ing many families that might have undergone adaptive evolution in the past 300 million years (*55*).

A natural annotation of the planetary proteome will require, of course, additions to the paleontological, geological, and molecular records. Already, funding agencies (such as NASA through its Planetary Biology, Exobiology, and Astrobiology programs) are working to improve these records. The consequences will certainly take time to percolate through our educational system, as geologists learn more biology and biologists learn more geology. The past is the key to the present. When we understand where we came from, and how we got here, we understand better who we are. This cannot help but have profound and beneficial impact on health, the environment, and the human condition.

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REVIEW: NEUROSCIENCE

Axonal Self-Destruction and Neurodegeneration

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Neurons seem to have at least two self-destruct programs. Like other cell types, they have an intracellular death program for undergoing apoptosis when they are injured, infected, or not needed. In addition, they apparently have a second, molecularly distinct self-destruct program in their axon. This program is activated when the axon is severed and leads to the rapid degeneration of the isolated part of the cut axon. Do neurons also use this second program to prune their axonal tree during development and to conserve resources in response to chronic insults?

Much effort is being devoted to understanding the nature of neuronal cell death in various neurodegenerative diseases such as motor neuron disease, glaucoma, and Alzheimer, Parkinson, and Huntington diseases (*1*–*5*). It may be, however, that neuronal death in these diseases occurs too late to be clinically important. Degeneration of the neuron's long process—the axon—often precedes the death of the cell body and may make a more important contribution to the patient's disability.

Here, we discuss some examples of axonal degeneration in disease and in normal development. We consider one neurodegenerative disease in which axonal degeneration, rather than neuronal death, seems to be responsible for clinical progression and death. We review the evidence that axonal degeneration may occur through a local self-destruct program, which is distinct from the proteolytic program that mediates apoptosis (programmed cell death). We speculate that the same axonal self-destruct program may be used by developing neurons to eliminate unwanted axonal branches, and by unhealthy neurons to eliminate an injured axon or to disconnect from their postsynaptic targets to conserve resources.

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Some Examples of Pathological Axonal Degeneration

A classical example of axonal degeneration is Wallerian degeneration (*6*), which occurs when an axon is cut. The part of the axon that is now disconnected from the cell body disassembles in a characteristic and orderly way (Fig. 1A). In vertebrates, this part of the axon can continue to conduct action potentials for a day or two when electrically stimulated, but it then quickly degenerates: The endoplasmic reticulum breaks down, the neurofilaments degrade, the mitochondria swell, and the axon breaks up into fragments that are phagocytosed (*7*). Wallerian degeneration can occur in both the peripheral nervous system (PNS) and central nervous system (CNS) whenever trauma, a vascular accident, infection, or an immune response locally injures axons.

From the perspective of neurodegenerative diseases, a more relevant form of axonal degeneration occurs in a process called "dying back." Here, the axon of an unhealthy neuron progressively degenerates over weeks or months, beginning distally and spreading toward the cell body (Fig. 1B) (*8, 9*). This is the most common pathology seen in peripheral nerve diseases caused by a wide variety of toxic, metabolic, and infectious insults. It occurs, for example, in the polyneuropathies associated with diabetes (*10*), alcoholism (*11*), acrylamide poisoning (*9*), and AIDS (*12*). It also seems to occur in CNS neurodegenerative diseases, including motor neuron disease (*13*) and Alzheimer and Parkinson diseases (*14*), although it has been less well documented in these cases. The dying-back process is intriguing: How can a cell eliminate part of itself while leaving the rest intact? It contrasts with Wallerian degeneration, in which the axonal lesion itself both starts the destructive process and compartmentalizes it.

Localized axonal degeneration that resembles dying back (and raises the same question) can also occur in cell culture. If the distal part of an axon of a cultured sympathetic neuron is locally deprived of nerve growth factor (NGF), that part of the axon degenerates while the rest of the cell and axon survives (Fig. 1C) (*15*). Normally, NGF acting at the end of an axon not only saves the axon from degeneration but also signals back to the cell body to keep it from undergoing apoptosis, even if the cell body itself is not exposed to NGF (*16*).

