distal nerve stumps begin to produce neurotrophins and other trophic molecules of the sort described in Chapter 46. Together, these molecules nourish neurons and guide growing axons in the embryonic nervous system, so it makes sense that they also promote the regrowth of axons. By contrast, central neuronal tissue is a poor source of these molecules, containing little laminin and low levels of trophic molecules. Thus, in the embryo, both central and peripheral nervous systems provide environments that promote axon outgrowth. But only the peripheral environment retains this capacity in adulthood or is able to regain it effectively following injury.

The practical implications of this view are that supplementing the central environment with growth-promoting molecules might improve regeneration. To this end, investigators have infused neurotrophins into areas of injury or inserted fibers rich in extracellular matrix molecules such as laminin to serve as scaffold for axonal growth. In some attempts, Schwann cells themselves, or cells engineered to secrete trophic factors, have been grafted into sites of injury. In many of these cases, injured axons grow more extensively than they do under control conditions. Yet regeneration remains limited, with axons generally failing to extend long distances. More important, functional recovery is minimal.

Components of Myelin Inhibit Neurite Outgrowth

What accounts for such disappointingly limited regeneration? One part of the explanation is that the environment encountered by severed central axons is not only poor in growth-promoting factors but also rich in growth-inhibiting factors, some of which are derived from myelin. In culture, fragments of central but not peripheral myelin potently inhibit neurite outgrowth from co-cultured central or peripheral neurons. Conversely, sprouting of spinal axon collaterals following injury is enhanced in rats treated to prevent myelin formation in the spinal cord (Figure 50–7).

These findings implied that although both central and peripheral environments might contain a supply of growth-promoting elements, central nerves also contain inhibitory components. The fact that myelin inhibits neurite growth may seem peculiar, but not if we consider that myelination normally occurs postnatally, after axon extension is largely complete.

Searches for the inhibitory components of central myelin turned up an embarrassment of riches. Several classes of molecules that occur at higher levels in central myelin compared to peripheral myelin are able to inhibit neurite outgrowth when presented to cultured neurons. The first to be discovered was identified when an antibody generated against myelin proteins proved

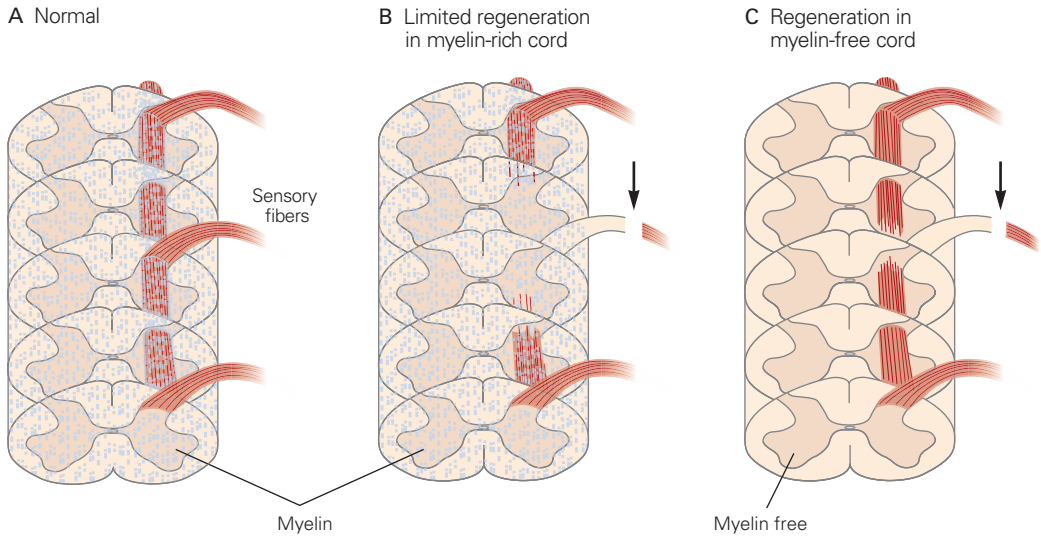


Figure 50–7 Myelin inhibits regeneration of central axons. (Adapted, with permission, from Schwegler, Schwab, and Kapfhammer 1995.)

A. Sensory fibers normally extend rostrally in a myelin-rich spinal cord.

B. Right dorsal root fibers were sectioned in 2-week-old normal rats. Regeneration of the fibers was assessed histochemically 20 days later. The central branches of the sectioned axons degenerated, leaving a portion of the spinal cord denervated. Little regeneration occurred in the myelin-rich cord.

C. Some littermates received local x-irradiation to block myelination. In these animals, sensory fibers that entered the cord through neighboring uninjured roots sprouted new collaterals following denervation.

to be capable of partially neutralizing myelin's ability to inhibit neurite outgrowth. Use of this antibody to isolate the corresponding antigen yielded the protein now called Nogo. Two other proteins, myelin-associated glycoprotein (MAG) and oligodendrocyte-myelin glycoprotein (OMgp), initially isolated as major components of myelin, have also been found to inhibit the growth of some neuronal types.

