Axonal degeneration and regeneration: a mechanistic tug-of-war

Massimo A. Hilliard

The University of Queensland, Queensland Brain Institute, Brisbane, QLD 4072, Australia

Abstract
Axonal degeneration is a common hallmark of both nerve injury and many neurodegenerative conditions, including motor neuron disease, glaucoma, and Parkinson’s, Alzheimer’s, and Huntington’s diseases. Degeneration of the axonal compartment is distinct from neuronal cell death, and often precedes or is associated with the appearance of the symptoms of the disease. A complementary process is the regeneration of the axon, which is commonly observed following nerve injury in many invertebrate neurons and in a number of vertebrate neurons of the PNS. Important discoveries, together with innovative imaging techniques, are now paving the way towards a better understanding of the dynamics and molecular mechanisms underlying these two processes. In this study, I will discuss these recent findings, focusing on the balance between axonal degeneration and regeneration.

Keywords: axonal regeneration, neurodegenerative diseases, pruning, spinal cord injury, Wallerian degeneration, Wld<sup>S</sup>.


Different triggers of axonal degeneration
Degeneration of the axon has been observed in at least four different conditions: nerve trauma, toxic insults, neurodegenerative diseases, and normal neuronal development (pruning). Axonal truncation as a result of injury causes degeneration of the distal part of the axon that is detached from the cell body. This process, which proceeds in a characteristic and orderly way in which the axon beads, fragments and is finally removed, is commonly referred to as Wallerian degeneration (Waller 1850). It was originally thought that the degeneration of the distal fragment of a severed axon was a passive process due to the lack of trophic support from the cell body. However this concept was challenged in 1989, when Lunn et al. identified a strain of mice, Wld<sup>S</sup>, which displays a much slower rate of axonal degeneration following damage (Lunn et al. 1989). In these animals, the axons survive and maintain function for up to 3 weeks, rather than a few days as observed in wild-type severed axons. The acquired survival capacity of the injured neuronal processes of Wld<sup>S</sup> mutants revealed that the distal axons degenerate actively by triggering a degeneration program, and not by passive lack of support from the cell body. It was later shown that the Wld<sup>S</sup> protective effect also extends to axons and synapses of the CNS (Ludwin and Bisby 1992; Gillingwater et al. 2006).

In addition to mechanical injury, several chemical and toxic insults, including acrylamide, the anticancer drug vincristine, the antibiotic nitrofurantoin, and heavy metals, can cause axonal degeneration and peripheral neuropathy (Prineas 1969; Schlaepfer 1971; Spencer and Schaumburg 1974; Wang et al. 2000; Rubens et al. 2001; Silva et al. 2006). In these cases, axons ‘die back’; with the degenerating phenotypes appearing first on the distal segment of the axon, before progressing proximally toward the cell body (Cavanagh 1964). This dying back phenotype can be generated by damage occurring directly to the distal part of the axon, as a consequence of damage to the mid section of the axon inducing degeneration of the distal fragment, or as a secondary effect of damage to the neuronal cell body (reviewed in Coleman 2005; Conforti et al. 2007a).
In recent years, axonal degeneration has been proposed to be a leading or contributing cause of several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), spinal muscular atrophy, multiple sclerosis, glaucoma, and Alzheimer’s and Parkinson’s diseases (Trapp et al. 1998; Cifuentes-Diaz et al. 2002; Fischer et al. 2004; Stokin et al. 2005; Schlamp et al. 2006; Reviewed in Raff et al. 2002 and Conforti et al. 2007a). In these conditions, axonal degeneration often occurs in a dying-back fashion and is frequently characterized by intracellular protein accumulation. Aggregates of tau, neurofilaments, and α-synuclein are found in the neuronal tissues of Alzheimer’s, Huntington’s, and Parkinson’s disease patients, respectively. In a number of neurodegenerative conditions, axonal degeneration overlaps with degeneration of the cell body (neuronal cell death and apoptosis) and the causal relationship between these events and the symptoms of the disease are not always clear (reviewed in Raff et al. 2002 and Conforti et al. 2007a). However, genetic evidence indicates that axonal degeneration and neuronal cell death are distinct events. In a mouse model of progressive motor neuropathy (pmn mice), the mutant animals develop a neuropathy in which the axons of motor neurons die back and the neurons undergo apoptosis (Sagot et al. 1995). The animals die at around 6 weeks after progressive weakening. Interestingly, when cell death is genetically inhibited by over-expression of bcl-2 in motor neurons, axonal degeneration still occurs, and the onset and progression of the disease, as well as the time of death, remain the same (Sagot et al. 1995). Recent studies using the superoxide dismutase 1 (SOD1) transgenic mouse model of ALS, also mutated in the proapoptotic gene Bax, further support the idea that the clinical symptoms of ALS result specifically from damage to the distal motor axon and not from activation of the cell death pathway (Gould et al. 2006). These studies separate axonal degeneration from neuronal cell death and indicate that axonal degeneration is the leading cause of the disease.