Other forms of axonal degeneration that seem distinct from typical dying back occur in various neurological diseases. Degenerating segments of axons and dendrites containing hyperphosphorylated tau protein, for example, are seen in association with amyloid plaques in Alzheimer disease (*17*). Axonal degeneration associated with accumulations of neurofilaments (*18*), α-synuclein–containing Lewy bodies (*19*), or aggregates of huntingtin protein (*20*) is seen in motor neuron, Parkinson, and Huntington diseases, respectively. Even in multiple sclerosis (MS), a prototypic demyelinating disease, axonal degeneration occurs early and may be responsible for much of the chronic disability (*21*); it is still uncertain whether the axonal damage in MS is secondary to the loss of the myelin sheath or is a direct result of the local inflammatory response.

Importance of Axonal Degeneration in Motor Neuron Disease

A study in a mouse model of motor neuron disease points to the overriding importance of axonal degeneration in at least one type of neurodegenerative disease. The *pmn/pmn* mutant mouse develops a progressive motor neuronopathy, in which the axons of motor neurons degenerate in a dying-back pattern and the neurons die by apoptosis (*22*). The mice progressively weaken, beginning a few weeks after birth, and die at around 6 weeks of age. These mice have been crossed with transgenic mice expressing the human *bcl-2* gene in many of their neurons (*23*). The *bcl-2* gene has been shown to inhibit apoptosis in many cell types (*24*). As expected, introduction of the *bcl-2* transgene into the *pmn/pmn* mice prevented the death of the motor neuron cell bodies but had no detectable effect on the axonal degeneration, progressive weakness, or time of death (*25*). Apparently, it is motor neuron axonal degeneration and not motor neuron death that weakens and kills *pmn/pmn* mice.

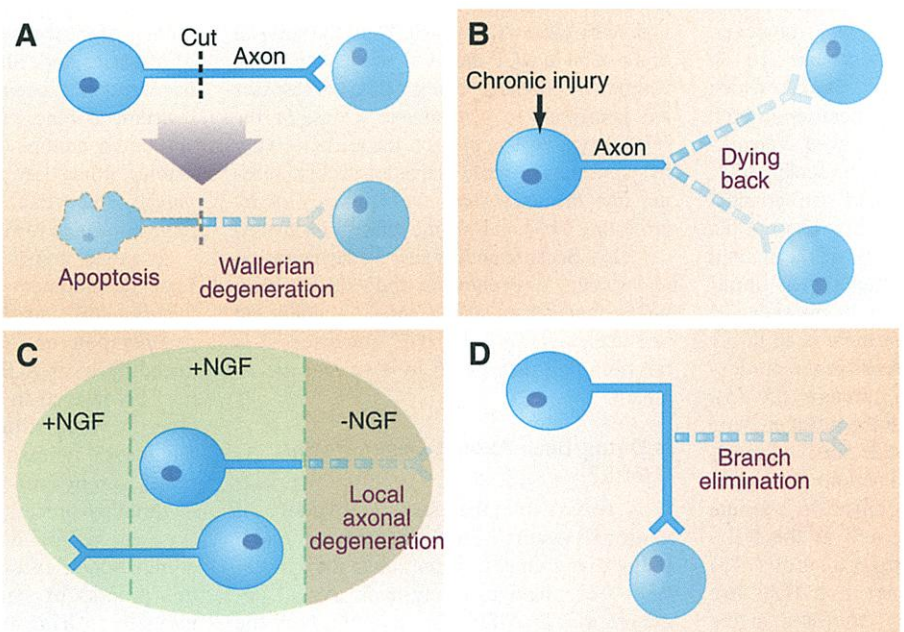

Fig. 1. Various forms of axonal degeneration. **(A)** When an axon is cut, the isolated distal segment rapidly undergoes Wallerian degeneration. When the axon of a developing neuron is cut, the cell body frequently undergoes apoptosis. **(B)** In dying-back axonal degeneration, the axonal tree of an unhealthy neuron slowly degenerates, beginning distally and progressing proximally. **(C)** When the distal part of an axon of a sympathetic neuron is locally deprived of NGF in a three-chamber culture dish, the deprived axon segment degenerates, whereas the rest of the axon and the cell survive. **(D)** During normal development, inappropriate axonal branches are frequently eliminated; in some cases, at least, this seems to occur by branch degeneration.

