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Review

Spinal Cord Regeneration

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Three theories of regeneration dominate neuroscience today, all purporting to explain why the adult central nervous system (CNS) cannot regenerate. One theory proposes that Nogo, a molecule expressed by myelin, prevents axonal growth. The second theory emphasizes the role of glial scars. The third theory proposes that chondroitin sulfate proteoglycans (CSPGs) prevent axon growth. Blockade of Nogo, CSPG, and their receptors indeed can stop axon growth in vitro and improve functional recovery in animal spinal cord injury (SCI) models. These therapies also increase sprouting of surviving axons and plasticity. However, many investigators have reported regenerating spinal tracts without eliminating Nogo, glial scar, or CSPG. For example, many motor and sensory axons grow spontaneously in contused spinal cords, crossing gliotic tissue and white matter surrounding the injury site. Sensory axons grow long distances in injured dorsal columns after peripheral nerve lesions. Cell transplants and treatments that increase cAMP and neurotrophins stimulate motor and sensory axons to cross glial scars and to grow long distances in white matter. Genetic studies deleting all members of the Nogo family and even the Nogo receptor do not always improve regeneration in mice. A recent study reported that suppressing the phosphatase and tensin homolog (PTEN) gene promotes prolific corticospinal tract regeneration. These findings cannot be explained by the current theories proposing that Nogo and glial scars prevent regeneration. Spinal axons clearly can and will grow through glial scars and Nogo-expressing tissue under some circumstances. The observation that deleting PTEN allows corticospinal tract regeneration indicates that the PTEN/AKT/mTOR pathway regulates axonal growth. Finally, many other factors stimulate spinal axonal growth, including conditioning lesions, cAMP, glycogen synthetase kinase inhibition, and neurotrophins. To explain these disparate regenerative phenomena, I propose that the spinal cord has evolved regenerative mechanisms that are normally suppressed by multiple extrinsic and intrinsic factors but can be activated by injury, mediated by the PTEN/AKT/mTOR, cAMP, and GSK3b pathways, to stimulate neural growth and proliferation.

Key words: Nogo; Phosphatase and tensin homolog (PTEN); Myelin; Glial scar; Chrondroitin sulfate proteoglycans (CSPGs)

INTRODUCTION

In 2000, Horner and Gage (232, p. 963) began a widely cited review with "It is self-evident that the adult mammalian brain and spinal cord do not regenerate, but recent discoveries have forced a reconsideration of this accepted principle." At its conclusion, the article (232, p. 969) cited Ramon and Cajal's decree, translated by Raoul May, that "once the development has ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centres the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated. It is for science of the future to change, if possible, this harsh decree." Horner and Gage concluded that "the decree is lifted but the solution remains elusive."

Does regeneration of the spinal cord still elude us? In this review, I will first consider three theories of regeneration that have dominated neuroscience since the early 1990s. The first theory proposes that axonal growth inhibitors (495), particularly myelin-based Nogo (78,200) and ligands that activate the Nogo receptor (167,168), prevent axonal growth in white matter. The second theory emphasizes the role of glial cells in blocking axon growth (475). The third theory emphasizes the role of chrondroitin sulfate proteoglycan (CSPG) in stopping axon growth. Chondroitinase ABC (ChABC) degradation of CSPGs allows regeneration and function recovery in spinal cord injury (SCI) models (48,649).

All three theories have significant weaknesses. Nogo is not the only axonal growth inhibitor, and knocking out

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Nogo does not always allow regeneration. Transgenic mice that have their Nogo genes and even Nogo receptor genes knocked out do not necessarily regenerate (189,324,546). Neither glial scars nor CSPG necessarily stop axonal growth. Many investigators have reported axons growing through dense fibrotic glial scars surrounded by CSPG and white matter, suggesting that Nogo, gliosis, and CSPG do not stop axon regeneration in many situations.

Axons grow under certain circumstances and not in others. For example, when axons are in the growth mode, they grow right through white matter containing Nogo and dense glial scars. On the other hand, when not stimulated by injury or other factors, axons are extraordinarily reluctant to grow. This is not surprising since unregulated growth in the central nervous system would be quite disruptive and unfavorable from a functional standpoint. In 2010, Liu et al. (349) reported that deleting the phosphatase and tensin homolog (PTEN) gene allows massive regrowth of the corticospinal tract in mice. Blocking expression of PTEN also allows regeneration of the optic nerve (443) through activation of phosphokinase B and mammalian target of rapamycin (AKT/mTOR) pathway (442). PTEN is expressed during development but not in mature central nervous system (CNS) neurons. These findings suggest a different perspective on spinal cord regeneration.

I propose that mammalian spinal cords have evolved robust regenerative mechanisms, but these mechanisms are under tight regulatory control by both extrinsic and intrinsic factors in adult spinal cord. Nogo and CSPG are among several extrinsic factors that inhibit axonal growth via receptors that stimulate Rho and Rho-kinase to stop axonal growth. Likewise, several intrinsic mechanisms suppress axonal growth by downregulating the AKT/mTOR pathway (438), which normally responds to growth factors, cytokines, and inflammation. For example, PTEN normally inhibits the AKT/mTOR pathway (565), which stimulates axonal growth. AKT also inhibits glycogen synthetase kinase 3-β (GSK3b). This ubiquitous enzyme normally phosphorylates and inhibits the nuclear factor of activated T-cells (NFAT) and wingless-type mouse mammary tumor virus (MMTV) integration site family member (WNT)–β-catenin that stimulate genes for cell proliferation, differentiation, and growth (74). However, during development and after injury, these growth-suppressive mechanisms are turned off, allowing growth and regeneration to occur. Certain drugs, such as lithium (625) and those that increase cyclic adenosine monophosphate (cAMP) (94,424,448,458) also turn off these mechanisms. I will critically review the evidence underlying this proposal.

THE NOGO THEORY

In 1981, David and Aguayo (108,109) used peripheral nerves to bridge the spinal cord above the injury site to the spinal cord below. Axons from the spinal cord grew long distances into these peripheral nerve bridges but failed to grow back into the spinal cord. They concluded that CNS axons could grow in the peripheral nerve but not in the spinal cord, initiating an intense worldwide search for axon growth inhibitors in the CNS. In 1989, Schwab and Schnell (496) found that myelin inhibits axonal growth and subsequently showed that an antibody (IN-1) raised against a myelin component allowed corticospinal tract regeneration in rats (491). The latter study attracted a great deal of attention and was widely heralded as the first study to show spinal cord regeneration. Subsequent studies indicated that IN-1 stimulates not only regeneration but also sprouting and plasticity in the spinal cord (27,50,490,492).

In 2000, Chen et al. (78) identified Nogo-A (reticulon 4) as the myelin-associated neurite outgrowth inhibitor. Expressed by neurons and oligodendroglia, but not astrocytes or Schwann cells (266), Nogo-A expression did not change significantly after injury. Many laboratories (201) subsequently confirmed that Nogo-A blocks axonal growth. In 2001, Fournier et al. (167–169) identified the Nogo receptor. Blocking Nogo receptors with Nogo-66 enhanced corticospinal tract growth (199) and recovery (336). Antibodies against Nogo promote recovery after spinal cord injury in rats (341) and monkeys (173). Transgenic inhibition of the Nogo-66 receptor function promotes axonal sprouting and improved locomotion after SCI (334). Myelin-associated glycoprotein (MAG) and oligodendroglial myelin glycoprotein (OMgp) synergize with Nogo-A to restrict axonal growth and neurological recovery after SCI (61). Soluble Nogo receptor, which binds ligands to the receptor, increases plasticity of spinally projecting neurons and improves recovery in contused spinal cords (577,578). These findings indicate that Nogo-A blocks axonal growth.

Three Nogo receptors have been identified, that is, NgR1, NgR2, and NgR3 (25). Many ligands bind the Nogo receptors. MAG (114,115,333,408,542) and OMgp (238,244) collapse growth cones by binding to Nogo receptors (25,133,238,319,335,494,509). NgR1 is the founding member of the receptor family and is bound by Nogo-A. Several other ligands may bind NgR1. For example, soluble NgR1 sequesters amyloid β (Aβ) peptide in Alzheimer's disease (382). BLyS, a B lymphocyte stimulator, stimulates the NGR1 receptor (634). MAG binds to NgR2 but not NgR3 (25). CSPGs may activate both NgR2 and NgR3 (500). Blockade of NgR1 and upregulation of LOTUS (lateral olfactory tract usher substance, an endogenous antagonist of NgR1) increase NgR2 and NgR3 expression (282). Finally, LINGO-1 (leucine-rich repeat and Ig domain-containing Nogo receptor-interacting protein 1) is a coreceptor of the NgR1, promotes spinal cord remyelination, and preserves axonal integrity in autoimmune encephalitis (395).

The role of Nogo turned out to be more complicated than anybody anticipated. Nogo-A downregulates cytoskeletal systems responsible for neurite growth and long-term potentiation (451). Blockade of Nogo-A or its receptors enhances sprouting and plasticity of surviving white matter tracts in injured spinal cords (16,148,172, 212,217,231,296,335,336,371,409,451,530,532,546,570, 578,626,637) and stroke (198,291,312,325,558,570,589). Nogo-A contributes to autoimmune demyelination (283) and multiple sclerosis (163). Nogo-66 blockade of Nogo receptors promotes differentiation of neural progenitors into astrocytic cells through the mTOR-STAT3 (mammalian target of rapamycin–signal transducer and activator of transcription 3) pathway (571). Genetic deletion and pharmacological blockade of NgR1 impairs cognitive recovery after traumatic brain injury in mice (212), suggesting that Nogo plays a role in cognitive recovery after brain injury. Finally, Hunt et al. (244) have pointed out that Nogo, MAG, and OMgp and their receptors are present on adult peripheral myelin, neurons, and axons during development. The roles that these Nogo receptor ligands play in peripheral nerves and during development are not well understood.

Genetic studies have challenged the role of Nogo as the primary inhibitor of CNS axonal growth. The Strittmatter Laboratory (296) had reported that Nogo A/B knockout mice were able to regenerate, but other laboratories could not confirm these results with other knockout animals, including Nogo A, B, and C knockout mice (596). Teng and Tang (546) found that mice with targeted genetic disruption of both Nogo-A and Nogo receptors had only modest (if any) increase of regenerative capacity. Cafferty and Strittmatter (62) reported that Nogo-AB gene trap (atg/atg) and ngr1 knockout (–/–) mice showed robust corticospinal tract growth and improved forelimb fine motor skill after unilateral pyramidotomy, but Dimou et al. (129) found that the effects of Nogo knockout are strain dependent. Lee et al. (324) found that deleting any or all three major myelin inhibitors, that is, Nogo, MAG, and OMgp, enhanced sprouting of uninjured corticospinal or raphespinal serotonergic axons but did not improve regeneration or behavioral recovery in the mice.

