

## CELLULAR AND MOLECULAR INTERACTIONS AFTER PERIPHERAL AND CENTRAL NERVE INJURY

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*Injuries to the central nervous system (CNS) result in virtually irreversible neurologic deficits compared to the peripheral nervous system (PNS) where injuries may be followed by some functional recovery. This sharp difference in the regenerative capacity of CNS and PNS is attributed to intrinsic properties of the injured neurons, and the glial cells, specifically the Schwann cell of PNS and the oligodendrocyte of CNS. The myriad of cellular and molecular changes that result following nerve injury are intimately related to whether a regenerative-permissive environment is provided to injured neurons. In this review, we highlight some of the key injury-related cell-molecular changes that are triggered in neurons and glia and how these changes may be related to the promotion of axonal regeneration of injured PNS compared to CNS.*

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### INTRODUCTION

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Injuries to the nervous system often have significant consequences due to profound functional deficit that alters patient lifestyle and employability. The mammalian central nervous system (CNS) axons are virtually incapable of regenerating functionally viable axons after injury in contrast to their peripheral nervous system (PNS) counterparts which do regenerate, albeit slowly and incompletely (1,2). This difference in the non-regenerating CNS and regenerating PNS lies in the normal state of growth-permissiveness to regenerating axons in the two systems.

The cellular environment of CNS neurons consists of macroglia and microglia. The former comprise the myelinating oligodendrocytes and the astrocytes. The microglia are believed to originate as bone marrow cells and function as brain resident macrophages. The myelinating glial cell of PNS is the Schwann cell (SC), which in contrast to the oli-

godendrocyte of CNS, supports axonal regeneration in both PNS and CNS, particularly in association with phagocytic macrophages which infiltrate denervated distal nerve stumps to phagocytose the myelin of denervated SCs (3-7). This review highlights some of the key cellular and molecular interactions that ensue following an injury, that are implicated in the difference between the growth-permissiveness provided to regenerating axons after CNS and PNS injuries.

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### PREREQUISITES FOR AXONAL REGENERATION AND FUNCTIONAL RECOVERY

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In order to establish structural and functional recovery, injured neurons that survive axotomy must be able to: (i) regrow the damaged axon (axonal outgrowth), (ii) continue this regrowth through the lesion site (i.e. overcome inflammation-induced scar at the lesion site), (iii) elongate the axons in the correct direction (correct endoneurial tubes), (iv) topographi-

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cally reinnervate their original target (target reinnervation), and (v) restore normal electrophysiological properties (8-10). In order to accomplish these prerequisites for functional recovery, injured neurons must have the potential to upregulate required regeneration-associated genes (RAGs, e.g. GAP-43, tubulin, actin, and transcription factors such as c-Fos, c-Jun and KROX24 (11-16) to optimal levels (*intrinsic properties* of injured neurons). In addition, an optimal growth-permissive environment must be made available to the injured neurons *via* the inflammatory response of glial and immune cells (*extrinsic factors*). The extrinsic factors include (i) presence at optimal levels of neurotrophic/neurite-growth promoting factors required for the maintenance of axonal regrowth, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), fibroblast growth factor (FGF), insulin growth factor (IGF), and ciliary neurotrophic factor (CNTF), and extracellular matrix proteins such as laminin and fibronectin (17-22), and (ii) absence and/or removal of growth-inhibitory components such as NI35/250, myelin associated glycoprotein (MAG), tenascin C, and proteoglycans such as chondroitin, heparan and keratan sulphate proteoglycan (23-27). Therefore, successful axonal regeneration depends on the interplay between extrinsic cues and intrinsic properties of the lesioned neurons.

Virtually all injured neurons may initiate spontaneous axonal outgrowth after injury but their capabilities to upregulate RAGs and maintain regenerating axons differ. Extrinsic neurons whose axons are in PNS are able to upregulate RAGs and regenerate in the permissive growth environment provided by the denervated SC (28-30). The CNS neurons either fail to upregulate RAGs or do so at very low levels and regeneration aborts within the inhibitory environment of the denervated oligodendrocytes (31). However, these prerequisites are not absolute, because some mature CNS neurons with sustained expression of *c-jun* may fail to exhibit axonal regeneration and certain populations of regenerating neurons express little or no GAP-43 (32,33).