Finally, axonal degeneration also occurs during normal development of the nervous system when neurons lose some of their branches in a process known as ‘pruning’. Many neurons extend their processes in a redundant and excessive manner and some of these branches are selectively removed to achieve the final organized and complex connectivity of the circuit. Pruning has been observed during nervous system development in vertebrates, as well as in invertebrates, such as Drosophila and Caenorhabditis elegans, and this mechanism is necessary to generate a precise neural circuit with flawless neuronal connections (O’Leary and Koester 1993; Lee et al. 1999; Kage et al. 2005; Luo and O’Leary 2005).

Great efforts are being made to discover the molecular machinery underlying the axonal degeneration process, and to determine if the molecular components employed are the same when axonal degeneration is triggered by different conditions. This is a crucial step needed for a full understanding of this highly dynamic process, and some important recent developments are discussed below.

**Molecular mechanisms of axonal degeneration**

After its initial discovery in mice (Lunn et al. 1989), Wld	extsuperscript{S} was also found to protect physically injured axons in rats (Adalbert et al. 2005), as well as in invertebrate systems, as shown for different classes of surgically severed Drosophila olfactory receptor neurons (Hooper et al. 2006; MacDonald et al. 2006). Furthermore, the protective effect of Wld	extsuperscript{S} is not only restricted to physically injured axons, but also extends to axons damaged by toxic insults and neurodegenerative diseases. In mice, Wld	extsuperscript{S} can delay axonal degeneration and neuropathy induced with the toxic agents taxol or vincristine (Wang et al. 2001, 2002a), as well as with 6-hydroxydopamine (6-OHDA), which generates a Parkinson-like disease (Sajadi et al. 2004). Similarly, a Wld	extsuperscript{S} protective effect has been observed in mouse models of different neurodegenerative diseases, including progressive motor neuropathy (pmn mice; Ferri et al. 2003), Charcot–Marie–Tooth disease (myelin protein zero null mutants; Samsam et al. 2003), and gracile axonal dystrophy (gad mutant mice; Mi et al. 2005). However, the role of Wld	extsuperscript{S} is not universal as it cannot protect degenerating axons in either the SOD1 transgenic mouse model of ALS (Vande Velde et al. 2004; Fischer et al. 2005), or the proteolipid protein (Plp) null animal model of hereditary spastic paraplegia (Edgar et al. 2004). In addition, in both Drosophila and mice, Wld	extsuperscript{S} cannot prevent developmentally regulated axonal pruning (Hooper et al. 2006). These lines of evidence indicate an overlap among the mechanisms underlying different axonal degeneration events, but also suggest the existence of alternative, as yet undiscovered, axonal degeneration pathways (Fig. 1). In principle, alternative pathways might exist because of different triggering conditions, different neuronal types, or different developmental stages. In mice, the same class of neurons (retinal ganglion cells) undergoing pruning (and thus not protected by Wld	extsuperscript{S}), if physically severed at the same stage, undergo Wallerian degeneration that can be delayed by Wld	extsuperscript{S} (Hooper et al. 2006). At least in this case, the triggering mechanisms seem crucial for the activation of specific pathways sensitive or insensitive to Wld	extsuperscript{S}-mediated protection.