Physiological Axonal Degeneration

Axonal degeneration may also occur during normal development. Many projection neurons in the brain initially extend axonal branches to inappropriate regions of the CNS; these branches are later lost by a process called branch elimination or pruning (Fig. 1D) (*26*). It may be that a lack of trophic signals from appropriate target cells causes the inappropriate branches to degenerate, much as occurs with the axon of a sympathetic neuron locally deprived of NGF in culture (see Fig. 1C). Similarly, during metamorphosis in holometabolous insects, many of the larval neurons that persist in the adult insect reorganize their axonal tree: Some branches are lost, and new branches form (*27*). Although in most cases it is still uncertain whether axonal branch elimination in vertebrate development or insect metamorphosis occurs by degeneration or by retraction into the parent axon, in some cases it seems to occur by degeneration, as degenerating branches have been directly observed (*28, 29*). Developmental axonal branch degeneration

again raises the intriguing question of how a neuron avoids having the self-destruct process spread to the rest of the axon and cell.

Evidence for Active Axonal Degeneration: The *Wld*^{s} Mouse

The mechanism of Wallerian degeneration is unknown, although at least one part of the process—the breakdown of neurofilaments—depends on an influx of Ca^{2+} and the activation of the Ca^{2+}-dependent protease calpain (*30*). Because severing of the axon (axotomy) cuts off the supply route from the cell body, it has long been thought that the disconnected axon degenerates as a result of "starvation" and just withers away. The discovery of a spontaneous mutation in mice called *Wallerian degeneration slow* (*Wld*^{s}), however, suggests that the degeneration may be an active process (*31*). In these mice, which seem normal, Wallerian degeneration in both the PNS and CNS is greatly slowed. Remarkably, the distal portion of a transected *Wld*^{s} axon can remain viable, and can conduct action potentials for up to 3 weeks, as the result of an intrinsic property of the mutant axon (*32, 33*). The *Wld*^{s} mutation is dominant and has been mapped to the distal end of chromosome 4 (*34*), where there is an 85-kb tandem triplication that results in the production of an abnormal fusion protein (*35, 36*). The fusion protein contains the intact enzyme nicotinamide mononucleotide adenylyl transferase (NMNAT), which functions in the synthetic pathway for nicotinamide adenine dinucleotide (NAD^+), as well as the NH_2-terminal 70 amino acids (of a total of 1173) of the ubiquitination factor E4b (UbE4b). The fusion gene is highly expressed in the *Wld*^{s} nervous system and induces a *Wld*^{s} phenotype when expressed from a β-actin promoter in wild-type mice (*37*). Although the fusion protein has NMNAT activity (*37*), it is not known how it interferes with Wallerian degeneration. NAD^+ levels (*36*), axonal transport (*38–40*), neurofilament phosphorylation and stability (*41*), and levels of Ca^{2+}-dependent proteases (*41*) are apparently normal in *Wld*^{s} axons. As the fusion protein is primarily nuclear, it presumably acts indirectly to protect axons (*37*).

Several lines of evidence suggest that both Wallerian degeneration and the axonal degeneration induced by local NGF withdrawal discussed above occur by mechanisms that are molecularly distinct from that of apoptosis. First, expression of a human *bcl-2* transgene in mouse neurons blocks the axotomy-induced apoptosis of developing retinal ganglion cells, but not the Wallerian degeneration of their axons (*23, 42*). Second, whereas apoptosis depends on a family of cysteine proteases called caspases (*43*), Wallerian degeneration and axonal degeneration induced by local NGF withdrawal apparently do not: Caspase activation is not detected in either form of axonal degeneration in sensory neurons, and caspase inhibitors do not block or slow the degeneration (*44*). Third, whereas Wallerian degeneration is greatly slowed in *Wld*^{s} neurons, apoptosis is not. The cell body of a *Wld*^{s} sympathetic neuron in culture, for example, rapidly undergoes apoptosis when globally deprived of NGF, whereas the axon survives for 6 days or more (*45*).