## PERIPHERAL NERVE REGENERATION

### *Response of Distal Nerve Stump to PNS injury*

The complex cell-molecular interactions that ensue between SC and macrophages that infiltrate the injury site result in the provision of growth-permissive environment for regenerating axons.

### *Wallerian degeneration*

Following injury, the axon distal to the injury site is disconnected from the cell body and undergoes Wallerian degeneration (29,34,35). Wallerian degeneration is characterized by axonal and myelin breakdown and phagocytosis initially

(first 3 days) by SCs which express complement factor 3 (C3; 36), and later by both SC and macrophages recruited to the injury site (37-39). It has been suggested that, in addition to other chemoattractive forces, SC help to recruit macrophages to the injury site *via* the secretion of the inflammatory cytokine, interleukin-1 $\beta$  (IL-1 $\beta$ ), in the first 3 days after nerve injury (40,41). Active phagocytosis of myelin debris by macrophages is essential for axonal regeneration because: (i) myelin-derived proteins (NI-35 and NI-250) and myelin-associated glycoprotein (MAG) have been shown to inhibit neurite growth in both CNS and PNS (25,42,43), and (ii) SC migration and proliferation, and axonal regeneration are severely retarded in the C57Bl/Ola mutant mice, in which macrophage invasion is sluggish and Wallerian degeneration is delayed (6,44,45).

Macrophage and SC-derived cytokines are implicated in phagocytosis. Interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) increase while transforming growth factor- $\beta$  (TGF- $\beta$ ) reduces the phagocytic activity of SCs and macrophages (46-48). TNF- $\alpha$  is also implicated in the termination of SC proliferation (48). Thus, the temporal pattern of expression and release of IL-1 $\alpha$ , TNF- $\alpha$  and TGF- $\beta$  may be critical in the co-ordination of cellular repair of injured nerve by its modulation of phagocytosis of axonal and myelin debris, SC proliferation as well as ensheathment and remyelination of regenerating axons.

### *Cytokines and the denervated SC proliferation and phenotype*

Loss of axonal contact initiates SC proliferation and a switch in gene expression from a myelinating to a non-myelinating SC phenotype in which myelin-associated proteins such as P<sub>0</sub> and MAG, are downregulated and p75<sup>NTR</sup>, glial fibrillar acidic protein (GFAP), neural cell adhesion molecule (N-CAM) and GAP-43 are upregulated (30,49-51). An important component of the non-myelinating phenotype is the expression of growth factors, which include NGF, BDNF and GDNF, all of which are associated with axonal growth (22,29,52,53). In addition, SC secrete a number of cytokines, such as IL-1 $\beta$  and TNF- $\alpha$ , which may, in turn, induce the expression and secretion of cytokines and growth factors by macrophages in a manner similar to the interaction of macrophages and other cell types in different tissues (41,54). The interplay of cytokines derived from SC and macrophages may be essential to maintain the expression of growth-associated proteins (GAPs) by the non-myelinating SCs in the denervated distal nerve stump, because of two reasons: (i) proteins such as p75 are downregulated concurrent with a decline in macrophage number (55), and (ii) the evidence cited above from the Ola mice experiments of an association between macrophages and phagocytosis.

Schwann cell proliferation has been associated with their

autocrine capability to synthesize and express SC-associated growth factors, the neuregulins (neu differentiation factor, glial growth factor, heregulin) and their erb receptors B1, B2 and B3 (56), as well as neurotrophic factors such as NGF and BDNF which may have autocrine actions *via* p75<sup>NTR</sup> (22, 67-69). Macrophages also secrete numerous growth factors that are mitogenic for SCs. These include platelet-derived growth factor (PDGF), transforming growth-factor-beta (TGF- $\beta$ ), epidermal growth factor (EGF) and other neurotrophic factors like basic fibroblast growth factor (bFGF) (61-66). Therefore, SC-macrophage interaction appears to be bidirectional.