Positional cloning has revealed that the dominant Wld	extsuperscript{S} mutation is an 85 kb tandem triplication that results in the production of a chimeric molecule (Wld	extsuperscript{S} protein), which includes the N-terminal 70 amino acids of the ubiquitin fusion degradation protein 2a (Ufd2a), the complete sequence of the NAD\textsuperscript{+} synthesizing enzyme NMN adenylyltransferase 1 (Nmnat1), and a linker region of 18 amino acids (Lyon et al. 1993; Coleman et al. 1998; Conforti et al. 2000; Mack et al. 2001). Considerable experimental evidence suggests an important role of Nmnat1 and the NAD\textsuperscript{+} pathway in protecting axons from degeneration (Araki et al. 2004; Wang
et al. 2005; Sasaki et al. 2006). In the Wld\textsuperscript{S} mutation, part of the protective effect could arise from the over-expression of Nmnat1 with a consequent increase in NAD\textsuperscript{+} levels (Araki et al. 2004). Araki et al. have also shown that the sirtuin silent mating type information regulation 1 (SIRT1), a NAD\textsuperscript{+}-dependent histone deacetylase (the mammalian ortholog of Sir2), is a downstream effector of Nmnat1 activation that leads to axonal protection. A particularly interesting and relevant finding is that resveratrol, a polyphenol found in red grapes and an enhancer of silent mating type information regulation 2 activity, is able to mimic the axonal protective effect of NAD\textsuperscript{+} (Araki et al. 2004). However, in different conditions Nmnat1 alone cannot fully recapitulate the effect of the Wld\textsuperscript{S} mutation, suggesting the involvement of other components of the chimera protein (Conforti et al. 2007b; Watanabe et al. 2007).

Extensive data indicate that the ubiquitin proteasome system (UPS) is a critical player in axonal degeneration, although its role appears more complex (Fig. 1) (Saigoh et al. 1999; Zhai et al. 2003; Watts et al. 2003; reviewed in Korhonen and Lindholm 2004; Hoopfer et al. 2006). In Drosophila, axonal pruning and axonal degeneration following injury depend on a functional UPS (Watts et al. 2003; Hoopfer et al. 2006). Similarly in rat, axonal degeneration following injury is delayed by inhibition of the UPS (Zhai et al. 2003). In the Wld\textsuperscript{S} mutation, the truncated UPS molecule (Ufd2a) might function as a dominant negative and provide some axonal protection. However, different mutations reducing the function of UPS molecules can also be the cause of neurodegenerative diseases and axonal degeneration, as observed in Parkinson’s disease patients carrying mutations in the gene parkin (ubiquitin-protein ligase) (Kitada et al. 1998; Shimura et al. 2000) and in gad mice (ubiquitin carboxy-terminal hydrolase-L1) (Saigoh et al. 1999). This apparent paradox of UPS functioning in both directions (degeneration–protection) could be explained by different levels of UPS triggering diverse responses, by UPS having alternative effects in different neuronal compartments.
(cell body, axon, or synapse), or by mutation in different components of the UPS in turn affecting different molecular substrates. Recent important findings have shown that the N-terminal 70 amino acids of WldS bind directly to vasolin-containing protein (VCP/p97), a protein with a key role in the ubiquitin proteasome system (Laser et al. 2006). Interaction with WldS targets VCP in discrete intranuclear foci where other UPS components can also accumulate (Laser et al. 2006). Thus, the N-terminal domain of WldS influences the intranuclear location of the ubiquitin proteasome as well as its intrinsic NAD⁺ synthesis activity, although VCP itself can also regulate WldS intracellular distribution (Wilbrey et al. 2008). Differential proteomics analysis on isolated synaptic preparations from the striatum in mice has revealed 16 proteins with modified expression levels in WldS synapses (Wishart et al. 2007). Interestingly, downstream protein changes were found in pathways corresponding to both Ufd2a (including ubiquitin-activating enzyme 1) and Nmnat1 (including voltage-dependent anion-selective channel protein and aralar1, calcium-binding mitochondrial carrier protein) (Wishart et al. 2007). Furthermore, increased expression of a broad spectrum of cell cycle-related genes was found in the cerebellum of WldS mice and in WldS-expressing human embryonic kidney 293 cells (Wishart et al. 2008), suggesting a correlation between modified cell cycle pathways and altered vulnerability of axons.

Recently, axonal pruning and axonal degeneration following injury have been shown to have other common effectors. Cell death abnormality (CED)-1/Draper and CED-6 are scavenger receptor-like molecules essential for the clearance of apoptotic cells in C. elegans and Drosophila (Liu and Hengartner 1998; Zhou et al. 2001; Freeman et al. 2003). In worms they are expressed in the phagocytic cell, whereas in flies they are expressed in the glia. Mutations in ced-1/draper inhibit clearance of the distal fragment of severed axons in Drosophila olfactory receptor neurons (MacDonald et al. 2006). Similarly, in axons of the Drosophila mushroom body, ced-1/draper and ced-6 are necessary for the clearance of axonal fragments undergoing pruning (Awasaki et al. 2006). The finding that cell death genes such as ced-1 and ced-6 are involved in the axonal degeneration process suggests a partial commonality in the mechanisms, at least in the later stages of these events, such as the removal of axonal fragments or cell bodies after damage. The activation of the glia and the function of these receptor molecules indicate the existence of specific signals coming from the damaged axon to which the glia are responding. Discovering these cues is a key step towards understanding further how axonal degeneration is triggered and achieved.