Intriguingly, Nogo, MAG, and OMgp bind to common membrane receptors, NogoR and PirB (Figure 50–8). NogoR, as well as related receptors such as LINGO that have been implicated in growth inhibition, all interact with the neurotrophin receptor p75 (Chapter 46). This interaction converts p75 from a growth-promoting to a growth-inhibiting receptor. Perhaps because there are so many growth inhibitory factors and receptors, regeneration of central axons is not greatly enhanced in mutant mice lacking any one of them. However, many of the inhibitory components trigger the same intracellular signaling pathway in which RhoA is activated, thereby stimulating Rho kinase (ROCK); ROCK in turn leads to the collapse of growth cones and blocks actin and tubulin polymerization required for neurite growth. Current studies are

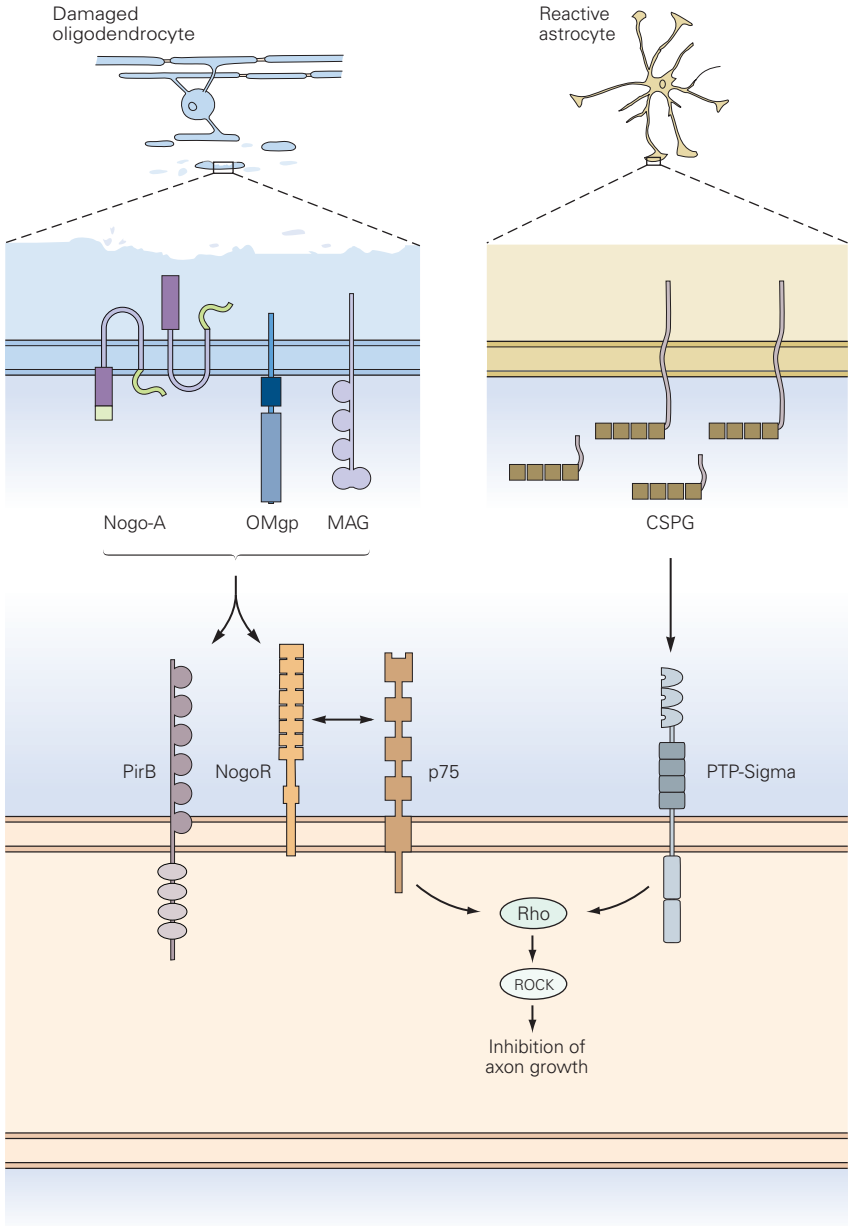


Figure 50–8 Myelin and glial scar components that inhibit regeneration of central axons. (Adapted from Yiu and He 2006.)

Left: Myelin contains the proteins Nogo-A, oligodendrocyte-myelin glycoprotein (**OMgp**), and myelin-associated glycoprotein (**MAG**). All three proteins are exposed when myelin breaks down. They can bind to the receptor protein NogoR, which can associate with the neurotrophin receptor p75, as well as an immunoglobulin-like receptor protein PirB. Inactivation of PirB results in a modest enhancement of corticospinal axon regeneration. *Right:* Chondroitin sulphate proteoglycans (**CSPG**) are major components of the glial scar and are thought to suppress axon regeneration through interaction with the receptor tyrosine phosphatase PTP-sigma, which activates intracellular mediators such as Rho and ROCK.

exploring whether interference with that shared pathway might neutralize the impact of many inhibitors in one fell swoop.

Injury-Induced Scarring Hinders Axonal Regeneration

Myelin debris is not the only source of growth-inhibiting material in the injured brain or spinal cord. As noted earlier, astrocytes become activated and proliferate following injury, acquiring features of reactive astrocytes that generate scar tissue at sites of injury. Scarring is an adaptive response that helps to limit the size of the injury, reestablish the blood-brain barrier, and reduce inflammation.