The importance of cytokines in peripheral nerve regeneration and in SC-macrophage interaction has been demonstrated in several experiments (65,66). IL-1 $\beta$  has been shown to induce NGF in fibroblasts and implicated in maintaining NGF in SC (67). Macrophages can upregulate the expression of p75<sup>NTR</sup> by SC *via* the production of PDGF (67). TGF- $\beta$  secreted by macrophages and SCs has the same effect as cAMP in the induction of mRNA<sup>NGF</sup> in SCs, an effect that is augmented by PDGF and bFGF (68-70). However, effects of TGF- $\beta$  on SCs are state-dependent as in other cells (46,71). For instance, TGF- $\beta$  is mitogenic for SCs in the presence of serum *in vitro* but inhibits proliferation of SC once they express the non-myelinating phenotype (72). The latter effect arises, may be because only proliferating SCs convert TGF- $\beta$  to active form (41).

### **Glial cell responses at the cell body after PNS injury**

Glial cells which surround the cell bodies of motoneurons undergo a number of characteristic changes after axotomy which have been associated with their trophic support and possibly with the capacity of the neurons to regenerate their axons (73). Following injury to a peripheral nerve (e.g. facial, hypoglossal and sciatic nerves), the astrocytic cells which are in very close proximity with the injured neuron (undergoing chromatolysis), sense the altered homeostasis and respond quickly by changing their gene expression and activating the microglia (74). This results in a series of changes in the gene expression of these microglial cells which become highly reactive and immunocompetent but not phagocytic. They initiate bidirectional cross-talk with astrocytes.

#### • *Astrocytes*

Neurons and astrocytes display intimate structural relationships and functional interactions. Therefore, it seems conceivable that astrocytes would be the first glial cells to sense any disturbance in the normal homeostasis. This is supported by the rapid (within 1 hour) upregulation of connexin-43 in astrocytes after facial nerve axotomy and hence cell-to-cell communication (74). Adaptations in the functions of the perineuronal astroglia may induce production and release of macrophage-colony stimulating factor (M-CSF) and granu-

locyte-macrophage colony stimulating factor (GM-CSF) (75,76) which can act on microglia. M-CSF also appears to be trophic for neurons (73) implying that axotomised neurons may be trophically supported by astroglial derived M-CSF. Within 24 hours there is increased immunoreactivity for GFAP (77) and upregulation of mRNA<sup>GFAP</sup> and protein (78).

Astrocytes do not proliferate following peripheral axotomy (79) but they develop slender, sheet-like processes that cover the non-synaptic areas of neuronal membrane. They express lesion-induced molecules including glycoproteins, laminin (80,81), clusterin (82) and fibronectin (83), different types of collagen (84), proteoglycans (26,85,86), tenascin C (87) and growth factors such as PDGF and its receptor (88). Laminin and collagen type IV are generally considered to provide a very attractive substrate for axonal elongation (89). Tenascin C and proteoglycans are constituents of the extracellular matrix (26,90,91). Clusterin is capable of inhibiting complement-mediated cell lysis and is involved in cell adhesion, lipid transport and in processes associated with whether a cell survive or die (92) but its role in the axotomy-induced astroglial response is unknown.

mRNA<sup>TGF- $\beta$ 1</sup> is expressed in both astrocytes and microglia, and astrocytes respond to TGF- $\beta$ 1. This suggests that this cytokine is involved in autocrine or paracrine interactions, influencing neighbouring cells including other astrocytes. In addition, astrocytes also upregulate TGF- $\alpha$  and its receptor (93). Finally, reactive astrocytes are immunoreactive for the N-methyl-D-aspartate (NMDA) receptor (94) and MHC antigens (95). The upregulation of NMDA receptor is suggested to be associated with an increased demand for astroglial uptake of potentially cytotoxic glutamate and/or other NMDA-receptor ligands which are secreted after injury (96).

#### • *Microglia*

The microglial cells were first described by Del Rio Hortega in 1932 and constitute about 5-10% of the total glial cell population in the CNS, with a gradual increase with aging (97). These cells originate from the bone marrow and belong to the system of mononuclear phagocytic cells (98). They form a network of cells, constituting the defence system of the organism, and are organized in a way which allows rapid response to virtually any kind of disturbances (99). Resting microglia show a down-regulated immunophenotype, they express no MHC class I and II antigens or leukocyte common antigen (CD45) in the normal rodent brain, although MHC antigens have been reported on human microglia in the white matter (14) and microglia are more activated in the brain of aged rodents.

