 used to reduce ectopic regrowth, which can potentially cause pain and autonomic dysreflexia, effectively restricted the growth of CGRP positive axons to their normal location within superficial dorsal horn (Tang et al. 2007). More recently, Wang et al. reported almost complete and long-lasting restoration of sensory function after dorsal root injury by systemic artemin, a member of the GDNF family (Wang et al. 2008). Artemin induced multiple classes of dorsal root axons to re-enter correct target layers in the dorsal horn with restoration of complex sensorimotor behavior (Harvey et al. 2010). The caveat of these observations however are the lack of the molecular basis of the non-selective effects of artemin because GFRα3, the major artemin receptors, have been detected primarily in non-myelinated, subclass of the DRG neurons (Orozco et al. 2001).

5.2 Grafts and transplants

After spinal cord injury, peripheral nerve grafts provide neurotrophic support and growth substrate that permit CNS axons to regenerate (Cheng, Cao, and Olson 1996; Fernandez et

al. 1985). This strategy has also been applied to promote dorsal root regeneration across the DREZ. Dam-Hieu et al. found that a peripheral nerve autograft (NAG) bridge between the stumps of transected L3 and L4 roots and ipsilateral rostral cord about 10 mm away from DREZ, successfully bypassed the nonpermissive PNS/CNS border, and enabled primary afferents to regenerate through the graft and into the dorsal column over a distance of at least 30 mm (Dam-Hieu et al. 2002). Behavior improvement was also observed. Liu et al. also tested a microsurgical technique that sutured an injured cervical dorsal root to an intact dorsal root via a nerve graft and observed regeneration of dorsal root axons into dorsal horn and functional recovery. Greater recovery occurred when the nerve graft was genetically modified to overexpress neurotrophic factors (Liu et al. 2009).

Embryonic spinal cord transplants have also been used to help injured dorsal root axons to regrow and reconnect with the denervated CNS. For example, after dorsal root injury, embryonic day (E)14 or 15 rat spinal cord transplants were grafted into the dorsolateral quadrant of adult rat spinal cord. Transganglionic labeling and CGRP immunostaining showed regenerated primary sensory fibers within the transplants (Tessler et al. 1988; Itoh, Mizoi, and Tessler 1999). Light and electron microscopy showed that these axons formed synapse-like structures (Itoh and Tessler 1990) and electrophysiological studies demonstrated functional connections between regenerating axons and grafts (Itoh et al. 1996; Houle et al. 1996).

5.3 Olfactory ensheathing cells (OECs)

OECs myelinate olfactory axons and support growth of these axons from PNS to CNS throughout life (Farbman 1990). Transplanted OECs have been reported to promote axon regeneration, remyelination and functional recovery after spinal cord injury (Kato et al. 2000; Pascual et al. 2002; Ramon-Cueto et al. 1998; Ramon-Cueto et al. 2000; Lu et al. 2002; Plant et al. 2003). Corticospinal and noradrenergic axons are among those reported to regenerate but studies of dorsal root afferent regeneration have obtained conflicting results. Pascual et al. transected dorsal roots L6 to S2 bilaterally in rats, which eliminated sensory transmission from the bladder and produced an atonic bladder (Pascual et al. 2002). Transganglionic labeling showed sensory fiber regeneration into dorsal horn and parasympathetic nucleus when OECs were grafted into spinal cord immediately after rhizotomy. Bladder activity was also restored, indicating functional reconnection between the regenerating axons and CNS neurons. Li et al. also found that OECs implanted into the spinal cord and transection site interacted with host astrocytes to promote dorsal root axon regeneration across DREZ into spinal cord grey matter and for long distances in the dorsal columns (Li et al. 2004). Other investigators, however, reported minimal effects of OECs on dorsal root regeneration at the DREZ (Ramer et al. 2004; Riddell et al. 2004). Different sources of OECs and different transplantation techniques may account for these discrepancies.

6. Clinical perspectives

The most common dorsal root injury in adults is caused by traction injury of the brachial plexus (C5-T1), usually from high-speed motor vehicle accidents, particularly motorcycle accidents, in which the head and neck are violently wrenched in the opposite direction from the ipsilateral shoulder and arm (Sherlock and Hems 2004; Yoshikawa et al. 2006). The

presenting features of brachial plexus injuries include neck and shoulder pain, and numbness, tingling and weakness of the affected upper limb. In patients whose dorsal roots have been avulsed from the spinal cord numbness is commonly accompanied by severe, often intractable, crushing pain in the hand that intermittently bursts down the arm (Htut et al. 2006).