Nogo, MAG, and OMgp activate receptors that turn on the Ras homolog gene family member A (RhoA) and its effector Rho-kinase (ROCK) to inhibit axonal growth (306). The Rho proteins are low molecular weight guanosine triphosphate (GTP) binding proteins. RhoA controls cellular motility (3,76,228,368,507,528,574,607,615) by regulating cytoskeletal rearrangements (4,15,70,298,305,461, 479,515,576,641). RhoA also activates phospholipase D (285,313,372,393), C (489), and A2 (293,322), as well as serine–threonine kinases (12,429). Protein kinase A phosphorylates RhoA to mediate the morphological and functional consequences of cAMP (317). RhoA regulates many other cellular functions, including potassium channels (15), thrombin-induced cell death (138), assembly of extracellular fibronectin (640), neurotransmitter exocytosis (139), cellular uptake of low-density lipoprotein (615), cyclin D1 expression (585), basal muscle tone (445), interleukin 8 (506), gap junctions (123), and neurite growth cones (468,497). RhoA integrates signaling events produced by myelin-associated inhibitors and astroglial-derived inhibitors (CSPG), preventing axonal outgrowth on nonpermissive substrates (342).

Many factors influence ROCK and Rho activity in the spinal cord. Injury upregulates Rho proteins within the spinal cord (150). Blocking ROCK and Rho allows axonal growth (170) by preventing inhibition of axonal growth by Nogo, MAG, and OMgp, as well as CSPG (307). Some natural substances affect Rho expression. For example, curcumin, a spice ingredient, reduces protein levels of phosphokinase C, focal adhesion kinase (FAK), nuclear factor κ-light-chain-enhancer of activated B-cells (NF-κB), and RhoA (343). The best known Rho inhibitor is *Clostridium botulinum* toxin A (541) or ADP-ribosyltransferase C3 (176,177,269,270,311,419), which directly binds and inhibits Rho. Other bacteria also make Rho-ADP-ribosylating enzymes (271,590). McKerracher et al. (124,146,328,386–388) used C3 to inhibit Rho and show that it stimulates spinal cord regeneration. To increase entry of C3 into cells, Winton et al. (594) developed a new recombinant form of C3 that has short transport peptides attached to the carboxyl terminal. Called BA-210 or Cethrin, this molecule is a potent Rho inhibitor (351) that prevents secondary damage and promotes functional recovery in rats after acute spinal cord injury. McKerracher et al. (155,389) reported that Cethrin improved neurological recovery in cervical spinal-injured patients, who received 3 mg of Cethrin placed onto their dural surface.

Nonsteroidal anti-inflammatory drugs (NSAIDs) also block Rho. In 2003, Benitah et al. (30) reported that activating RhoA promotes expression of cyclooxygenase-2 (COX-2) at the transcription level that depends on NF-κB but not STAT3 and that treatment with the NSAIDs Sulindac and NS-398 inhibited Rho. Subsequently, Zhou et al. (642) showed that NSAIDs reduced secretion of the highly amyloidogenic agent Aβ42 (56). Fu et al. (179) demonstrated that NSAIDs promote axonal regeneration in the spinal cord. Xing et al. (604) found that RhoA-inhibiting NSAIDs promote axonal remyelination. Kopp et al. (304) observed that the NSAIDs ibuprofen and indomethacin not only inhibit Rho but enhance axonal sprouting and regeneration, as well as protect the spinal cord against secondary damage. However, Sharp et al. (502) were unable to confirm that subcutaneous ibuprofen increased regeneration or recovery after dorsal overhemisection injuries.

Fasudil is a ROCK inhibitor that has been reported to be beneficial in many pathological conditions, from

cardiovascular diseases to pulmonary hypertension and erectile dysfunction (338) and diabetic neuropathy (302). Early studies (216,536) reported that fasudil promoted locomotor recovery in a rat SCI models. However, Nishio et al. (426) were not able to confirm these findings. Chiba et al. (81) reported that while fasudil improved the number of axons crossing the injury site after SCI, the combination of fasudil with bone marrow stromal cells (BMSCs) did not boost these therapeutic effects nor improve neurological recovery. Nevertheless, fasudil continues to attract interest. Several studies reported that fasudil and two other ROCK inhibitors, Y-27632 and dimethylfasudil (H-1152), stimulate neurite outgrowth in culture (347) and peripheral nerve regrowth (369). Fasudil reverses CSPG-induced neurite growth inhibition (197). Several investigators reported that fasudil is neuroprotective in SCI. For example, Ding et al. (130) reported that fasudil protected neurons and mobilized neural stem cells through a granulocyte macrophage–colony-stimulating factor (GM-CSF)-dependent mechanism. Furuya et al. (180) found that intrathecal fasudil and BMSC transplants each reduced lesion volumes and improved locomotor recovery but the combination was not better than the individual therapies. Impellizzeri et al. (251) reported that fasudil reduced secondary injury in acute injured spinal cord. The ROCK-specific inhibitors Y27632 and fasudil both significantly reduce interleukin 6 (IL-6) synthesis (550), which contributes to inflammation-induced CNS regeneration (329). Thus, fasudil may stimulate regeneration in some circumstances and may be neuroprotective in others.

THE GLIAL SCAR THEORY

Astrocytes proliferate in injured CNS (279). Astrocytes normally line capillaries with endfeet to form the blood–brain barrier (277). In 1975, Symon et al. (537, p. 482) described cerebral infarct sites containing "many dilated blood vessels of non-capillary nature scattered among fibrous tissue in what was virtually a glial scar." Subsequent investigators used the term "glial scar" to indicate gliosis of cerebral white matter (196), cerebral cortical gray matter (13,141), lesioned optic nerves (71,92,157,284,503,557), brain, or spinal cord surrounding fetal cell transplants (1,17,49,105,106,183,236, 316,383,452,464–466,473), spinal cord hemisection or transections (42,90,487,493), cerebellum injected with 6-hydroxydopamine (511), retrochiasmatic knife cuts (481), periaqueductal changes in epileptic encephalopathy (484), laser lesions of the retina (563), surgically resected epileptic foci (275), and excitotoxic lesions (142).

The glial scar was not initially considered an impediment to axon growth. In 1979, Reier (463, p. 61) described regenerating optic nerves penetrating "extremely dense glial scar, formed by mature, hypertrophic astrocytes" and concluded that the astrocytes do not "represent a major obstacle to axonal outgrowth." In 1981, Guth et al. (210, p. 297) studied spinal transections in hibernating squirrels, finding that the lesions contained minimal glial and collagenous scarring, but "axons grew to the margin of the lesions where they turned abruptly and continued growing along the interface between the lesion and the spinal cord." They concluded "that 1) mammalian spinal cord neurons have considerable regenerative potential and that 2) such mechanical impediments as collagenous and glial scarring, cyst formation, and cavitation cannot provide the sole explanation of why regeneration in the mammalian CNS is abortive." In 1989, Dahl et al. (101, p. 154) found axons growing through plaques removed from two patients with multiple sclerosis and concluded that "reactive astrocyte forming glial scars do not constitute a non-permissible substrate for axonal growth."

In 1990, Rudge and Silver (475, p. 3594) developed an in vitro model of "astroglial-mesenchymal scar" to ascertain whether it is a "physical barrier blocking the advancement of the growth cone or chemical factors actively inhibiting axon outgrowth." They inserted nitrocellulose filters into the cortex of neonatal rats (1–6 day) and older rats (1–30 day) to collect astrocytes. E18 rat hippocampal neurons grew longer neurites on 1–6-day explants (50% >400 μm) compared with 1–30-day explants (50% >350 μm) or on glial scar (50% >180 μm). When they looked at the neurite outgrowth on cultures with different fibroblast/astrocyte ratios, mean neurite outgrowth did not differ significantly until the fibroblasts exceeded 60% of the cultured cells or a 60:40 ratio of fibroblast to astrocytes. Rudge and Silver considered several mechanisms by which the glial scar could inhibit axonal growth. One possibility is that astrocytes were expressing or secreting an inhibitory factor. A second possibility is that basal lamina forming between astrocytes and fibroblasts blocks axons, but Rudge and Silver (475, p. 3600) considered this possibility to be an "enigma" since basal lamina contains laminin, a potent neurite growth promoter. A third possibility is that fibroblasts are inhibiting axonal growth.

In subsequent studies, McKeon et al. (384,385) from the Silver Laboratory systematically explored each of these possibilities. In 1991, McKeon et al. (385) found that reduction of neurite outgrowth on glial scars correlates with expression of inhibitory molecules on reactive astrocytes, including CSPG and cytotascin/tenascin. McKeon et al. (384) further reported in 1995 that injury-induced proteoglycans inhibit laminin-induced axon growth on astrocytic scars. They treated explants with ChABC, a bacterial enzyme that breaks down CSPG. ChABC significantly increased mean neurite length on glial scars. However, application of antibodies to β-1 and β-2 chains of laminin reversed the beneficial effects of ChABC, suggesting that the laminin contributed to the axonal growth and that eliminating CSPG alone is

not enough. They proposed that CSPG prevents axonal growth, ChABC allows axonal growth, and laminin supports the growth of axons across glial scars.

The concept of glial scar posing an obstacle to axonal regeneration had become firmly entrenched by the early 1990s (44,206,233,384,475). Many investigators started to investigate therapies that may reduce glial scars. Smith and Miller (518) reported that the immature type-1 astrocytes suppress glial scar formation. Soares and McIntosh (519) then showed that fetal cortical transplants can attenuate glial scarring within 2 weeks but not 4 weeks after injury. Houle (233, p. 120) found that transplantation of fetal spinal cord tissues alters the "structural integrity of established scars" in chronic spinal cord injury (233). Some have claimed that lasers reduce scar formation (470). Hermanns et al. proposed that the basement membrane of a collagenous scar obstructs axonal regeneration (224) and that its formation can be prevented by administration of an iron chelator (225). In 2013, Soderblom et al. (520) described perivascular fibroblasts that express collagen in contused spinal cords, suggesting that this is the main source of fibroblasts contributing to glial scars in nonpenetrating injuries of the spinal cord.