Following motor axonal injury, microglia become highly reactive and immunocompetent. They rapidly up-regulate complement receptor 3 (CR3) (101) and the  $\beta$ -amyloid pre-

cursor protein ( $\beta$ -APP) (102). They retract their fine ramification, enlarge, and become mitotic within 24 hours after axotomy (79,103). At the early stage, microglia also express vimentin (105) and the adhesion molecules leukocyte function antigen (LFA)-1 $\alpha$  and - $\beta$  (104) which may be linked to their migration towards the injured neuronal perikarya where they establish a tight structural relationship with the axotomised motoneurons. They surround the cell body and "strip" them of synaptic connections (i.e. synaptic stripping) but thin astrocytic processes may still separate microglia from the neuronal membrane early after injury (103), and as well as later on, when the astrocytes completely replace microglia around the axotomised cell body (105).

M-CSF and GM-CSF (106) produced by astrocytes (76, 108) readily bind to receptors on microglial cell surfaces and, studies in a mouse mutant lacking the gene for M-CSF (osteopetrotic mice), suggest that M-CSF is involved in regulating mitosis of microglia following axotomy (100). Activated microglia as well as motoneurons express mRNA<sup>TGF- $\beta$</sup>  after axotomy which may act in both autocrine or paracrine manner (107,109,110). Microglia assume the role of antigen-presenting cells to the immune system and express MHC class I and II antigens (111). Complement components C1, C1q, C3, C3d, C4d and C9 are upregulated (112). The expression of C4d indicate that in addition to the so-called classical pathway, the alternative pathway may be activated as well. The C9 component is a part of the terminal complement complex, which induces cell death by producing holes in the cell membrane thereby inducing cell death (112).

- *Microglia and astrocyte cross-talk after peripheral nerve injury*

Cultured microglia respond to astrocyte-derived CSFs by synthesising IL-6 (113). In turn, astrocytes can respond to IL-6 via the IL-6 receptors that they express (114), consistent with the finding that IL-6 plays a role in the activation of perineuronal astrocytes after motor axon injury (114). Also, astrocytes of mice overexpressing IL-6 appear to be permanently activated as demonstrated by a constant upregulation of GFAP (115,116). These findings strongly indicate that IL-6 plays a critical role in the induction of astroglial hypertrophy after injury. However, IL-6 overexpression also increases complement C3 expression by microglia (117), suggesting that IL-6-mediated activation of astrocytes causes further activation of microglia. Furthermore, IL-6 may be produced by the astrocytes themselves (118), thereby creating autocrine and paracrine loops between astrocytes and microglia.

IL-1 is released by cultured microglia (75,119) and stimulates astrogliosis *in vivo* (120-122). Astrocytes express IL-1 binding sites *in vitro* (123) and administration of IL-1 receptor antagonist reduces trauma-induced astrogliosis (124). However, there is no evidence for the expression of IL-1 in the facial nucleus after axotomy (107). TGF- $\beta$  is upregulated in

perineuronal microglia and axotomised motoneurons and its administration stimulates astroglial hypertrophy (125,126). Ciliary Neurotrophic Factor, whose retrograde axonal transport is increased after axotomy (127), and bFGF, which is upregulated in axotomised motoneuron, increase the expression of GFAP by astrocytes (128-130). Therefore, complex interactions appear to exist among injured neurons, astrocytes and, microglia in a tripartite manner, so that injured motoneurons influence neighbouring astrocytes, and together they activate microglia, modify their interactions, and organize auto- or paracrine circuits. In addition, microglia promote astrocyte activation, contribute in an autocrine way to their self-activation and may affect the injured neurons, e.g. *via* secretion of growth factors and cytokines. Subsequently, a relatively long-lasting growth response is mobilized. Whether or not glial cell trophic support to injured motoneuron declines with time is not known. Chronically axotomised motoneurons progressively fail to regenerate (131), concurrent with a downregulation of previously upregulated RAG (132). It is therefore possible that the interactions between neurons, astrocytes and microglia, which initially may sustain their growth, change with time to precipitate the decline in growth capacity of the injured motoneurons.