But the scar itself hinders regeneration in two ways: through mechanical interference with axon growth and through growth-inhibiting effects of proteins produced by cells within the scar. Chief among these inhibitors are a class of chondroitin sulfate proteoglycans (CSPG) that are produced in abundance by reactive astrocytes and directly inhibit axon extension by interaction with tyrosine phosphatase receptors on axons (Figure 50–8). Attention has therefore focused on ways of dissolving the glial scar by infusion of an enzyme called *chondroitinase*, which breaks down the sugar chains on CSPG. This treatment promotes axon regeneration and functional recovery in animals. Drugs that reduce inflammation and decrease scarring, notably prednisolone, are also beneficial if administered shortly after injury, before the scar forms.

An Intrinsic Growth Program Promotes Regeneration

So far, we have emphasized differences between the local environments of peripheral and central axons. However, environmental differences cannot completely account for the poor regeneration of central axons. Even though they can regenerate in peripheral nerves, central axons grow much less well than peripheral axons when navigating the same path. Thus, adult central axons may be less capable than peripheral axons of regeneration.

In support of this idea, experiments in tissue culture have shown that the growth potential of central neurons decreases with age, whereas mature peripheral neurons extend axons robustly in a favorable environment. One potential explanation for this difference is variation in the expression of proteins thought to be critical for optimal axon elongation. One example is the 43 kDa growth-associated protein, or GAP-43. This protein is expressed at high levels in embryonic central and peripheral neurons. In peripheral neurons, the level remains high in maturity and increases even more following axotomy, whereas in central neurons, its expression decreases as development proceeds. Transcription factors required to coordinate axonal growth programs are also expressed at high levels during development, and then are downregulated in maturity.

Is this reduced ability of central axons to regenerate reversible? Hope is provided by two sets of studies. One involves what has been called a "conditioning lesion." Recall that primary sensory neurons in dorsal root ganglia have a bifurcated axon, with a peripheral branch that extends to skin, muscle, or other targets, and a central branch that enters the spinal cord. The peripheral branch regenerates well following injury, whereas the central branch regenerates poorly. However, the central branch will regenerate successfully if the peripheral branch is damaged several days before the central branch is damaged (Figure 50–9). Somehow, prior injury or conditioning lesion activates an axonal growth program.

One component of the growth program responsible for regeneration of the central branch appears to be cyclic adenosine monophosphate (cAMP). This second-messenger molecule activates enzymes that in turn promote neurite outgrowth. Levels of cAMP are high when neurons initially form circuits; they decline postnatally in central but not peripheral neurons. In some instances, increased supplies of cAMP or proteins normally activated by cAMP can promote regeneration of central axons following injury. Accordingly, drugs that increase cAMP levels or activate targets of cAMP are being actively considered as therapeutic agents to be administered following spinal cord injury.

A second group of investigations has manipulated developmentally regulated intrinsic factors to restore regenerative ability in adults. For example, injury sometimes leads to formation of cytokines such as ciliary neurotrophic factors (CNTFs) that promote growth by activating a signaling pathway involving molecules called JAK and STAT that travel to the nucleus and regulate a growth program. In adults, however, the pathway is inhibited by a protein called suppressor of cytokine signaling 3 (SOCS3). Deletion of the *SOCS3* gene in mice relieves the inhibition and augments the ability of cytokines to promote regeneration of injured axons (Figure 50–10A).

Similarly, a signaling pathway involving the kinase mammalian target or rapamycin (mTOR) regulates energy metabolism, promoting an anabolic growth-promoting state required for axon regeneration. However, mTOR is downregulated as central neurons