Some researchers tried to prevent gliosis with drugs. Early studies suggested that cAMP (514), basic fibroblast growth factor (bFGF) (144), diffusible factors from injured neurons (431), and proinflammatory cytokines (156) induce gliosis. Giulian et al. (193) showed that IL-1b regulates astrocytic growth, and GM-CSF is a potent microglial mitogen that regulates microglial component of glial scars, suggesting that inflammation stimulates gliosis. Sievers et al. (512), however, found that application of IL-1b does not induce reactive astrogliosis, neovascularization, or scar formation in immature rat brains. The glucocorticoid drug methylprednisolone (MP) is a potent anti-inflammatory drug that suppresses IL-1 expression. In 1995, Anghelescu et al. (14) treated one group of rabbits with 30 mg/kg MP at 2, 24, or 48 h after injury, another group with 15 mg/kg MP at 0.5, 2, 24, 48 h after injury, and a control group with saline. MP-treated groups had significantly better hindlimb recovery than control groups. Paradoxically, many regenerated nervous fibers entered the "dense scar of the injured cord" (14, p. 241) in all three groups, suggesting that MP did not prevent gliosis, and gliosis did not prevent axon growth.

Many investigators have studied the causes of gliosis. Rudge et al. (474) found that astrocytes in glial scars express neurotrophin receptors, particularly the low-affinity nerve growth factor receptor $p75^{LNGFR}$ and ciliary neurotrophic factor receptor, suggesting that neurotrophins may contribute to gliosis. Stichel and Muller (533) observed that an early microglial reaction preceded the astrocytic responses, suggesting that the microglial response stimulates astrocytosis. Microgliosis frequently accompanies astrogliosis (549). Frisen et al. (175) observed widespread and long-lasting induction of nestin in astrocytes in injured spinal cords and proposed that nestin contributes to reactive glial scar formation. Oxygen and glucose deprivation also induces astrocytes to adopt glial scar-like properties (575). Finally, albumin stimulates astrocytic proliferation (415). Since albumin is absent from the uninjured CNS and enters where the blood–brain barrier has been damaged, it is a convenient signal for initiating astrogliosis to repair the blood–brain barrier.

Recent studies suggest that astrogliosis involves signaling through the retinoic acid-inducible gene (125), epidermal growth factor (340), or fibroblast growth factor (326). Bone morphogenic proteins (477), type I interferon (254), and STAT3 knockout suppress reactive astrocytosis (226). Lithium blocks STAT3, reduces astrogliosis (644), stimulates regeneration after SCI (126,618). Myelin basic protein (MBP) causes a twofold increase in astrocyte proliferation (410), possibly explaining why MBP vaccines stimulate regeneration (219,220), although such vaccines can also exacerbate the injury (264,265). Iseki et al. (253) showed that the old astrocyte specifically induced substance (OASIS) gene, a member of the cyclic AMP-responsive element-binding protein and activating transcription factor (CREB/ATF), is upregulated in gliotic tissues. Kamei et al. (276) reported that endothelial progenitor cells promote astrogliosis through Jagged1-dependent Notch signaling. Transforming growth factor-β1 (TGF-β1) may play a role in regulating glial activation in vivo (290), although overexpressing TGF-β1 may be beneficial and not deleterious in brain injury (161,602). Lipopolysaccharide or proinflammatory cytokines cause astrocytes to secrete chemokines that are antagonized by TGF-β1 (209).

Astrogliosis repairs the blood–brain barrier and vasculature, restricting inflammation and protecting neurons and oligodendrocytes. Sofroniew (211,521,522) pointed out that reactive astrogliosis has both beneficial and deleterious effects. Like in the gut (521,523), brain astrocytes (485,486) limit the infiltration of peripheral inflammatory cells. Herrmann et al. (226) showed that STAT3 regulates astrogliosis and scar formation after SCI, finding that blocking STAT3 to prevent astrogliosis causes more inflammation, increased lesion volume, and attenuates motor recovery after SCI.

The glial scar theory has led some investigators to cut out the injury site and reopposing the spinal cord stumps to remove the glial scar (623). Since cutting the spinal cord causes glial scar, therapy is needed to prevent glial scar reformation after transection. One approach is to transplant neural stem cells (425), mesenchymal stem cells (446,545), or umbilical cord blood cells (239,630) to reduce glial scars. Several groups have reported beneficial effects of transplanting glial-restricted precursors

to injured spinal cords (584). Davies et al. (110,112,113) have reported that decorin, a small leucine-rich proteoglycan, reduces astrogliosis and basal lamina formation in injured spinal cords.

Some efforts to prevent glial scar formation have worsened chronic outcomes by increasing lesion volumes and neuronal loss in spinal cord injury (211,521,522) and stroke (400). Selective ablation of proliferating astrocytes in mouse models of amyotrophic lateral sclerosis did not alter disease outcome (331). In fact, reactive astrocytes form "scar-like perivascular barriers to leukocytes during adaptive immune inflammation of the CNS" (568, p. 11511). Wanner et al. (583, p. 12870) reported that proliferated elongated astrocytes "corral inflammatory and fibrotic cells via STAT3-dependent mechanisms" after SCI. Stat3 is a critical regulatory of astrogliosis and scar formation after SCI (226). Delayed expression of cell cycle proteins contributes to astroglial scar formation and chronic inflammation in the spinal cord (599). Treatments that block astrogliosis not only do not improve regeneration but may worsen the injury (523).

CHONDROITIN SULFATE PROTEOGLYCAN THEORY

Astrocytes line the interfaces of the central nervous system and peripheral tissues (203). The extracellular matrix at the interface contains chondroitin sulfate, a sulfated glycosaminoglycan (GAG) that consists of unbranched chains with alternating sugars: *N*-acetylgalactosamine and glucuronic acid. GAG chains may have over 100 sugars that are sulfated in different positions and to different extents. Sulfation at the 4-positions of the *N*-actylgalactosamine inhibits neurite extension (191,573), while sulfation at the 6-position may have a positive influence on axon regeneration (345). Interestingly, *N*-acetylglucosamine 6-O-sulfotransferase-1-deficient mice show better functional recovery after SCI (255). Proteins attached to chondroitin sulfate are called chondroitin sulfate proteoglycans (CSPGs).

ChABC removes GAG chains from proteoglycans. Many investigators used ChABC to facilitate regeneration in injury models (47). In 1998, Zuo et al. (649) showed that sections of injured spinal cords treated with ChABC supported more neuritic growth than sections treated with enzymes that broke down dermatan sulfate or hyaluronan. Lemons et al. (330) found that injury upregulated CSPG in the spinal cord, and ChABC reduced CSPG in the spinal cord. Yick et al. (619) showed that ChABC stimulated Clarke's neurons to sprout and to grow beyond glial scar and that lithium reinforces the regeneration-promoting effects of ChABC on the rubrospinal tract (617). In 2002, Bradbury et al. (48) found that chABC degraded CSPG GAGs, promoted regeneration of ascending sensory projections and descending corticospinal axons, restored postsynaptic activity in caudal spinal cord, and improved locomotor recovery and proprioceptive behaviors in rats after spinal cord hemisection. This seminal paper attracted much attention to CSPG as the cause of regeneration failure. Many investigators subsequently studied the effects of ChABC on axon growth in other spinal cord injury models.

Investigators have applied ChABC directly into injured spinal cords (43,48,60,73,165,184,185,243,252,257,330, 378,379,418,531,547,552,617–619), intraventricularly (186), in subdurally implanted materials (247), or intrathecally (24,63,64,100,186,240,248,252,294,332,344, 418,428,436,439,505,547,603). ChABC has been part of many combination therapies, including transplanted neural progenitor cells (249,280,281,510), olfactory ensheathing glia (166,241,566,632), bone marrow cells (96,259,300,367,560,581,639), peripheral nerve grafts (80,95,234,235,237,327,552,554,555,617,619), Schwann cells (203,591), and Schwann cell-seeded bridges (55,75, 165,166), neural stem cells (54,165,249,294,566), immature astrocytes (159), adult olfactory mucosa (241), neurotrophins (188,350,378), Nogo receptor blockers (87,99, 188,378), L1 cellular adhesion molecule (321), or other drugs (417,579,637).

ChABC may act though multiple mechanisms. Many studies have shown that ChABC degrades CSPG (19,247, 260,344,365,572,580,613,618) and promotes morphological plasticity with (24,60,64,184,314,320,379,547) and without functional recovery (140,218,234,553), regenerates spinal respiratory pathways (9), reduces glial scars (9) and axon dieback (58), reverses rubrospinal atrophy (72,257), improves axonal conduction (243) and locomotor recovery (243), stimulates remyelination (281,450), and increases migration of oligodendroglial (510) and neural progenitor cell (516) migration.

ChABC has a short half-life at body temperatures. Lee et al. (320) reported that sustained release of thermostabilized chABC enhanced axon sprouting and functional recovery after spinal cord injury. Nazari-Robati et al. (420) also showed that cosolvent thermal-stabilized chABC is better than standard chABC for degrading CSPG and improving recovery after SCI. Pakulska et al. (439) developed a modified methylcellulose hydrogel that releases ChABC over time. Some have genetically modified cells to secrete ChABC (63,100,300,367,407,428).

Other enzymes break down CSPG or interfere with CSPG interactions with membrane receptors. For example, DNA enzymes degrade CSPG and improve axonal growth (204). Sialidases improve axonal growth (405, 610), perhaps by modifying membrane receptors to CSPG. Bukhari et al. (53) reported that mice lacking tissue plasminogen activator (tPA) have blunted axonal growth to ChABC therapy applied after SCI, suggesting that the chABC effects depends on tPA. Imagama et al. (250) used keratanase II to degrade keratin sulfate and found that it

promoted sprouting and improved functional recovery but was neither additive nor synergistic with ChABC. Matrix metalloproteinases (MMPs) degrade the core proteins of CSPG (98). An endogenous MMP called A disintegrin and metalloprotease with thrombospondin motifs 4 (ADAMTS-4) promotes functional recovery after SCI (544). Finally, Yoo et al. (621) used arylsulfatase B to degrade chondroitin sulfates and observed significant improvements of locomotion.