### ***Functional recovery in injured PNS***

Despite the capacity for axonal growth and the permissive environment provided by SC of the distal stumps of injured peripheral nerves, functional recovery is often disappointing after PNS injury with or without surgical repair. Clinical experience has established that functional recovery is particularly poor for injuries which sever large nerves such as brachial and lumbar plexus nerve trunks (29,133-136,138). This is because, first, regenerating axons often traverse long distances to reinnervate denervated targets. The slow rate of regeneration (1-3mm/day) translates into many months and even years before regenerating axons might be expected to reach denervated targets. This creates substantial time lags between the provision of growth permissive environment by denervated SC and axonal regeneration through the denervated distal nerve stumps. Associated with the time lag is a progressive retardation of axonal regeneration associated with the prolonged axotomy of the injured neurons and the chronic denervation of the distal nerve stumps (29,131,137,139). Secondly, many regenerating axons may fail to enter their original endoneurial tubes after their disruption, with the result that regenerating axons frequently are directed towards foreign and often inappropriate targets which further exacerbate poor return of function (29,133).

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## **CENTRAL NERVE REGENERATION**

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### ***CNS injury and failure of axonal regeneration***

As already mentioned, injuries to the adult mammalian CNS

are characterized by a failure of regrowth of transected axons. The reasons for the lack of regenerative capacity are multifactorial which include both intrinsic factors such as death of injured neurons, reduced capacity of injured neurons to grow when injured, and extrinsic factors such as lack of the necessary trophic molecules to support growth, and the presence of an environment hostile for any growth (31). Oligodendrocytes do not produce a growth-permissive environment like SC. On the contrary, CNS myelin-associated molecules such as MAG (25), Nogo-A (140,141), and oligodendrocyte-myelin glycoprotein (OMgp) (142) are strongly linked to growth inhibition. Furthermore, in contrast to the reaction of astrocytes and microglia to injury of extrinsic neurons, astrocytes show minimal response to injury of intrinsic neurons concurrent with sluggish proliferation and phagocytosis of myelin debris by microglia (144,145). However, in the event of neuronal death, microglia in the vicinity of the dead neurons become highly phagocytic but do not express the components of the complement system.

#### ***Response of intrinsic neurons and their surrounding glia to axotomy***

The response of intrinsic CNS neurons to axotomy is very limited in comparison to axotomised extrinsic neurons. Upregulation of RAG may be minimal although RAG expression may be enhanced by administration of exogenous neurotrophic factors (28). Moreover, they fail to trigger the inflammatory responses seen normally in glial cells surrounding motoneurons, which include the activation and hypertrophy of the astrocytes and the inflammatory response of the microglial cells. For example, lesions to rubrospinal or corticospinal tracts of intrinsic CNS neurons at high cervical level trigger only a comparably minimal response in the perineuronal astrocytes and microglia and minimum cell death (145,162). Upregulation of GFAP protein or mRNA is not observed (93,163), and neither is microglial proliferation (145). The immunoreactivity for microglial markers, such as the CR3 receptor shows only a minimal increase above normal levels (163,164).

#### ***Microglia and CNS Wallerian degeneration***

Lesion to the efferent sensory axons of the dorsal root ganglion cells which results in anterograde Wallerian degeneration in specific areas of the spinal cord grey and white matter, without any disturbance of the CNS itself (93) has been used as a model of Wallerian degeneration of injured CNS axons. After axotomy, oligodendrocytic processes are withdrawn from disrupted myelin sheaths. Microglial cells proliferate, slowly ingest and digest the myelin bodies (146) and up-regulate the macrophage-associated scavenger receptor (149). Mild activation of microglia is associated with intense labeling for the marker ED1 (147). Denervated axonal

fragments, together with degenerating myelin form myelin bodies which, as a result of sluggish phagocytic activity of microglia, can remain at the degenerated zone for months or even years (93). Hematogenous macrophages and oligodendrocytes do not contribute to phagocytosis of myelin bodies (148,150) as their PNS counterparts, the macrophages and SC normally do in the injured PNS.