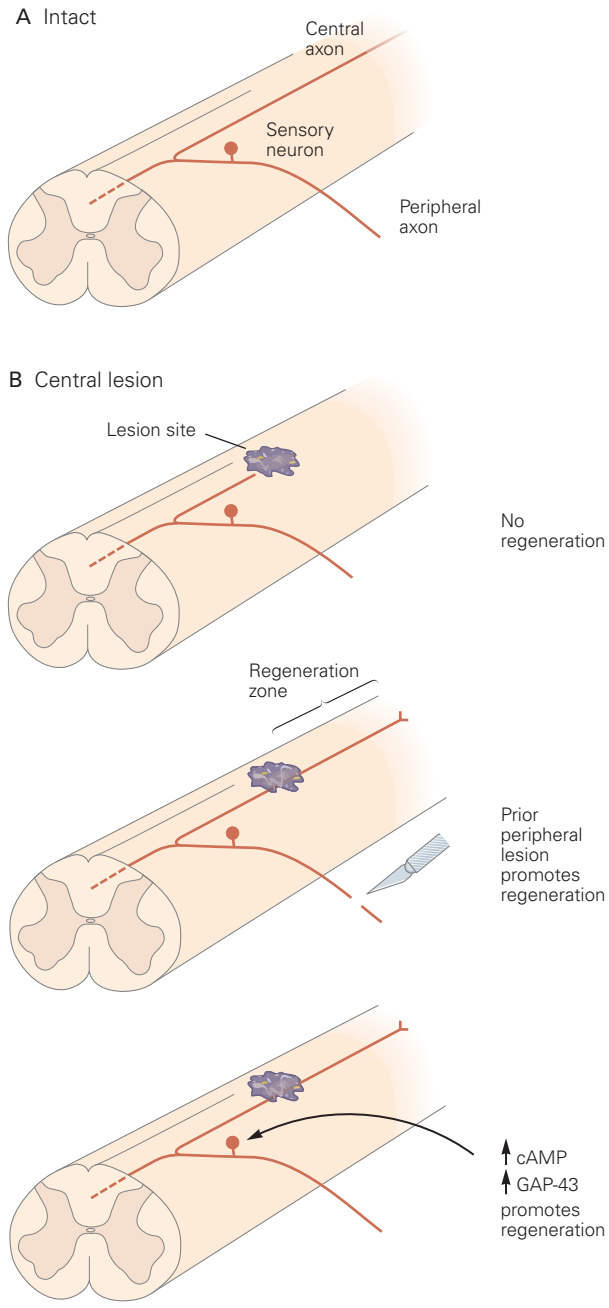


Figure 50–9 A conditioning lesion promotes regeneration of the central branch of a primary sensory neuron axon. After lesions of the spinal cord, there is little regeneration of the central branch beyond the injury site. However, if the peripheral branch of the axon is sectioned before the central branch is damaged, the latter will grow beyond the lesion site. The impact of such a "conditioning lesion" can be mimicked by elevating levels of cyclic adenosine monophosphate (**cAMP**) or of the growth-associated protein GAP-43 in the peripheral branch.

mature and is further inhibited by a phosphatase called PTEN. Analogous to SOCS3 and JAK/STAT signaling, deletion of the *PTEN* gene in mice promotes axonal regrowth following injury to the optic nerve or spinal cord (Figure 50–10B). Moreover, loss of SOCS3 and PTEN stimulates regeneration significantly more than loss of either one. Although their multiple roles make it unlikely that either SOCS3 or PTEN is a useful target for therapy, the signaling pathways they regulate provide multiple starting points for designing drugs that could augment regeneration.

Formation of New Connections by Intact Axons Can Lead to Recovery of Function Following Injury

So far, we have discussed interventions designed to enhance the limited regenerative capacity of injured central axons. An alternative strategy focuses on the significant, although incomplete, functional recovery that can occur following injury even without appreciable regeneration of cut axons. If the basis for this limited recovery of function can be understood, it may be possible to enhance it.

A rearrangement of existing connections in response to injury may contribute to recovery of function. We have learned that axotomy leads to changes in both the inputs to and the targets of the injured neuron. Although many of these changes are detrimental to function, some are beneficial. In particular, the central nervous system can, following injury, spontaneously undergo adaptive reorganization that helps it regain function. For example, after transection of the descending corticospinal pathway, which occurs with many traumatic injuries of the spinal cord, the cortex can no longer transmit commands to motor neurons below the site of the lesion. Over several weeks, however, intact corticospinal axons rostral to the lesion begin to sprout new terminal branches and form synapses on spinal interneurons whose axons extend around the lesion, thereby forming an intraspinal detour that contributes to limited recovery of function (Figure 50–11).

Similar instances of functional reorganization have been demonstrated in the motor cortex and brain stem. These compensatory responses attest to the latent plasticity of the nervous system. The ability of the nervous system to rewire itself is most vigorous during the critical periods of early postnatal life but can be revived by traumatic events in adulthood (Chapter 49).

How can the rewiring ability of the central nervous system be improved? It is possible that some of the beneficial effects of grafts in experimental animals reflect reorganization of intact axons rather than regeneration of transected axons. As the nervous system's