Many other factors affect the production of CSPG. In 1987, Erickson and Turley (149) found that epidermal growth factor (EGF) stimulates the release of both heparan sulfate proteoglycan (HSPG) and CSPG in cultures of quail trunk neural crest cells. High-dose MP reduces CSPG (620). The growth factor midkine (MK) is produced by activated astrocytes and binds CSPG to overcome its inhibition of neurite growth (411). Conditional sex-determining region Y box 9 (Sox9) ablation reduces CSPG and improves locomotor recovery in rats after SCI (390). Many enzymes that cleave CSPG are induced by injury (122), including metalloproteinases (98).

There are other ways to reduce CSPG. For example, lentivirus delivery of interfering RNA (RNAi) targeting two key CSPG-synthesizing enzymes, chondroitin polymerizing factor and chondroitin synthetase-1, reduced CSPG and inhibition of neurite growth (560). Acidic fibroblast growth factor (FGF-1) reduces CSPG deposition in animals grafted with peripheral nerves (326). In 2004, Davies et al. (112) reported that decorin, a small leucine-rich proteoglycan that has been previously shown to reduce astrogliosis and basal lamina formation, suppresses neurocan, brevican, phosphacan, and NG2 expression and promotes axon growth in spinal-injured rats. Decorin also promotes plasminogen/plasmin expression in acute SCI and adult microglia in vitro (111). In addition, decorin directly stimulates neurons to grow on inhibitory CSPG and myelin (398) and improves recovery in contused spinal cords (397).

CSPG tends to associate with certain situations and cells. In arteries, CSPG tends to associate with low-density lipoproteins (245). One CSPG expressed on cell surfaces and immunologically similar to cluster of differentiation 44 (CD44) appears to contribute to the metastasis of melanoma (69,223,246) and glioblastomas (194). B lymphocytes secrete a soluble CSPG that inhibits complement fixation (297). Mammalian CSPG is rich with an unusual amino acid isoaspartate (107). CSPG and HSPG compete for the same heparin III domain of fibronectin (406). During development, CSPGs expressed along tracts contribute to guiding axonal growth (593).

Exposure to CSPG affects many proteins inside cells. Yu et al. (627) recently identified 118 of 2,215 phosphopeptides, corresponding to 1,118 phosphoproteins that varied significantly in response to exposure to CSPG. Proteins regulated by CSPG include cytoskeletal and related proteins that regulate neurite growth and nuclei acid-binding proteins. Interestingly, the effects of CSPG on neurite growth depend on several intracellular messengers, including protein kinase C (390). Intra-axonal translation of RhoA promotes axon growth inhibition by CSPG.

One important member of the CSPG family is NG2 (neuron-glia antigen 2), also called chondroitin sulfate proteoglycan 4 (CSPG4). Expressed by proliferating oligodendroglia precursor cells (OPCs), NG2 shows up early in injured spinal cords and remains for at least 4 weeks after injury (392). Clonal analyses of $NG2^+$ cells isolated from injured spinal cord indicate that the cells are glial progenitors (622) that interact with microglia (600) and can form both oligodendroglia and astrocytes (267). $NG2^+$ cells are present in injured human spinal cords (59) and can be produced from human embryonic stem cells (535). NG2 is also expressed in brain injury (616).

$NG2^+$ cell proliferation peaks at 3 days after SCI (363,364), and $NG2^+$ cells colocalize with axons (391). Other CSPGs, including versican, brevican, neurocan, and phosphacan, are only modestly upregulated or downregulated shortly after SCI (263). After stab wounds of the spinal cord, neurocan, NG2, and tenascin-C peak at 8 days, and phosphacan and brevican peak at 1 month (543). In transected spinal cords, the stumps are separated by collagenous connective tissues bordered by $NG2^+$ OPCs (116) that express retinoic acid (288,394) and are associated with stem cells expressing radial glia markers (598).

Manipulations of NG2 expression have yielded conflicting results. Genetic deletion of NG2 is not associated with regeneration or improved recovery, although lentiviral vector-mediated knockdown of NG2 promotes neurite outgrowth in culture models of glial scars (137). Adult $NG2^+$ cells promote neurite outgrowth and prevent axon dieback (57). MMP-9 controls proliferation of NG2 cells (348). ChABC breaks down NG2 (428). Silencing NG2 with short hairpin siRNA promotes locomotor recovery and neutralization of NG2 with antibodies and also improves locomotor recovery after SCI (136). Injections of NG2 into the spinal cord acutely depressed axonal conduction through the injected region with a dose–response curve (243). However, the soluble glial growth factor 2 (GGF2) and bFGF stimulate growth of $NG2^+$ cells and improve functional recovery in mice after SCI (588).

Scientists have long thought that CSPG blocked axonal growth by hindering binding of membrane receptors to extracellular matrix molecules (500). In 2004, Jain et al. (256) reported that inhibiting Rho alleviated CSPG-induced inhibition of neurite extension, suggesting that CSPG acts on Rho-based receptors. CSPG may activate NgR2 and NgR3 to turn on Rho (500). Inhibition of ROCK

prevented CSPG inhibition of axonal regeneration and oligodendrocyte process outgrowth and myelination (450). Finally, intra-axonal translation of RhoA promotes axon growth inhibition by CSPG (569), suggesting that CSPG effects are mediated by Rho and ROCK.

In 2005, Sapieha et al. (480) reported that receptor protein tyrosine phosphatase ς (RPTPς) inhibits axon regrowth in adult injured optic nerve. In 2009, Shen et al. (504) found that RPTPς and other members of the leukocyte antigen-related (LAR) family are receptors for CSPGs. Ablation of Ptprs, the gene encoding for PTPς, promotes neurite outgrowth into CSPG-rich scar tissue following SCI (140). Fry et al. (178) reported that RPTPς-deficient mice regrow corticospinal axons over long distances after dorsal hemisection or contusion injury. RPTPς acts bimodally, mediating both CSPG inhibition of axonal growth and HSPG facilitation of axonal growth (82). When RPTPς expression is low on axons, they can grow on CSPG surfaces (289). CSPG inhibits oligodendrocyte myelination through RPTPς (450). Small molecule blockers of RPTPς are being developed (377).

MANIPULATING GROWTH CAPABILITY OF NEURONS

Scientists have long known that a conditioning lesion will enhance peripheral nerve growth. In 1983, Bisby et al. (33) reported that a conditioning crush lesion of the sciatic nerve at the knee 7 days before a lesion of the nerve at the hip will increase axon growth rates from 4.02 ± 0.03 mm/day to 5.73 ± 0.06 mm/day, an increase in growth rate by 68%. In 1985, Bisby and Keen (32) confirmed that conditioning lesions enhanced growth rates of both small- and large-diameter axons. Conditioning lesions also work for sudomotor axons. The conditioning is ineffective <2 days after the test lesion (258), is significant after 5 days, and continues for 14–28 days and not only enhances the rate of growth and the number of regenerated axons (40) but also the ability of the axons to grow in different environments (258). For example, in 1989, Cho and So (85) discovered that a concurrent optic nerve crush enhances regrowth of a retinal ganglion axon into a peripheral nerve graft in an adult hamster. Conditioning lesions of peripheral nerves improves the ability of axons to regrow across a predegenerated portion of the nerve (21,145,437). Inflammation enhances the conditioning effect (102,360). The conditioning effect can be achieved by compression without cutting the nerve (103,104).

Conditioning peripheral nerve lesions changes the behavior of sensory dorsal root ganglion (DRG) neurons. In 1998, Lankford et al. (318) examined changes in DRG neurons after peripheral nerve lesions. They found that isolated DRG neurons from lesioned peripheral nerves showed earlier neurite initiation after injury. Exposure of the cells to denervated peripheral nerves stimulated greater initial rates of neurite outgrowth. The conditioned neurons grew longer neurites and branched less frequently than neurons that had not been conditioned. Clearly, a prior injury to the peripheral nerve causes significant changes in the behavior of dorsal root ganglionic neurons that persist even when the cells are isolated in culture.

The effects of conditioning lesions were initially thought to be limited to the peripheral branch of DRG neurons because Oblinger and Lasek (430) reported that peripheral nerve axotomy did not affect regenerative properties of the central branch of DRG neurons. However, in 1989, Ebner et al. (143) demonstrated that peripheral nerve damage facilitates functional reinnervation of brain grafts in the adult sensory cortex. They were studying embryonic neocortical transplants that typically did not survive long after transplantation unless they were innervated by thalamic neurons. However, when they transected peripheral nerves before grafting, the grafted cells survived better because they receive more innervation. In 1995, Woolf et al. (597) revealed that peripheral nerve lesions caused massive reorganization of central terminals in the dorsal gray horn. In 1999, Neumann and Woolf (423) showed that peripheral nerve injuries enhanced central DRG axon growth across dorsal column lesions made 2 weeks later.

Peripheral nerve lesions upregulate transcription factors and gene expression in DRG neurons (423). Peripheral nerve injury and neurotrophins upregulate activating transcription factor 2 (ATF-2) in nociceptive DRG neurons and may be responsible for development of neuropathic pain (120). In 2005, Qiu et al. (456) showed that the sciatic nerve transection causes transient phosphorylation and activation of the transcription factor STAT3 in DRG neurons. Blockade of STAT3 prevents the effects of peripheral nerve injury conditioning. For example, infusion of AG490, a janus kinase 2 (JAK2) inhibitor, blocks STAT3 phosphorylation and attenuates dorsal column axon regeneration after a sciatic nerve lesion. In 2006, Seijffers et al. (498) proposed that ATF-3 promotes the neurite outgrowth of DRG neurons after peripheral lesions. Peripheral nerve, but not spinal cord, lesions induce ATF-3 expression in DRG neurons. ATF-3 promoted growth of long and sparsely branched neurites in cultured DRG neurons. Seijffers et al. (499) subsequently reported that ATF-3 increases intrinsic growth state of DRG neurons but does not overcome the inhibitory effects of myelin or promote central axon regeneration in the spinal cord.