The last observation is remarkable, especially as one can detect activated caspases in both the cell body and axon when a wild-type sensory neuron is globally deprived of NGF (*44*) and when neurons undergo apoptosis during normal development (*46*). Activated caspases have also been seen in CNS axons that are injured by local trauma (*47*). Thus, the survival of the axon in NGF-deprived *Wld*^{s} sympathetic neurons implies that either activated caspases are innocuous to sympathetic axons, or the *Wld*^{s} fusion protein protects the axons—either by preventing caspase activation from spreading into the axon from the cell body or by protecting the axon from the effects of activated caspases. Because both Wallerian degeneration and axonal degeneration induced by local NGF deprivation are caspase-independent and are slowed by the *Wld*^{s} mutation, it is possible that they occur by a similar mechanism.

Is Dying-Back Axonal Degeneration Useful?

It is remarkable that such a diversity of neuronal insults—including toxins, metabolic disturbances, infections, and mutations—can lead to dying-back axonal degeneration. In AIDS, for example, both the HIV infection itself and some of the drugs used to treat it can give rise to an identical dying-back sensory neuropathy (*48*). A stereotypic cell response to a diversity of insults is reminiscent of apoptosis, which can be induced by extracellular signals or problems in the cytosol, nucleus, mitochondria, or endoplasmic reticulum (*49*). In retinitis pigmentosa, for example, mutations in many different genes encoding proteins in various parts of rod photoreceptors can lead ultimately to apoptotic death of these cells (*50*). Perhaps, in a similar way, dying-back axonal degeneration results from the activation of a self-destruct program in the distal parts of an axon in response to a neuronal insult. It might be, for instance, that the nature, extent, and time course of an insult determines whether a neuron kills itself by activating its caspase-dependent death program or activates its caspase-independent, axonal self-destruct program distally to disconnect from its target cell, thereby conserving energy. In the PNS, at least, the latter strategy enables the neuron to regrow its axon if conditions improve, which frequently happens in peripheral neuropathies. In this view, a severed axon uses the self-destruct program to disassemble quickly and neatly, whereas an unhealthy neuron may use it as a protective mechanism to disconnect from its target cells to conserve resources.

The Way Ahead

Wld^s mice have already provided an important clue that some forms of axonal degeneration may occur by an active process (*31, 51*). If axonal degeneration rather than cell death is responsible for many of the symptoms and signs of various neurodegenerative diseases, as it seems to be in the *pmn/pmn* mouse (*25*), then crossing the *Wld*^{s} mouse with mouse models of these diseases may slow the course of disease. Indeed, *Wld*^{s} sensory neurons have recently been shown to be relatively resistant to vincristine-induced axon degeneration in culture (*52*), and, in preliminary studies, it has been found that (*Wld*^{s} × *pmn/pmn*)F_1 mice live significantly longer than *pmn/pmn* mice (*53*).

If axonal branch elimination during vertebrate development occurs by a mechanism that is similar to that underlying Wallerian degeneration and axonal degeneration induced by local NGF withdrawal, then it too may be delayed in *Wld*^{s} mice. If this is the case, it would strongly suggest that branch elimination normally occurs by degeneration rather than by retraction into the parent axon.

Another process whereby neural connections are refined during development is the elimination of excess synapses (*54*). Because this process of synapse elimination occurs normally in *Wld*^{s} mice, at least at the neuromuscular junction (*55*), it may depend on a mechanism that is distinct from Wallerian degeneration. Indeed, morphological studies suggest that synapse elimination at developing neuromuscular junctions occurs by retraction rather than by degeneration (*56*).

Axonal branch elimination during insect metamorphosis may occur by an axonal self-destruct program that has been conserved in vertebrates and invertebrates during evolution. If so, one route to identify the proteins that mediate and regulate the program could be through classical genetics. A genetic screen for mutations that prevent the loss of specific axonal branches during metamorphosis could be carried out in *Drosophila*, for example (*57*). An alternative route would be to use the *Wld*^{s} fusion protein in "pull-down" or yeast two-hybrid experiments to identify interacting proteins.

Even if the speculative ideas discussed here turn out to be incorrect, the time seems right to divert some of the effort in neurodegeneration research from neuronal death to axonal degeneration. For many neurodegen-

erative diseases, stopping the death of neurons without stopping the degeneration of their axons is unlikely to be helpful.

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