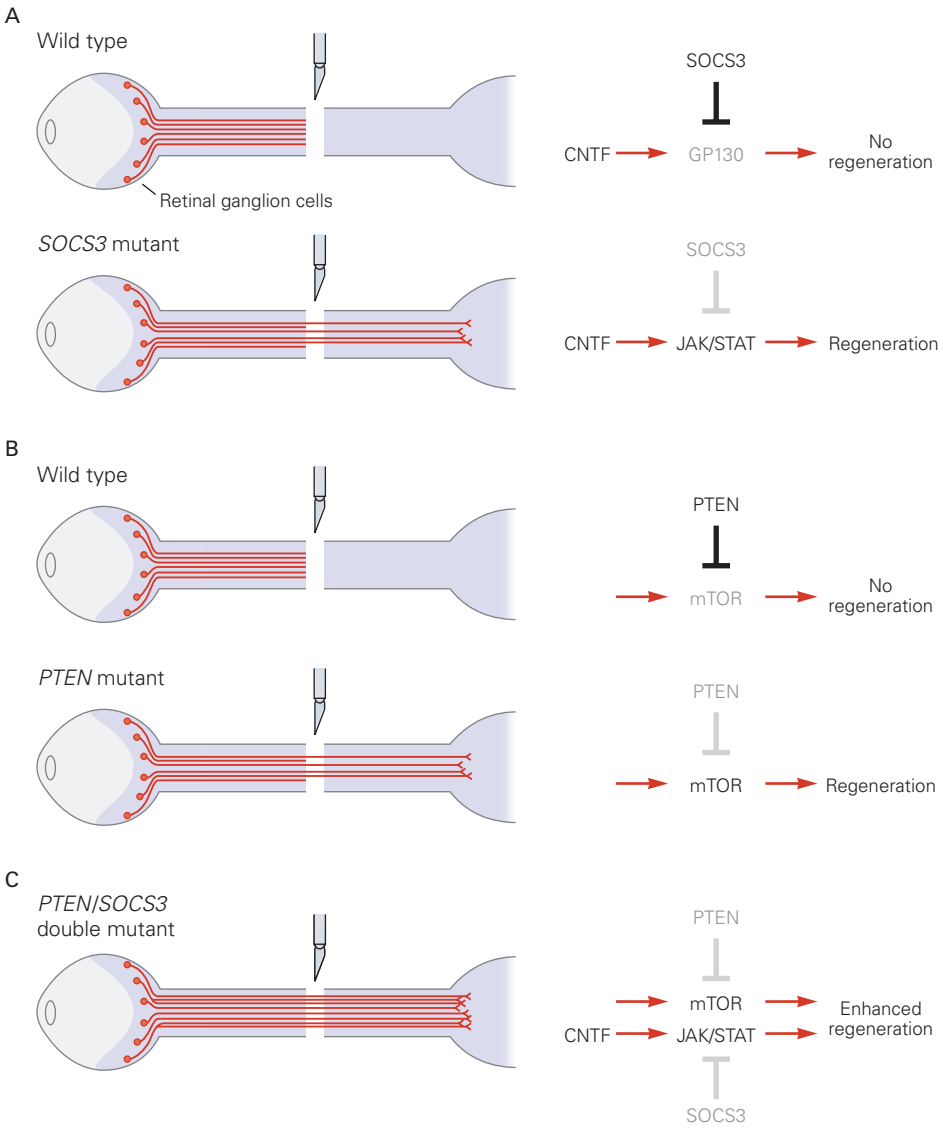


Figure 50–10 Signaling pathways that regulate axon regeneration in the optic nerve.

A. The regeneration of retinal ganglion cell axons in the optic nerve is normally constrained by neuronal expression of several genes. One encodes SOCS3, which blocks the ability of ciliary neurotrophic factor (**CNTF**) to bind its receptor GP130 and thus blocks CNTF from promoting regeneration. In *SOCS3* mutant mice, ambient levels of CNTF are sufficient to improve optic nerve regeneration. Elimination of GP130 as well as SOCS3 blocks the capacity for regeneration. Addition of extra CNTF enhances the capacity for regeneration in *SOCS3* mutant mice.

B. Another gene encodes PTEN, which blocks signaling through the mammalian target of rapamycin (**mTOR**) pathway, which regulates energy metabolism. Accordingly, regeneration is enhanced in *PTEN* mutant mice.

C. Because *SOCS3* and *PTEN* regulate different growth-promoting signals, mutant mice lacking both genes exhibit greater regenerative ability than either single mutant. (Adapted from Smith et al. 2009.)

plasticity becomes better understood, therapeutic strategies that promote specific changes in circuitry may become possible. Perhaps most promising is an approach in which cellular or molecular interventions that promote growth are combined with behavioral therapies that result in circuit rewiring.

Neurons in the Injured Brain Die but New Ones Can Be Born

The failure to grow a new axon is by no means the worst fate that can befall an injured neuron. For many neurons, axotomy leads to the death of the cell. Efforts

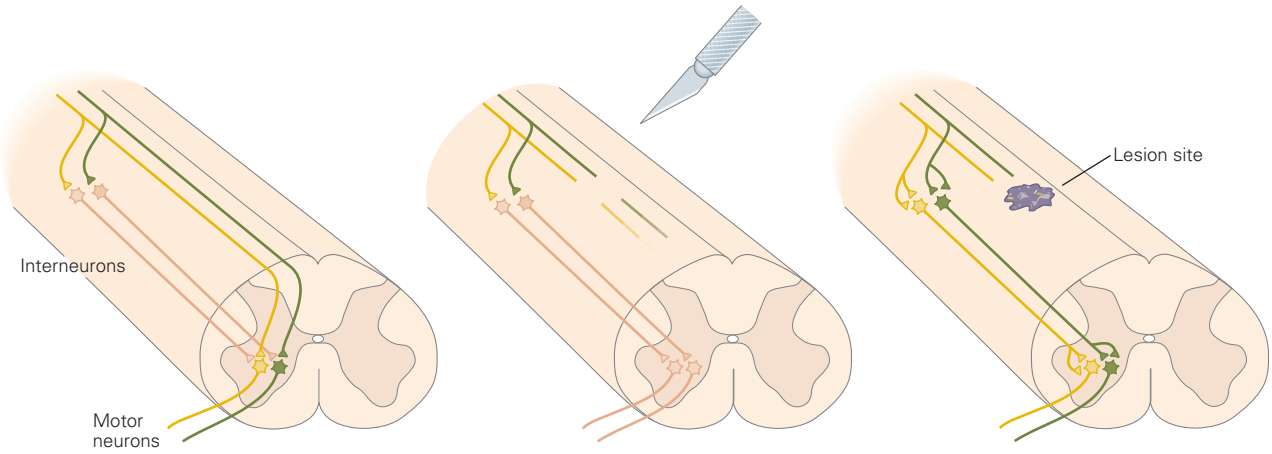


Figure 50–11 Function can be recovered after spinal cord injury through reorganization of spinal circuits. Severed corticospinal axons can reestablish connections with motor neurons by sprouting axon collaterals that innervate propriospinal interneurons whose axons bypass the lesion and contact motor neurons located caudal to the lesion site. (Adapted from Bareyre et al. 2004.)

to improve recovery following injury therefore need to consider survival of neurons and not simply the regrowth of axons. Since neuronal death is a frequent consequence of other neural insults, such as stroke and neurodegenerative disease, improved ways of retaining or replacing neurons would have broad utility.