Schwann cells may play a role in the conditioning effects. In addition to facilitating peripheral axon growth, Schwann cell implants may serve as preconditioning stimuli for the CNS. Wills et al. (592) transplanted Schwann cells into rat motor cortex and showed that the transplants

stimulated corticospinal tract (CST) to sprout in rostral spinal cord gray and white matter of rats, compared to rats that received only cortical vehicle injections. These findings provide further rationale to transplant Schwann cells to treat spinal cord injury, not just at the injury site but also close to cell bodies of neurons that one wants to regenerate (524). Schwann cells invade the injury site of severely contused spinal cords (29,38,52), and the Schwann cells not only myelinate central axons but facilitate axonal growth (35,88,222,478) and improve locomotor recovery (7,23,77, 187,195,308,309,376,447,606) in the animals.

cAMP contributes to peripheral nerve conditioning. In 2002, Neumann et al. (422) reported that elevating cAMP in DRG induces regeneration of sensory axons within injured spinal cord. Lu et al. (359) found that injecting cAMP preinjury and neurotrophin 3 (NT-3) postinjury into L4 DRG will stimulate dorsal column regeneration. One to 3 months later, long-projecting dorsal column sensory axons regenerated beyond cervical spinal cord lesions engrafted with autologous BMSCs. This did not occur in untreated animals or in animals that received only cAMP injection in the root or only NT-3 administration to the spinal cord. Blesch et al. (37) compared the effects of sciatic nerve crush with effects of cAMP elevations in the lumbar dorsal root ganglia, finding that the former has much greater and more persistent effects on central axonal growth than cAMP alone. In 1999, Cai et al. (66) reported that prior exposure to neurotrophins prevented inhibition of axonal regeneration by MAG and myelin via a cAMP-dependent mechanism. Cai et al. (65) found that cAMP levels are dramatically higher in young neurons, suggesting that cAMP regulates growth potential of young versus adult neurons.

The Filbin Laboratory (133,458,527) subsequently proposed that cAMP might be therapeutically beneficial for CNS regeneration. Scientists have long known that cAMP influences axonal growth (472). In 1980, Gunderson and Barrett (207) reported that chick DRG axons swerve toward sources of mono- and dibutyryl cAMP (dbcAMP) and cyclic guanosine monophosphate (cGMP). They proposed that both cAMP and cGMP play a role in the turning responses of growth cones. In 1981, Gunning et al. (208) found that dbcAMP and nerve growth factor (NGF) have additive or synergistic, different timing and half-maximal concentrations, and different effects on growth cone morphology. They concluded that cAMP and NGF affect growth cone growth through independent mechanisms. NGF increases microtubular density, while dbcAMP increases neurofilament density (131). While cAMP causes growth cone turning, cGMP does not (457). In 2002, Qiu et al. (458) showed that peripheral nerve lesions triple cAMP levels in DRG neurons, and MAG/myelin no longer inhibited axonal growth from affected DRG neurons. They proposed that cAMP is responsible for the preconditioning effect of peripheral nerve lesions. Qiao et al. (455) showed that cAMP-dependent protein kinase (PKA) inhibits RhoA activation.

Neuronal cAMP levels regulate growth cone behavior (65). In 1998, Song et al. (525) reported that neuronal growth cone can be converted from repulsion to attraction by cyclic nucleotides. Normally, collapsin-1/semaphorin IIID and MAG will, respectively, collapse and repulse growth cones. Activation of cGMP inhibits growth cone collapse and converts the repulsive effects of MAG to attraction. In 2005, Chierzi et al. (83) demonstrated that the ability of axons to produce growth cones depends on axonal type and age and is regulated by calcium, cAMP, and extracellular signal-regulated kinase (ERK). In 2008, Aglah et al. (6) showed that cAMP promotes neurite outgrowth through PKA but not ERK activation in cultured rat motoneurons. Xu et al. (605) reported that both cAMP and PKA activation increases neurite length in culture but that the cAMP analog 8-4(4-chlorophenylthio)-cAMP (cpt-cAMP) has a biphasic effect on neurite length.

Many ways are available to increase cAMP in neurons (158,213,214). Adenyl cyclase produces cAMP. In 1984, Kilmer and Carlsen (292) reported that forskolin, a potent activator of adenylate cyclase, stimulates nerve regeneration in vivo. Derived from the Indian herb *Plectanthus barbatus*, forskolin rapidly and reversibly activates adenylyl cyclase (8). Forskolin increases motoneuron axonal regeneration in peripheral nerves (440) and stimulates outgrowth of lamprey reticulospinal tracts. In 1988, Oh et al. (433) found that a muscle-derived substrate-bound factor promotes neurite outgrowth from neurons. Further analysis revealed that this factor is cAMP-dependent phosphokinase (cAMP-dPK). Chijiwa et al. (84) later showed that pharmacological inhibition of cAMP-dPK blocks the effects of forskolin on neurite growth. Yusta et al. (629) compared forskolin, dbcAMP, and butyrate effects on neuroblastoma cells, finding that both forskolin and dbcAMP caused extensive neurite outgrowth, but dbcAMP did so more than forskolin. Butyrate alone stimulated neurite growth and elevated histone concentration, which was not seen in forskolin-treated and untreated cells, suggesting that dbcAMP effects may be a combination of both butyrate and cAMP effects. Other factors can stimulate adenyl cyclase, including cholera toxin (501).

Another approach to increase cAMP is to block its degradation by phosphodiesterase 4 (PDE4). In 2004, Nikulina et al. (424) reported that rolipram, a CNS-specific PDE4 inhibitor that crosses the blood–brain barrier, increases spinal axon growth across a C4/5 hemisection bridged by embryonic spinal tissue. In the same year, Pearse et al. (448) found that a combination of dbcAMP, Schwann cell transplants, and rolipram treatment of contused spinal cords resulted in increased axonal sparing, myelination,

and serotonergic axonal growth into and beyond the injury site. Flora et al. (162) showed that neurotrophin-transduced Schwann cells and rolipram promotes functional recovery in rats. Rolipram reduces microglial activation (190) and is neuroprotective (488). Bao et al. (22) found that PDE4 inhibitor IC486051 reduced leukocyte infiltration, oxidation, and tissue damage after SCI.

Several investigators have reported beneficial effects of cAMP administration in various SCI models. In 2004, Lu et al. (359) observed that combinatorial therapy with neurotrophins and cAMP allows sensory axonal regeneration beyond the injury site. Pearse et al. (449) reported that the combination of Schwann cells, dibutyryl cAMP, and rolipram (a phosphodiesterase-4 inhibitor) promotes axonal growth and functional recovery after spinal cord injury. Kajana and Goshgarian (273,274) showed that activation of cAMP–PKA pathway induces respiratory motor recovery after high cervical SCI. Bretzner et al. (51) describe a combination of olfactory ensheathing glia and cAMP increasing the regeneration of rubrospinal tract. Montoya et al. (402) showed that cAMP promotes both survival and neurite outgrowth of adult spinal cord motoneurons. Murray et al. (412) found that cAMP in combination with cGMP promotes neurite outgrowth on spinal cord tissue. Myeku et al. (413) recently revealed that cAMP stimulates the ubiquitin proteasome pathways in rat spinal cord neurons, reducing the accumulation of ubiquinated proteins. Malone et al. (373) showed that neuronal activity promotes myelination via a cAMP-dependent pathway.

One worrisome possibility is that cAMP will aggravate neuropathic pain. Many people with SCI suffer from neuropathic pain. For example, cAMP contributes to mechanical hyperalgesia and allodynia induced by ID injection of capsaicin (517). Intrathecal injection of CREB attenuates tactile allodynia caused by partial sciatic nerve ligation (366), suggesting that increased cAMP stimulates sprouting that can lead to neuropathic pain. Activation of the ERK/CREB pathway in the spinal cord aggravates chronic constrictive injury-induced neuropathic pain in rats (526). However, preconditioning nerve lesions inhibit allodynia and mechanical pain hypersensitivity associated with a subsequent partial peripheral nerve lesion known to cause neuropathic pain (401). Thus, during administration of cAMP, care must be taken to avoid overstimulation of neuronal growth leading to neuropathic pain.

GENETIC MANIPULATION OF REGENERATION

In 2010, Liu et al. (349) reported that deletion of the PTEN gene enhances regeneration of the CST in rats, allowing large numbers of injured CST axons to grow beyond the injury site for the first time. This finding electrified the SCI research community because it provided the first demonstration that deletion of a single gene allowed substantive regeneration of the corticospinal tract after SCI, even though nothing was done to remove myelin-based axon growth inhibitors or CSPG.

PTEN deletion stimulates corticospinal tract growth through the AKT/mTOR pathway. As illustrated in Figure 1, adapted from Park et al. (442), PTEN affects AKT/mTOR through the following steps. Receptor tyrosine kinase (RTK) catalyzes conversion of phosphoinositol phosphate 2 (PIP2) to phosphoinositol phosphate 3 (PIP3). PTEN catalyzes the conversion of PIP3 to PIP2. When PTEN is knocked out or silenced, PIP3 accumulates and activates AKT through phosphoinositide dependent protein kinase-1 and 2 (PDPK1/2). AKT inhibits tuberous sclerosis complexes 1 and 2 (TSC1 and TSC2), which inhibit Ras homolog enriched in brain (Rheb1). Rheb1 normally stimulates mTOR. Therefore, deleting or silencing PTEN turns on mTOR to stimulate cell growth.

Many drugs activate AKT. For example, angiopoietin-1 promotes neuronal differentiation in neural progenitor cells through the AKT pathway (20). At doses that stabilize mood in manic depression, that is, 0.6–1.2 mM serum levels, lithium activates AKT (74,582,614). Cytokines and growth factors activate phosphoinositol-3-kinase (PI3K) to phosphorylate PDPK1, which activates AKT and other kinases (181). Mice lacking PDPK1 die during embryonic development, while PDPK1-deficient mice are small but resistant to hyperactivation of PI3K pathway induced by partial deletion of $PTEN^{+/-}$ (404). The growth factor bFGF also stimulates the PI3K/AKT/GSK3b and ERK1/2 pathways (633).

The AKT/mTOR pathway is closely related to the GSK3b pathway. AKT inhibits GSK3b, the same enzyme that lithium inhibits (299). GSK3b normally phosphorylates and activates glycogen synthetase, which converts glucose to glycogen when there is surplus of glucose. GSK3b also inhibits NFAT and Wnt/β-catenin, which respectively stimulate proliferation of neural stem cells (459) and neurogenesis (644). Finally, synaptic stimulation of mTOR is mediated by Wnt signaling and regulation of GSK3b (381). Thus, AKT activation by growth factors, PTEN suppression, or lithium converts the cell from a storage mode to a growth mode.

Suppression of PTEN and activation of the PI3K/AKT/mTOR pathway is an established oncogenic driver (438). Deletion of PTEN induces many types of cancers, including human liver cancer (79), bladder cancer (93), prostate cancer (34,89,635), glioblastoma (152,539), gastric and colorectal cancer (86,441), urothelial carcinoma (454), pleural mesothelioma (5), thyroid cancer (567), cholangiocarcinoma (624), and endometrial cancer (337). Indeed, PTEN mutations are among the most frequently found genetic changes associated with cancer (471). Therapies that suppress PTEN therefore must be cautiously applied to avoid tumorigenesis and cellular overgrowth. If possible, the PTEN suppression therapy should be restricted to only the cells that need to be regrown.