Brachial plexus injuries are classified by plexus injury location. Most common are C5-6 injuries, which generally have the best prognosis. Also relatively common is involvement of the C5-7 roots. Patients with these types of injury hold the arm internally rotated and adducted. Imbalance of force across the glenohumeral joint also causes abnormal joint development in children (Kozin 2011). More severe injuries involve the entire plexus and may be accompanied by an ipsilateral Horner's syndrome (ptosis, miosis, and anhidrosis). In such severe injury the arm is capable of little movement and long-term prognosis is poor. More severe injuries are also commonly associated with dorsal root avulsions. It is extremely important to distinguish dorsal root injuries (preganglionic) from injuries distal to the dorsal ganglia (postganglionic) because there continues to be no effective therapy for encouraging intraspinal regeneration of the damaged dorsal root whereas postganglionic injuries resemble those of injuries to other peripheral nerves and may be amenable to treatment.

Evaluation of traumatic plexus injury uses nerve conduction studies (NCS), electromyography (EMG), and imaging to classify the pattern of injury and to determine if root avulsions are present. Sensory nerve conduction studies, in particular, can be of great aid in determining if a plexus injury is pre or postganglionic. The DRG cell bodies reside outside of the spinal cord and have both a central process that enters the spinal cord at the dorsal root entry zone (DREZ) and a peripheral process. Root avulsion classically injures the central DRG process but leaves the peripheral process intact. Therefore, sensory NCS, which measure response of the peripheral process, remain normal in root injuries. Thus, normal sensory responses but clinical loss of sensation in a dermatomal pattern suggest preganglionic injury. Motor conduction studies and EMG are most useful in aiding localization and grading motor nerve injury. They cannot, however, help distinguish between root or nerve injury. The EMG is most informative when performed at least fourteen days after injury (Quan D 1999). As NCS/EMG may not detect all root avulsions, brachial plexus imaging is a useful adjunct. Though no imaging modality detects all avulsions, CT myelography is the current accepted standard, with a diagnostic accuracy of 70-95% (Doi et al. 2002). In both conventional and CT myelography, pseudomeningocele formation is a surrogate marker for avulsion.

Treatment of brachial plexus injury is often surgical. In children, ruptured plexus nerve may be repaired with donor nerve (usually the patient's sural nerve) or other graft material including processed cadaveric nerve or extracellular matrix tubes (Waters 2005; Moore et al. 2011). However, in adults the distance required for regeneration is often too lengthy for effective grafting. Nerve anastomosis to a nearby denervated nerve and muscle is useful in both children and adults (Fox and Mackinnon 2011; Pham et al. 2011). However, it must be emphasized that recovery even with these treatments is generally incomplete and that there is no effective therapy for dorsal root avulsions.

7. Summary

Although mechanisms of regeneration failure after direct traumatic lesions to the spinal cord have been explored intensively, regeneration failure at the PNS-CNS interface after

damage to the spinal nerve roots has received much less attention. It is largely assumed that inhibitory features of the CNS environment make an important contribution to regeneration failure at DREZ, but the decisive factor(s) and their mechanisms of action remain unclear. Also unknown is whether the growth inhibitory activities at the DREZ are the same or different from those elsewhere within the CNS.

Efforts to overcome regeneration failure at the DREZ have included enhancing the regeneration capacity of sensory axons with neurotrophic factors and neutralizing growth inhibitors. These efforts have been only partially effective, perhaps because they did not treat the stabilizing activity that our laboratory has observed at the DREZ. Continued application of innovative techniques, including *in vivo* imaging, advanced optics, and mouse genetics will be necessary to gain fundamental new insights into why sensory axons stop at the DREZ and fail to regenerate into spinal cord. Of the many possible future directions, we will be particularly interested to learn: 1) the identity of the non-neuronal cells that stabilize regenerating axons at the DREZ; 2) the relative importance of the growth inhibitory cues and the synapse-inducing activity of non-neuronal cells; 3) how this information can be used to optimize recovery of sensory function after spinal cord and root injuries.

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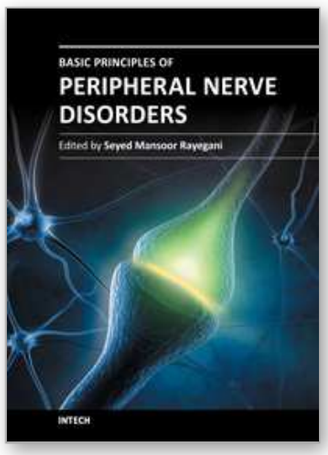

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Peripheral nerve disorders are comprising one of the major clinical topics in neuromusculoskeletal disorders. Sharp nerve injuries, chronic entrapment syndromes, and peripheral neuropathic processes can be classified in this common medical topic. Different aspects of these disorders including anatomy, physiology, pathophysiology, injury mechanisms, and different diagnostic and management methods need to be addressed when discussing this topic. The goal of preparing this book was to gather such pertinent chapters to cover these aspects.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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