Phagocytic microglia express several cell adhesion molecules, which include LFA-1, very late antigen-4 (VLA-4) and its ligand, and ICAM-1 (151). These may be important for their migration and attachment to the myelin bodies prior to phagocytosis. MHC class I and II antigens are upregulated (152) indicating that microglia can act both as antigen-presenting cells and phagocytes. However, there are several differences between the phagocytic capacity of the microglia in the CNS and the phagocytic macrophages of PNS Wallerian degeneration. Microglia (*i*) are lysosome-negative (153), (*ii*) downregulate components of the complement system - C3 and CR3, and fail to express C3d or C9 (36), and (*iii*) phagocytose myelin bodies very slowly (148). These differences result in less efficient and very sluggish phagocytic activity of microglia which leads to a prolonged presence of CNS myelin and, consequently, inhibition of axonal growth. Additionally, the cytotoxic effect of microglia on oligodendrocytes is minimal leading to persistent presence of these cells, which have been shown to inhibit axonal regrowth (154).

#### ***Non-permissive CNS growth environment and role of macrophage inhibitory factor***

The non-permissive environment of the CNS has been attributed to the prolonged persistence of growth-inhibitory myelin-derived proteins such as MAG (26,42), Nogo-A (140,141,143), and oligodendrocytes (155). The prolonged persistence of myelin and related molecules after CNS injury is demonstrated to be due to the inhibition of the phagocytic activity of macrophages and/or microglia by macrophage inhibitory factor (MIF) (156). Macrophage inhibitory factor is absent in PNS as evident from the active phagocytic activity of infiltrating macrophages after PNS injury. In fact, macrophages, which are activated by exposure to the sciatic nerve in the PNS, exhibit active phagocytic activity when transplanted into CNS nerve, such as the optic nerve. This activity eliminates the growth-inhibitory myelin and thereby induces axonal growth of the injured optic nerve (155,157). Sciatic nerve-activated macrophages also eliminate the other inhibitory component of the CNS, the oligodendrocytes, *via* their cytotoxic activity possibly mediated by nitric oxide and TNF- $\alpha$  (154,158,159).

Exposure of microglia to sciatic nerve or sciatic nerve-conditioned medium strongly induces their phagocytic activity (7), indicating a counteractive effect of PNS nerve on the suppressive action of MIF on phagocytosis in the CNS envi-

ronment. Microglia which have been activated by exposure to sciatic nerve are partly deactivated upon exposure to the optic nerve, but it is not known whether such deactivation is sufficient to prevent their ability to support regeneration of injured optic nerve. Findings that these microglia either induce axonal growth (160) or promote regeneration of axotomised dorsal root ganglion neurons (161) suggest that sciatic nerve-activated microglia may indeed support regeneration in the CNS.

### **Microglial phagocytosis of dying CNS neurons**

The optic nerve has been used intensely as a model for studying the responses of the perineuronal glial cells to traumatic injury of intrinsic CNS neurons. Because of the proximity of the lesion to the cell body, lesions of the optic nerve generally are associated with extensive degeneration and death of retinal ganglion cells (165). Consequently, the responses of the retinal microglia, astrocytes and Muller cells (144), are generally associated with the cell death of the retinal ganglion cells. Microglial cells become intensely phagocytic in contrast to their response after axotomy of extrinsic axons, and they phagocytose dead retinal ganglion cells (166). Evidence that reduced microglial activation by intravitreal MIF (167) and increased activation by exogenous tuftsin markedly attenuates and increases axotomy-induced retinal ganglionic cell death (93), respectively, concurs that neuronal cell death may be linked to the activation of microglial cells after axotomy.

### **CONCLUSION**

Understanding the cellular and molecular mechanisms underlying regeneration or lack of regeneration after nerve injuries has met intense research. However, while tremendous amount of progress has been made in understanding the factors involved in poor axonal regeneration, efforts aimed at counteracting or neutralizing such factors have been generally futile in regards to reinstatement of functionally significant regeneration after injury. Nonetheless, the progress made thus far is encouraging, and it is only through sustainable active research that the problem of failed regeneration and devastating loss of function after nerve injuries can be resolved. We can only hope that one day paralysis will cease to be an irreversible devastating ailment.

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