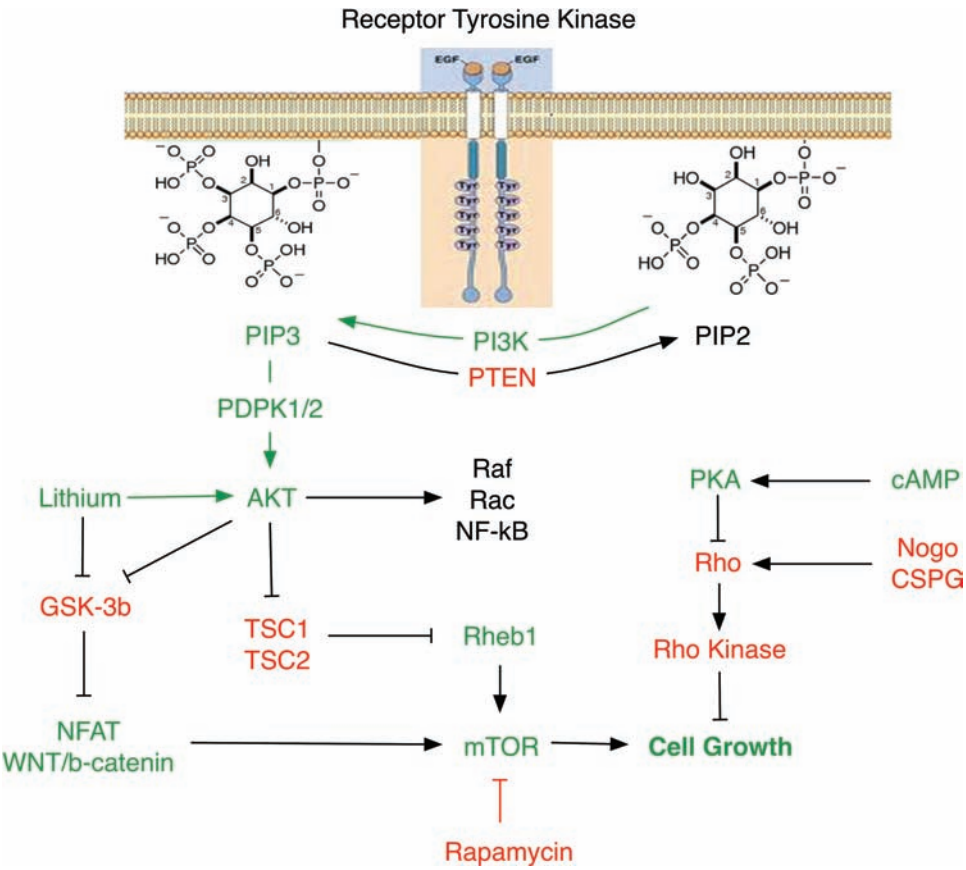

Figure 1. Interacting pathways for PTEN, cAMP, and GSK3b. PTEN (phosphatase and tensin homolog) catalyzes conversion of PIP3 (phosphoinositol phosphatase 3) to PIP2 (phosphoinositol phase 2). PIP3 activates AKT (phosphokinase B) through PDPK1 (phosphoinositide-dependent protein kinase 1). AKT stimulates inflammatory messengers Raf/Rac/nuclear factor of κ light polypeptide gene enhancer in B-cells (NF-κB) and inhibits TSC1/2 (tuberous sclerosis complexes 1 and 2). TSC1/2 inhibits Rheb1 (Ras homolog enriched in brain 1). Rheb1 activates mTOR (mammalian target of rapamycin) to stimulate protein synthesis and cell growth. Thus, silencing PTEN results in PIP3 accumulation, which activates AKT through PDPK1. Lithium also activates AKT and inhibits GSK3b (glycogen synthetase kinase 3 beta), which normally inhibits NFAT (nuclear factor of activated T-cells) and wingless-type mouse mammary tumor virus (MMTV) integration site family member Wnt/β-catenin. AKT activation also inhibits GSK3b, which disinhibits Wnt/β-catenin and NFAT to stimulate cell proliferation and to activate mTOR. The messenger cAMP (cyclic adenosine monophosphate) turns on PKA (phosphokinase A), which inhibits Rho and Rho-kinase. Rho and Rho-kinase, when activated by axonal growth inhibitors Nogo and CSPG (chondroitin-6-sulfate-proteoglycan), inhibit cell growth. Red stops growth; green increases growth.

PTEN also may play a role in inducing pluripotent stem cells (147,268). Pomerantz and Blau (453) recently proposed that other evolutionarily conserved tumor suppressors, such as the retinoblastoma-like 1 (pRB1), tumor protein 53 (p53), and Hippo, also suppress regenerative processes. On the other hand, PTEN controls pancreatic β-cell regeneration in aged mice by regulating cell cycle inhibitor p16 (632) and microRNA-21 (miRNA-21), which inhibits the PI3K/AKT pathway to reverse insulin resistance (346). Transient silencing of PTEN in human $CD34^+$ cells enhance their proliferative potential and ability to engraft (295). PTEN inhibition improves wound healing in lung epithelia (396).

Deletion or mutations of PTEN strongly enhances neuronal growth and proliferation (41). PTEN mutations (471) are associated with macrocephaly, neuronal arborization (315), seizures (182), Lhermitte–Duclos disease (18,469), and synaptic abnormalities (171). These effects of PTEN loss result from activation of the AKT/mTOR/S6k pathways and inactivation of GSK3b and can be partly blocked by pharmacological inhibition of mTOR (438). Kazdoba et al. (286) recently described a novel conditional PTEN knockout mouse (NEX-PTEN) in which Cre, under the control of NEX promoter, drives PTEN deletion in early postmitotic excitatory neurons in the developing forebrain. Homozygous mutant mice develop a massive forebrain enlargement and die shortly after birth due to excessive mTOR activation.

Recently, Zukor et al. (646) used RNA-silencing treatment adeno-associated virus short hairpin PTEN (AAV-shPTEN) to shut down PTEN and found massive

regrowth of CST axons in mice. They showed that animals that have silenced PTEN are able to grow through fibronectin-expressing fibroblasts and CD68-positive macrophages (647). They were, however, surprised to find that almost all the regenerating CST axons grew through dense glial fibrillary acidic protein positive ($GFAP^+$) astrocytes. Zukor et al. (648) had earlier shown that regenerating axons grew readily through glial scars, suggesting that meningeal and glial cells provide a permissive environment for axonal regeneration.

Several other genes may regulate the growth potential of neurons. In particular, the suppressor of the cytokine signaling 3 (SOC3) gene negatively regulates the glycoprotein 130 (gp130)-STAT3 pathway (643). Both SOC1 and SOC3 play a role in Wallerian degeneration after peripheral nerve injury (192) and experimental autoimmune encephalomyelitis (529). Exercise-induced activation of STAT3 increases with age (556). Blackmore et al. (36) recently reported that overexpressing KLF7 (Kruppel-like factor 7) overcame the developmental loss of regenerative ability in cortical slice cultures. Adult corticospinal neurons do not upregulate KLF7 after injury.

Lithium has been used for more than 50 years as the reference therapy for manic depression and has many effects on bone marrow and brain (625). In 2002, Sassi et al. (483) reported that lithium increased gray matter volume in patients treated with lithium for bipolar disorder. Since then, many investigators have confirmed that lithium increases gray matter volumes in both bipolar and healthy subjects. In 2007, Kempton et al. (287) did a meta-analysis of 98 structural imaging studies of bipolar disorder and showed that gray matter volume significantly increased among patients taking lithium ($p = 0.004$), particularly the hippocampus (564) and dentate gyrus (39,215). In 2008, Moore et al. (403) found significant increases of gray matter volume after 4 weeks of lithium therapy. Lyoo et al. (362) confirmed that lithium induces sustained increases in cerebral gray matter volumes in patients with bipolar depression.

In 2004, Yick et al. (618) reported that lithium reinforces the regeneration-promoting effects of ChABC on the rubrospinal tract after spinal cord hemisection. Retrograde labeling of the red nucleus suggested that as much as 40% of the rubrospinal tract may have regenerated as a result of the combination of the two treatments, more than either treatment alone. Lithium inhibits GSK3b, which promotes axonal growth (126,618), stimulates proliferation of neural stem cells (534) and neurogenesis (31,160,416,435,562) through canonical Wnt/β-catenin activation (551,587) and suppresses astrogliogenesis by inhibiting STAT3 (644). In 2008, Dill et al. (126) demonstrated that the inactivation of GSK3b by lithium and specific GSK3b inhibitors markedly stimulates axonal growth of many neuronal types in culture and in several different SCI models, restoring locomotor function as well as stimulating growth of corticospinal and other long spinal tracts. GSK3b blockers will reverse the CSPG inhibition of neurite growth.

Lithium acts through multiple mechanisms to stimulate neuronal growth (625). In addition to directly inhibiting GSK3b (299), lithium inhibits phosphokinases (74) and activates phosphatases that, respectively, inhibit and activate GSK3b. GSK3b normally inhibits NFAT and Wnt/β-catenin, two nuclear factors that turn on genetic programs for cellular growth and differentiation. Thus, lithium disinhibits NFAT and Wnt/β-catenin. In addition, Zhu et al. (644) recently discovered that lithium strongly inhibits STAT3 to inhibit astrogliosis. STAT3 is a transcription factor that stimulate astrogliosis (2,226,414,434,559), oncogenesis (609), and hematopoiesis (432). Lithium treatment should reduce glial scarring and increase neurogenesis by neural stem cells. Injury activates STAT3 (608). STAT3 is implicated in glial scar formation in injured spinal cord (226,414,434) and microglia proliferation (2,134,135) that may contribute to neuropathic pain. STAT3 is also a well-known oncogene (399,609). In 2005, Qiu et al. (456) reported that conditioning injury-induced spinal axon regeneration requires STAT3 activation. Sustained perineural infusion of the JAK2 inhibitor AG490 to the proximal stump of the sciatic nerve prevents the spinal cord regeneration associated with a conditioning peripheral nerve injury.