Mechanisms of axonal regeneration

Following axotomy, while the distal segment of the severed axon undergoes Wallerian degeneration (Fig. 2a), the proximal fragment attached to the cell body confronts two potential fates: degenerate in a dying back fashion or attempt to reconnect with its target by regeneration. Successful axonal regeneration can be defined as the ability of a severed axon to re-establish connectivity with its target. This can happen through precise regrowth of the axon (proximal fragment) from the injury site toward its target following the original pathway (Fig. 2b), through regrowth from the injury site toward its target along an ectopic pathway (Fig. 2c), or through sprouting from an axonal section far from the injury site along an ectopic pathway (Fig. 2d). However, following nerve injury, functional recovery can also occur through other mechanisms, for example by sprouting from other non-damaged neurons compensating for the loss of a neighboring tract, or by plasticity of the system, with new contacts made among surrounding neurons. An alternative mechanism of axonal regeneration occurs in invertebrates (including the leech, crayfish, and C. elegans), where the proximal regenerating axon can directly contact its distal fragment, re-establishing connectivity and preventing it from degenerating (Fig. 2e) (Hoy et al. 1967; Carbonetto and Muller 1977; Deriemer et al. 1983; Yanik et al. 2006).

In humans and other mammals, axonal regeneration occurs in the PNS while it is reduced or absent in the CNS. In zebrafish, some CNS neurons are able to regenerate while others are not. Likewise, in C. elegans, with only 302 unmyelinated neurons, some axons regenerate after injury whereas others do not. Axonal regeneration fails due to two causes: a non-permissive external environment and neuronal intrinsic factors. A large body of work in vertebrates has revealed the crucial inhibitory role that the glia play in the regenerative ability of a CNS axon following injury (reviewed in Harel and Strittmatter 2006; Bradbury and McMahon 2006; Yiu and He 2006). Several myelin-associated inhibitors have been discovered, including Nogo (a member of the reticulon family) (Chen et al. 2000; GrandPre et al. 2000; Prinjha et al. 2000), myelin-associated glycoprotein (McKerracher et al. 1994; Mukhopadhyay et al. 1994), oligodendrocyte myelin glycoprotein (Wang et al. 2002b), ephrin B3 (Benson et al. 2005), and the transmembrane semaphorin 4D/CD100 (Moreau-Fauvarque et al. 2003). Identified receptors for these molecules include Nogo receptor (Fournier et al. 2001; Domeniconi et al. 2002; Liu et al. 2002; Wang et al. 2002b), P75 (Wang et al. 2002c; Wong et al. 2002; Yamashita et al. 2002; Domeniconi et al. 2005), TROY (Park et al. 2005; Shao et al. 2005), and LINGO1 (LRR and Ig domain-containing, Nogo receptor interacting protein) (Mi et al. 2004). An additional important source of inhibition comes from the glial scar. Here, reactive astrocytes, recruited to the site of injury, secrete inhibitory extracellular matrix molecules such as chondroitin sulfate proteoglycans. In these molecules, long unbranched glycosaminoglycan chains are attached to a proteic core, and

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evidence exists that these play an important role in the inhibition of axonal regeneration (reviewed in Silver and Miller 2004; Carulli et al. 2005).

In addition to extracellular elements, numerous studies have revealed the crucial role that neuronal intrinsic factors play in determining the regenerative ability of a neuron. An example of this lies in the inability of some injured axons to regrow even if placed in a permissive environment. Important findings have shown that pre-conditioning nerve lesions generated days in advance can influence and enhance the regenerative potential of a subsequent lesion of the same nerve (McQuarrie and Grafstein 1973). Similar results have been obtained more recently in mice, using neurons of the dorsal root ganglia (DRG). These neurons present two branches coming out of the unipolar axon, a peripheral branch that can regenerate and a second branch that enters the CNS and is unable to regenerate. Pre-conditioning lesions on the PNS side of the DRG axons can have a strong enhancing effect on the regenerative ability of the CNS side of these axons, allowing regeneration into and beyond the lesion site (Neumann and Woolf 1999). Thus, the pre-conditioning lesions are able to enhance the intrinsic growing capacity of these neurons. One mechanism underlying the increased axonal regrowth appears to be based on cAMP levels. In fact, similar results of increased axonal regrowth can be mimicked with pre-treatment of the DRG neurons with a membrane-permeable cAMP analog (dibutyryl cAMP; db-cAMP), which elevates the intracellular concentration of cAMP in these cells (Neumann et al. 2002). In addition, peripheral lesion or incubation with db-cAMP enables neurites to grow on inhibitory substrates (Neumann et al. 2002). These results have been extended further in zebrafish, based on a model using the Mauthner cells (M cells), the myelinated neurons necessary for escape