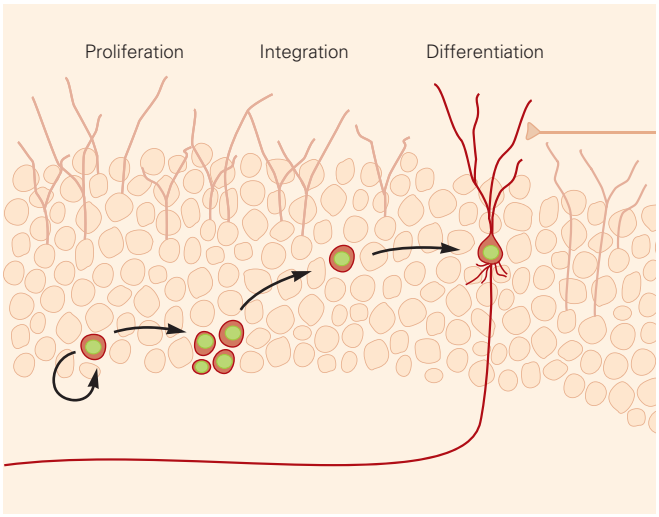
The loss of cells following injury is not unique to the nervous system, although in other tissues, new cells are often effective at repairing damage. This regenerative capacity is most dramatic in the hematopoietic system, where a few stem cells can repopulate the entire adaptive immune system. In contrast, it has long been believed that the generation of neurons is complete by birth. Because of this, approaches to regeneration have often focused on finding ways to spare neurons that would otherwise die.

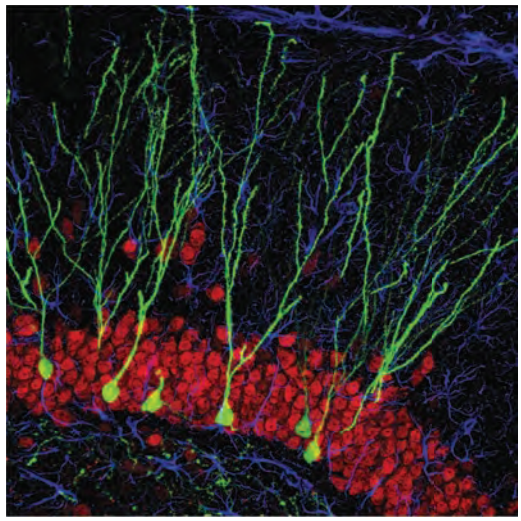
This traditional view has changed, prompted initially by Joseph Altman's discovery in the 1960s that neurogenesis continues into adulthood in some parts of the mammalian brain. Since this finding challenged fundamental tenets of prevailing dogma, the idea that new neurons could form in postnatal rodents was met with skepticism for three decades.

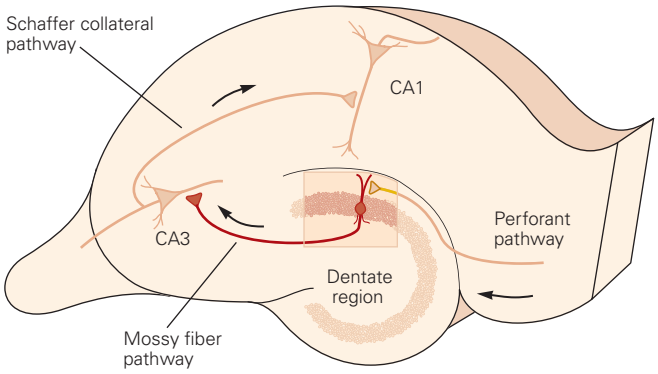
Eventually, however, the application of better cell labeling technologies amply supported Altman's conclusion and showed that it also applies to nonhuman primates and even, in a limited way, to humans. We are now confident that new neurons are added to the dentate gyrus of the hippocampus and to the olfactory bulb throughout life, although the rate of addition declines with age. Some of the newborn cells in the dentate gyrus of the adult hippocampus die soon after they are born and others become glial cells, but a substantial minority differentiate into granule cells that are indistinguishable from those born at embryonic stages (Figure 50–12). New neurons are also added to the adult olfactory bulb. They are generated near the surface of the lateral ventricles, far from the bulb itself, and then migrate to their destination (Figure 50–13). In both cases, the new neurons extend processes, form synapses, and become integrated into functional circuits. Thus, neurons born at embryonic stages are gradually replaced by later-born neurons, so that the total number of neurons in these regions of the brain is maintained.

The properties of neurons born in mature animals are not completely understood, but they appear able to recapitulate many of the properties of neurons that arise in the embryo. When the generation of new neurons in the adult is prevented, certain behaviors mediated by the olfactory bulb and hippocampus are degraded. Conversely, some behavioral alterations are accompanied by alterations in the tempo of adult neurogenesis. Adult neurogenesis can be decreased in animal models of depression and chronic stress, whereas enrichment of the habitat of an animal or an increase in the physical activity of otherwise sedentary rodents can increase the generation of new neurons.