Two clinical trials have evaluated the safety and efficacy of lithium treatment of chronic SCI. Wong et al. (595) did a 3-month open-label single-arm trial evaluating the safety and pharmacokinetics of oral lithium in people with chronic SCI, showing that the drug can be safely titrated and given to people with chronic SCI. Yang et al. (611) assessed the efficacy and safety of lithium carbonate therapy of chronic SCI in a double-blind placebo-controlled randomized clinical trial. No severe adverse event occurred in the study. Although lithium did not change motor or sensory scores of the patients, it revealed an unexpected beneficial effect of lithium on pain. Lithium-treated subjects with severe pain reported significant reduction of pain, not only during the 6-week period of lithium treatment but at 6 months, 4.5 months later. Usually, a rebound of pain occurs after an analgesic is stopped, suggesting that this effect of lithium is different from simply suppression of pain.

REGENERATING THE SPINAL CORD

Almost every paper reporting a therapy that regenerates the spinal cord starts by repeating the mantra that the spinal cord cannot regenerate. This mantra seems a bit silly since many laboratories have reported therapies that regenerate the spinal cord. For example, many investigators have reported that injured spinal axons will grow across SCI sites transplanted with mesenchymal stem

cells (230,444,460,476), neural stem cells (352,355,357–359,636), olfactory ensheathing glia (513,538,548,645), Schwann cells (23,67,195,591), or bone marrow cells (310,370). Spinal cords regenerate after treatment with cAMP and Schwann cells (164,448,457), lithium (126,618), or PTEN deletion (349,646).

In 1997, the Multicenter Animal Spinal Cord Injury Study (MASCIS) published a study of histological changes in 610 contused rat spinal cords, describing axon growth into the lesion site at 6 weeks after injury (29). Many fibers grew into the injury site. Paradoxically, the fiber ingrowth was greatest with the spinal cord with the most severe injuries. The more white matter was present, the less the fiber ingrowth. In spinal cords with little spared white matter, thousands of axons penetrated into the contusion site, particularly surrounding the central canal where there are usually relatively few axons. Electron microscope examination of toluidine-stained sections revealed both myelinated and unmyelinated axons in the cavity. These fibers must have grown through the gliosis that surrounds the contusion site. Many axons clearly originated from dorsal roots. In 2001, Hill et al. (227) assessed the origins of fibers that grew into the contusion site. The CST was destroyed by the contusion and died back with retraction bulbs present from 1 day to 8 months after injury. Between 3 weeks and 3 months, many CST axons penetrated into the lesion matrix. Reticulospinal fibers were observed at 3 months and more extensively at later time points. To get into the injury site, these axons grew through degenerated white matter and through gliotic tissues surrounding the contusion site.

Do reactive astrocytes stop axonal growth? In 1990, Mounsour et al. (374) classified reactive astrocytes into permissive and nonpermissive types based on expression of hyaluronate-binding protein (GHAP). Anisomorphic glia (reactive astrocytes at CNS stab wounds) did not express GHAP but isomorphic glia (reactive astrocytes found in areas of Wallerian degeneration in spinal cord) expressed GHAP for 5 months after injury. Axons grew into dense anisomorphic glial scars surrounding graft and stab wound sites but not into GHAP-expressing isomorphic glial scars. However, in 1992, Bovolenta et al. (44,45) reported that all cultured astrocytes, regardless of lineage, morphology, immunologic type, and treatment with differentiating agents, supported profuse neurite outgrowth from many types of embryonic CNS neurons. However, membrane fragments from isomorphic gliotic tissue induced by excitotoxic injury inhibited neurite growth like myelin. Growing neurites grew freely into areas covered with anisomorphic astrocytes.

Evidence that reactive astrogliosis stops axonal regeneration in vivo is often inferred, rather than directly observed. For example, Frisen et al. (174) found that PC12 cells (derived from a male rat pheochromocytoma) did not adhere to intact spinal cord sections or sections taken rostral to dorsal column sections, but they adhered to sections of injured spinal cords, suggesting that glial cells from injured cords prevent axon growth. Groves et al. (206) derived astrocyte cell lines that inhibit migration by oligodendroglial type 2 astrocyte progenitor cells, suggesting these astrocytes stop axonal growth. Yuan and He (628, p. 421) described an "extreme, uncontrolled form of reactive astrogliosis" around contusion injuries of the spinal cord, pointing out misaligned activated astrocytes and CSPG deposition, assuming that these stop growing axons. Wu et al. (601, p. 826) did not observe "substantial reactive astrocytic responses at the lesion border" but instead saw a "deposit of robust fibrotic scar" of hemisected monkey spinal cord (601), suggesting that primate and perhaps human SCI differs from rodent SCI. Finally, Conrad et al. (91) studied profibrotic and angiogenic connective tissue growth factors expressed by invading fibroblasts and endothelial cells, assuming that they block axon growth.

Many investigators who have studied axonal growth in injured spinal cords have observed axons growing through areas of gliosis. For example, Reier (463, p. 164) found that optic axons readily crossed areas of "dense glial scars." Alonso and Privat (10) found that reactive astrocytes in mediobasal hypothalamus allow axonal regeneration. Likewise, Farris et al. (154) showed that the medial cholinergic pathway regrows and restores laminar patterns in the cortex by growing across the "glial scars." In 2007, Lu et al. (355, p. 8) "grafted permissive autologous BMSC into mid-cervical SCI sites of adult rats, 6 weeks post-injury without resection of the chronic scar." Three months later, they found extensive astrocytosis surrounding the lesion site, together with dense depositions of inhibitory extracellular matrix molecule NG2. Axons penetrated the lesion site through this "chronic scar." Zukor et al. (646) described growth of axons across hemisection sites after PTEN deletion, finding that axons avoided dense clusters of fibroblasts and macrophages but crossed the lesion sites across "bridge-forming" astrocytes that express mature markers such as GFAP.

Perhaps it is not just astrocytes but a combination of fibroblasts and astrocytes that stops axon growth as originally suggested by Rudge and Silver (475). However, even combinations of astrocytes and fibroblasts do not always block regenerating axons. For example, Hirsch et al. (229) found that regenerating axons grew through fibronectin-expressing fibroblasts at transection sites of goldfish optic nerves, suggesting that these cells provide molecular support for axon growth. Kobayashi et al. (301, p. 191) reported that fibroblasts genetically modified to express the L1 cell adhesion molecule "drastically promoted regeneration of the axons in the injured spinal cord 2 weeks after grafting. Regenerating axons penetrated the glial scar at the host–graft interface and elongated into

the graft." In 2012, Li et al. (339) noted that astrocytes have three distinct surfaces: one facing other glia to form tight junctions, one facing fibroblasts to maintain protective covering of the CNS, and one facing neurons. They suggested that reorganization of the glial scar might be necessary to allow axonal regeneration.

Many investigators believe that CSPG is the critical element in glial scars that stop axon growth. However, CSPG does not always stop all axonal growth. For example, CSPG is present in peripheral nerves, and Neubauer et al. (421) found no difference between axons regenerating into peripheral nerve segments treated with ChABC or not. Some axons seem to prefer to grow in the presence of CSPG. For example, Hawthorne et al. (221) from the Silver Laboratory observed that serotonergic (5-HT) axons sprouted robustly in the presence of CSPG and growth-promoting laminin. Jones et al. (261–263) showed dense labeling of CSPG, NG2, brevican, neurocan, versican, and phosphacan in injured spinal cords after transplantation of NGF-secreting and control fibroblasts. Several classes of axons penetrated both control- and NGF-secreting fibroblast grafts, including dorsal column sensory, rubrospinal, and nociceptive axons, particularly in NG2-rich substrates, with or without NGF secretion by the transplanted fibroblasts. Finally, Mountney et al. (405) found that chondroitinase and sialidase, alone or in combination, do not increase spinal cord regeneration or improve recovery after contusion injuries.

Despite evidence that axons will grow through glial scars and white matter, many investigators believe that combinations of therapies that address CSPG, Nogo, and growth capacity are necessary to regenerate long tracts in injured spinal cords (11,97,153,164,205,272,278,352, 357,359,380,467,540,637,638) and optic nerve (121). However, therapies that do not eliminate the glial scar or Nogo have resulted in significant regeneration in the spinal cord (48,349,580,636). In particular, as Zukor et al. (646) showed, silencing a single gene, that is, PTEN, can result in massive regeneration of corticospinal tract in rats not only across in the injury site but through white matter to form synapses without substantial reductions of the glial scar. In fact, PTEN inhibitors can be applied late after stroke (375) or to peripheral nerves after injury to improve regeneration and recovery of function. These data strongly suggest that once axons are properly motivated to grow, they will do so despite CSPG or Nogo.

The most successful examples of spinal cord regeneration come from Lu et al. in the Tuszynski Laboratory (352–359), who showed that both central axons and axons of implanted neural progenitor cells grow through glial scars and chronic spinal cord injury sites to reinnervate the distal spinal cord. In 2007, Lu et al. (355) reported that axons crossed chronic scar in transected and hemisected spinal cords. In 2012, Lu et al. (358) transplanted human neural stem cells into transected rat spinal cords. The transplanted cells sent rivers of axons across glial scars and growing long distances in white matter to restore function. Also in 2012, Lu et al. (352) injected cAMP into brainstem to stimulate reticular motor axons to grow across C5 hemisections and T3 transection sites bridged with mesenchymal cells toward neurotrophin-expressing cells in the distal cord.

In 2012, Blesch et al. (37) published a study comparing effects of preconditioning of sensory fiber growth by peripheral nerve crushes and injecting cAMP into the dorsal root ganglia. They found significantly greater effects of conditioning lesions compared to cAMP elevation, particularly when combined with cellular grafts at the lesion site and virally mediated neurotrophin delivery. These conditioning effects were sustained for much longer periods of time than cAMP injections. They concluded that cAMP-mediated mechanisms account for only a small part of the conditioning effects of peripheral nerve injuries. Other mechanisms must contribute to the growth state.

While many investigators have clearly shown regeneration in the spinal cord, substantial functional recovery occurred only in animals with partially lesioned spinal cords, where improvements may result from sprouting of surviving axons. In animal models of complete transections or severe contusions, motor recovery has not been at a level that one can proclaim useful restoration of function. Likewise, sensory recovery has been limited. The presence of a large number of regenerated fibers that connect with distal neurons but not associated with functional recovery has caused consternation in the field. Other factors must be involved.

AN EVOLUTIONARY THEORY OF REGENERATION

Regeneration is an inefficient mechanism of recovery. The reason is self-evident. Axons grow slowly, probably no faster than hair can grow at about a millimeter a day (mm/day). Depending on the injury level, axons may have to grow 100–800 mm to reach their former connections. For example, corticospinal axons injured at C1 must grow >600 mm to reach the lumbosacral spinal cord, while posterior column sensory axons must grow from below the injury site to the brainstem. By the way, this may explain why Christopher Reeve recovered touch sensation in three quarters of his body by 2 years after injury, the ability to move an index finger at 3 years, but recovered relatively little other motor function (462,508). At 1 mm/day, regeneration cannot restore function for months or even years in the case of large mammals. No animal larger than several centimeters can evolve regenerative mechanisms and survive long enough to pass its genes onto its offspring.

Mammals therefore evolved other mechanisms to recover from spinal cord injury. The first and most obvious mechanism is of course the spine, which effectively

protects the spinal cord from mechanical damage. The effectiveness of the spine in preventing spinal cord injury is clearly illustrated from one statistic. Over a million people sustain whiplash injuries to their necks every year in the US (26), and less than 10,000 suffer from spinal cord injury. The second mechanism of recovery is redundancy. Less than 10% of the spinal cord is necessary and sufficient to support important survival functions such as locomotion in rats (28). An animal or person can lose as much as 90% of their spinal cord and still be able to recover walking. The third mechanism is plasticity or the ability of surviving fibers to do more than they normally would, including sprouting new connections. The fourth mechanism is programming of critical functions in the spinal cord so that relatively few axons are needed to control them. The central pattern generator (CPG) is located in the L2 spinal cord (127,128,202). Sacral nuclei coordinate the micturition reflexes (117–119), anal (303,427,561), and sexual functions (151,242).

While regeneration may not restore function sufficiently fast enough to improve survival of animals with complete SCI, animals with incomplete spinal cord injury should benefit not only from increased plasticity but from regeneration as well, even if the recovery takes a long time. Incomplete spinal cord injury allows for the preservation and rapid recovery of function so that the animal can survive and pass on the genes for plasticity and regeneration. Long-lived animals, such as humans, would benefit from regenerative mechanisms that add to and improve function over years. Indeed, recovery from spinal cord injury in people is very slow. Functional recovery is not over even at 1 year after spinal cord injury and may still occur over 2 or more years. While the standard dogma is that regeneration does not occur in transected spinal cords, there is no convincing evidence that spontaneous regeneration does not occur after incomplete spinal cord injury. The observation of many axons entering and possibly leaving the spinal contusion site strongly supports this notion (29,227).

Regeneration mechanisms, however, must have several characteristics to be beneficial for the organism. First, the mechanisms must be turned off in normal uninjured spinal cords. After development has completed, unnecessary growth of spinal tract will disrupt function. Therefore, robust mechanisms for regulating axonal growth must suppress growth when it is not needed. PTEN would appear to be one such regulatory mechanism. Second, regenerative mechanisms must be activated quickly when needed. The signal for regeneration appears to be injury, associated with inflammation and inflammatory cells entering the CNS. Third, rather than changing the entire environment of the spinal cord, the most efficient approach is for the organism to turn off axonal receptors to the axonal growth inhibitors. This seems to be the case in contused spinal cords where axons seem to ignore Nogo and CSPG when large numbers of axons grow into the injury site. Finally, because regeneration is such an important mechanism and it has important effects on survival, its regulation would not be entrusted to a single mechanism but rather to layers of regulation. Thus, three parallel systems appear to regulate neuronal growth: the Rho/ROCK, the AKT/mTOR, and the PKA/cAMP systems.

Most previous theories assumed that the CNS cannot regenerate and focused on mechanisms why the spinal cord does not. Much evidence now indicate that regenerative mechanisms did evolve, can be activated by injury, and play a major role in delayed functional recovery after injury. The theory explains several puzzling clinical characteristics of recovery form SCI. First, it explains why many people recover so much function, especially after incomplete SCI, and why it takes many months for this recovery to be evident. For example, Dobkins et al. (132) found that over 90% of people with sacral sparing go on to recover unassisted walking by 1 year after SCI. Second, it explains why people continue to recover for years after SCI (46,68). Third, many people get strange sensations and evoked movements, usually appearing years after injury. For example, a common finding is a thumb twitch associated with light touch of the ipsilateral thigh (personal observation). Many people report recovery of an isolated muscle group, often an index finger or big toe, many years after SCI.

Evolution of regenerative mechanisms would also provide several interesting predictions. For example, the theory predicts that smaller animals evolved different regenerative mechanisms than larger animals because smaller animals with regeneration distances of less than a centimeter would be able to rely on regeneration as a means of survival. Indeed, one striking characteristic of all vertebrate animals that can regenerate their spinal cords is their small size. For example, zebrafish and axolotyl can regenerate their spinal cords but not larger animals, even of the same species. Lamprey larvae and tadpoles can regenerate the spinal cords but not adult lampreys nor adult frogs, presumably because of the size difference. Another evolutionary prediction is that different layers of control over regeneration may have appeared at different times during phylogeny and ontogeny. Thus, for example, it would be of interest to determine when PTEN expression first appears in the different systems of the body not only during development and during evolution. Likewise, it would be of interest to determine when injury preconditioning appears during ontogeny and phylogeny.

The effects of injury preconditioning on sensory tracts in the spinal cord supports the hypothesis that injury activates regenerative mechanisms. While the sensory sprouting of dorsal column axons after peripheral nerve injury has long been documented, as well as the mechanisms

involving cAMP, growth factors, and various nuclear factors, the phenomenon of central injury conditioning is less well documented. However, if a recent observation by Wills et al. (592) that corticospinal tract sprouting in injured rat spinal cords can be stimulated by Schwann cell preconditioning of the motor is confirmed, this would provide an important tool to compare the mechanisms of central versus peripheral injury, as well as sensory versus motor conditioning. A comparison of regeneration mechanisms over phylogeny may provide insights into how the regenerative mechanisms have evolved. The assumption that the spinal cord can regenerate opens up new perspectives and provides new testable predictions.

The other advantage of an evolutionary approach to regeneration is that it can incorporate multiple regulatory as well as regenerative mechanisms. Obviously, growth of spinal tracts would be disruptive after development, and regenerative mechanisms must be subjected to multiple levels of regulatory control. The axonal growth inhibitors may also serve as guidance mechanisms rather than mechanisms that prevent regeneration. For example, Nogo, CSPG, and other axon growth inhibitors guide growth of white matter. When viewed from this perspective, expectations of dramatic regeneration in transgenic animals that have had knockouts of Nogo, CSPG, and their receptors are unreasonable. Likewise, glial scars may obstruct axonal growth in certain circumstances but should be regarded as mechanisms by which the CNS separates itself from surrounding tissues. As one might expect, elimination of glial scars may be deleterious as opposed to being beneficial for regeneration. Finally, there is no reason to expect that animals have evolved one mechanism of regeneration. Like all other crucial functions of the nervous system, multiple mechanisms of growth and regulation are likely.

Theories based on the premise that the spinal cord cannot regenerate are difficult to prove. For example, the Nogo theory predicted that knockout or reducing Nogo expression would allow spinal cord regeneration. While several laboratories reported that antibodies against Nogo A (586), transgenic Nogo A/B knockout (296), or Nogo receptor knockout (323) improved regeneration and more recent studies (361,612) suggest that silencing Nogo with siRNA promotes repair and recovery of function after spinal cord injury, other laboratories showed that this was not true of all Nogo or Nogo receptor knockout mice, including mice that have had the entire family of Nogo A, B, and C knocked out mice or combined genetic attenuation of myelin and semaphorin-mediated growth inhibition.

Likewise, the glial scar and CSPG theories have been remarkably difficult to prove. The theory predicts that elimination of glial scar would allow axons to regenerate. However, many studies showed that removing or preventing glial scar formation did not improve regeneration or recovery and, in fact, may have worsened functional outcomes. Not all axons seem to be deterred by the presence of glial scars, and in fact, serotonergic fibers appear to prefer to grow on CSPG. Worse, a number of studies have shown that axons will grow across dense glial scars. Such data argue strongly that glial scars are neither necessary nor sufficient to prevent axonal growth. On the other hand, these studies do not rule out the possibility that glial scars and CSPG inhibit axon growth under certain circumstances.

The beneficial effects of reducing Nogo and CSPG on functional recovery may be due to sprouting of surviving axons rather than long tract regeneration. In 1996, we (482) found that recovery of walking in rats after hemisection of the spinal cord is related to the return of 5-HT to the lumbosacral spinal cord after lateral thoracic hemisection. Examinations of the spinal cords revealed that the 5-HT fibers sprouted from the contralateral nonlesioned side. If there were no or too few surviving fibers, these therapies may not restore function.

The Nogo, glial scar, and CSPG theories predict that eliminating these obstacles would allow regeneration to occur. While some experiments did show that therapies that blocked Nogo and its receptors and enzymes that degraded CSPG increased sprouting and improved function, these therapies do not restore function in severe injury models, suggesting that the improved recovery resulted from sprouting of surviving axons rather than regeneration of injured tracts. Genetic knockout of Nogo genes and its receptors did not always allow regeneration. Finally, many investigators have now reported that the long spinal tracts can regenerate in circumstances where Nogo, CSPG, and glial scars were not affected. For example, the recent discovery that genetic deletion of PTEN allowed massive growth of corticospinal axons across glial scars and grow long distances in white matter raised questions whether Nogo or glial scars are necessary or sufficient to stop spinal cord regeneration.

I suggest that these theories have been difficult to prove because they are based on the premise that these obstacles are responsible for lack of regeneration in the spinal cord. However, many studies have shown that injured spinal axons can and do grow into the contusion site, that previous injury to peripheral nerves will facilitate central axonal growth in the spinal cord, and that axons frequently grow across glial scars in the brain and spinal cord. It should not be surprising that efforts to knock out Nogo and its receptors, to eliminate glial scars, and to break down CSPG have not consistently improved spinal cord regeneration or function. The spinal cord appears to have regenerative mechanisms that are normally suppressed but can be activated by injury. These regenerative mechanisms are likely to be responsible for restoring function after incomplete injuries but are less

effective after severe injuries. Such an admission would also change the goal of regenerative therapies. Rather than assuming that the spinal cord cannot regenerate and looking for the reasons why, we should consider therapies that facilitate natural regenerative mechanisms.

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