What cells give rise to adult-born neurons? The principle that embryonic neurons and glia arise from multipotential progenitors also applies to neurons born in adults. Stem cells are the source of neurons in the adult as well as the embryo. They are likely derived from radial glia, which also serve as a source of







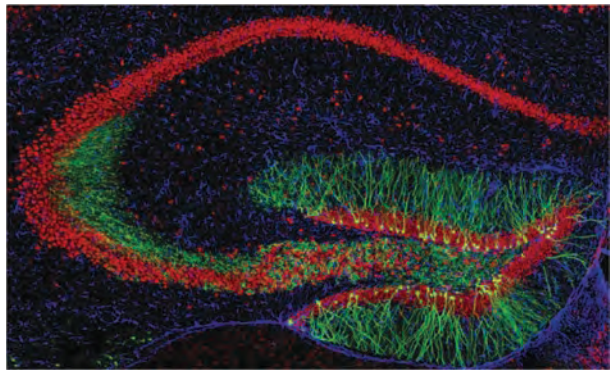


Figure 50–12 Neurons born in the germinal zone of the dentate gyrus in adult rodents are integrated into hippocampal circuits. The diagrams on the left show the pathways of neuronal differentiation and integration into dentate gyrus circuits. The images on the right show newly generated neurons and their dendritic arbors labeled with a virus expressing green fluorescence protein. (Micrographs reproduced, with permission, from F. Gage.)

neurons during embryonic development (Chapter 46). A subset of these cells exit the cell cycle during gestation, become quiescent, and take up residence near the ventricular surface. In adulthood, they are activated, reenter the cell cycle, and give rise to neurons.

Although so far adult neurogenesis has not been directly linked to repair of damaged tissue, its discovery has influenced research on recovery from injury in two important ways. First, the findings that endogenously generated neurons can differentiate and extend processes through the thicket of adult neuropil, and can be integrated into functional circuits, led researchers to test the idea that the same could be true for transplanted neurons or precursors. Second, since neural precursors can be induced to divide and differentiate, strategies designed to augment this innate ability are now being considered, with the goal of producing neurons in large enough numbers to replace those lost to injury or neurodegenerative disease. As we describe below, these ideas have progressed over the past few decades from science fiction to efforts that are tantalizingly close to clinical tests.

Therapeutic Interventions May Retain or Replace Injured Central Neurons

Transplantation of Neurons or Their Progenitors Can Replace Lost Neurons

For many years, neurologists have transplanted developing neurons into experimental animals to see if the new neurons could reverse the effects of injury or disease. These attempts have had promising results in a few cases.

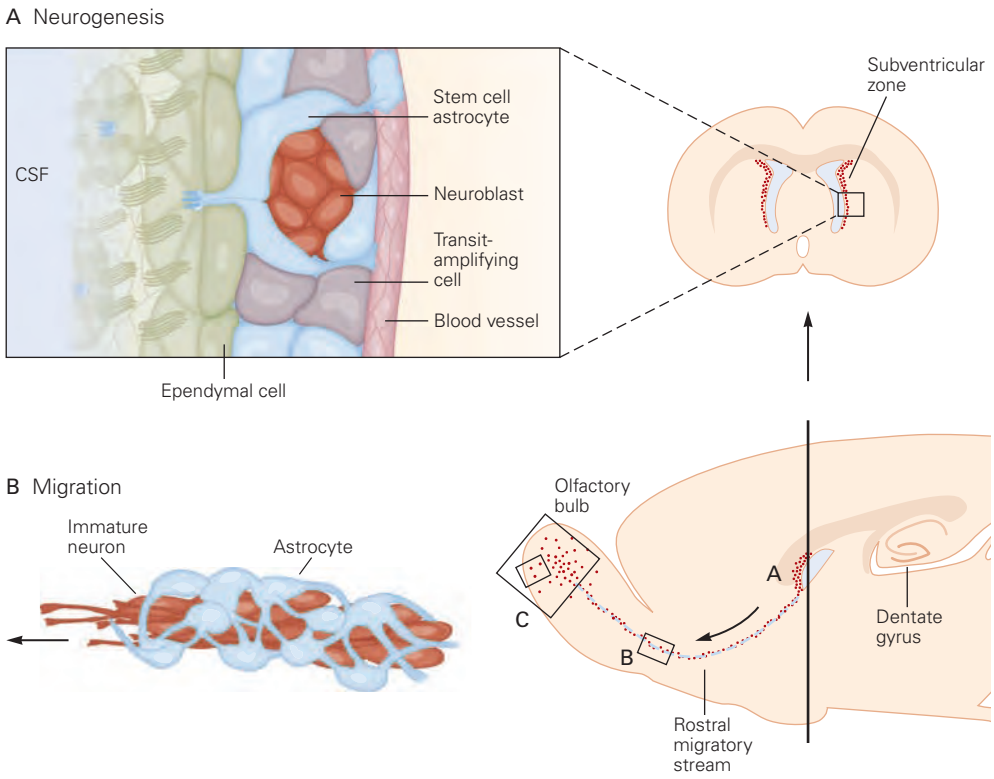


Figure 50–13 The origin and fate of neurons born in the adult ventricular zone. (Adapted from Tavazoie et al. 2008.)

A. Neuroblasts develop in an orderly progression from astrocytic stem cells via a population of cells within a local niche close to blood vessels in the subventricular zone. (Abbreviation: **CSF**, cerebrospinal fluid.)

B. Neuroblasts differentiate into immature neurons that migrate to the olfactory bulb using astrocytes as guides. They crawl along each other in a process called chain migration.

C. On arrival in the olfactory bulb, immature neurons differentiate into granule cells and periglomerular cells, two classes of olfactory bulb interneurons. (Image reproduced, with permission, from A. Mizrahi.)

One is to replace dopaminergic cells that die in Parkinson disease. When transplanted into the striatum, these neurons release dopamine onto their targets without the need to grow long axons or form elaborate synapses (Figure 50–14). Another is to transplant immature inhibitory interneurons from the ganglionic eminences in which they are produced (Chapter 46) to the cortex, where they mature and form synapses. By enhancing inhibition, these neurons attenuate the manifestations of disorders in which insufficient inhibitory drive plays a role, such as epilepsy and anxiety.

Unfortunately, application of these methods to human patients has been fraught with difficulties. One is the difficulty of obtaining and growing developing neurons in sufficient numbers and with sufficient purity. Second, it has been challenging to modify neurons by introducing new genes so as to improve their chances of functioning in a new environment. Third, in many cases, the grafted neurons are already too mature

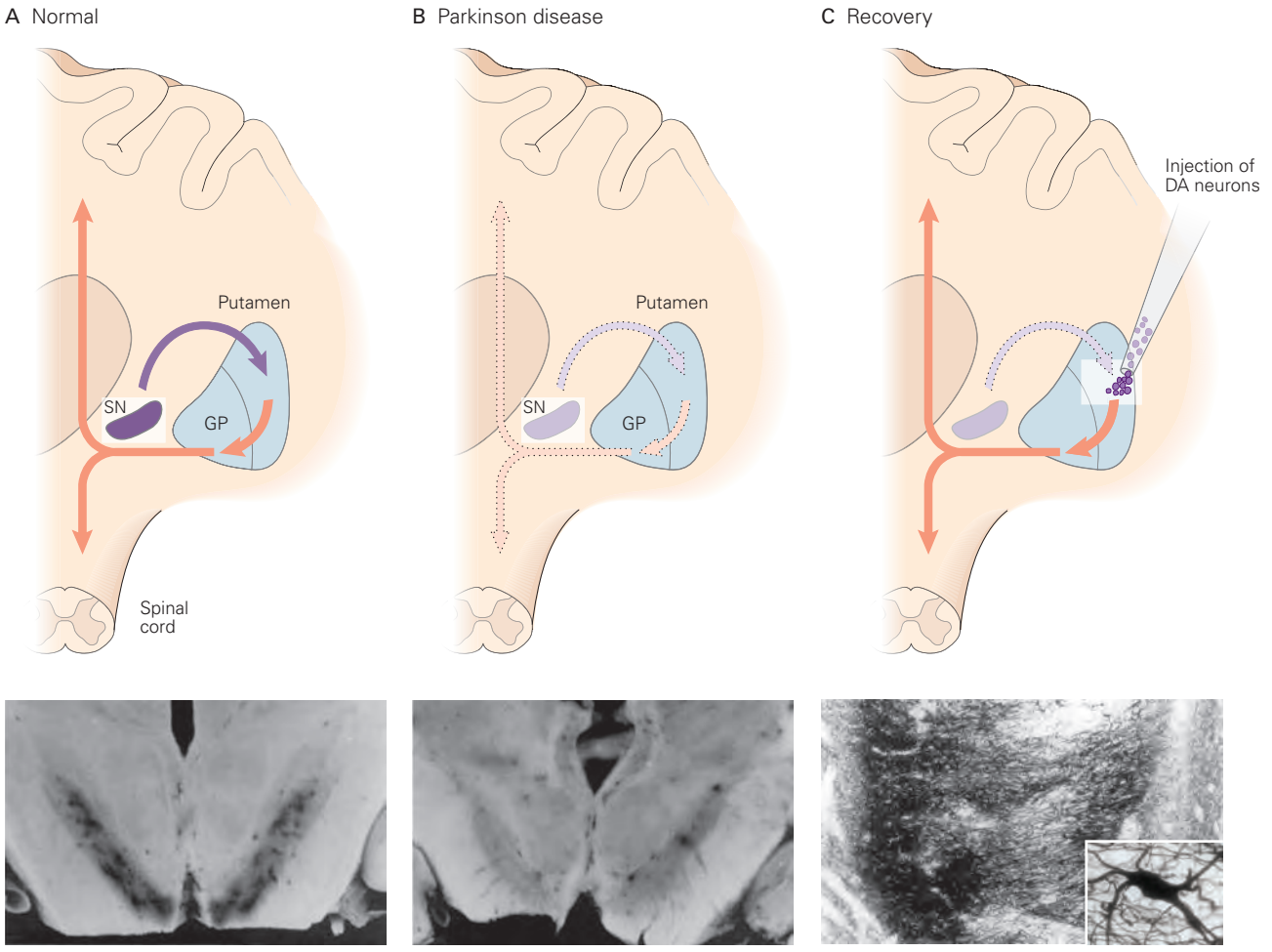


Figure 50–14 Loss of dopaminergic (DA) neurons in Parkinson disease can be treated by grafting embryonic cells into the putamen.

A. In the healthy brain, dopaminergic projections from the substantia nigra (**SN**) innervate the putamen, which in turn activates neurons in the globus pallidus (**GP**). Pallidal outputs to the brain and spinal cord facilitate movement. The image below shows melanin-rich dopaminergic neurons in human substantia nigra.

B. In Parkinson disease, the loss of dopaminergic neurons in the substantia nigra deprives the putamen–globus pallidus pathways of their drive. The image beneath the diagram shows the virtual absence of melanin-rich dopaminergic neurons in the substantia nigra of an individual with Parkinson disease.

C. Direct injection of embryonic dopaminergic neurons into the putamen reactivates the globus pallidus output pathways. The image below shows tyrosine hydroxylase expression in the cell bodies and axons of embryonic mesencephalic dopaminergic neurons grafted into the putamen of a human patient. (Image reproduced, with permission, from Kordower and Sortwell 2000. Copyright © 2000. Published by Elsevier B.V.)