Fig. 2 Schematic illustration of axonal regeneration mechanisms. After injury the distal fragment undergoes Wallerian degeneration (a). The proximal fragment can regrow (b) from the site of injury toward its target (neuron or muscle) along the same pathway where the distal fragment lay, (c) from the site of injury along new alternative pathways, or (d) through sprouting from an axonal section different from the site of injury along an ectopic pathway. Alternatively, as observed in Caenorhabditis elegans and other invertebrates, (e) the proximal regenerating fragment can directly contact its distal fragment, re-establishing connectivity and preventing it from undergoing Wallerian degeneration.
behavior (Bhatt et al. 2004). The axon of the M cell regenerates poorly after spinal lesion, although other neurons in the nerve cord are able to regenerate, indicating the permissive environment of this tissue. In this case, application of db-cAMP directly onto the somata of the M cells 3–5 days after the lesion allows axonal regeneration through and beyond the injury site (Bhatt et al. 2004). Thus, a cell-intrinsic mechanism can change the growth-state of neurons and provide them with an acquired ability to overcome inhibitory stimuli.

Additional evidence on the important role that neuronal intrinsic factors play in axonal regeneration comes from studies of brainstem neurons in chick. Changes within maturing brainstem neurons dramatically reduce their ability to regenerate their axons, even into a young spinal cord that allows abundant axonal regeneration from young brainstem neurons (Blackmore and Letourneau 2006a). L1/neuron–glia cell adhesion molecule, β1 integrin, and cadherins are crucial elements for axonal regeneration in these neurons as simultaneous blockage of these molecules reduces the axonal growth of embryonic neurons by 90% (Blackmore and Letourneau 2006a,b).

An important aspect in the understanding of such an active process as axonal regeneration is the identification of the dynamic events taking place at the injury site. Recent improvements of in vivo imaging following nerve injury have allowed this issue to be addressed, revealing key details of the precise dynamics of axonal degeneration and regeneration in the CNS (Bareyre et al. 2005; Kerschensteiner et al. 2005). Kerschensteiner et al. have used a transgenic strain of mice expressing green fluorescent protein in a subset of neurons, including those of the DRG. In this system, individual DRG axons in the spinal cord are monitored immediately after injury (induced with a small needle) and over the following several hours. In the first half an hour, the proximal and distal axonal fragments undergo a symmetrical acute degeneration phase, which causes them to separate (300 μm). The acute axonal degeneration is responsible for almost 90% of the total axonal loss occurring in the first 4 h after injury. The symmetry of this degeneration is very relevant because it eliminates part of the axon (proximal) that is still linked to the cell body, including branches if present. The onset of proper Wallerian degeneration of the distal segment takes place between 1 and 2 days after injury. Interestingly, in the first 2 days 30% of the proximal segments show active and rapid regeneration, in some cases starting as early as 6 h after injury. However, these sprouts grow in different directions without getting substantially closer to their targets, possibly because they lack correct guidance cues. These results support the idea that some adult neurons in the CNS possess an intrinsic potential to regenerate in vivo.

In a much simpler scenario of axonal regeneration, as observed in C. elegans (see below), the proximal segment of a severed axon would regrow, reconnecting with its distal fragment. This would prevent it from degenerating and lead to the recovery of neuronal function. For this to occur, the regenerating fragment would need to reach the distal fragment in a timely manner before Wallerian degeneration irreversibly takes place. However, earlier studies in mice have shown that axonal regeneration in PNS motor and sensory neurons is delayed in Wldε mutants compared with wild-type animals (Bisby and Chen 1990; Brown et al. 1992, 1994). In the proposed model, axonal regeneration is impaired when Wallerian degeneration does not follow its normal time course after injury. From this perspective, degeneration of the distal stump would enhance the active regrowth of the proximal segment into the damaged area. A delicate balance must be in place to ensure a certain degree of degeneration that allows functional regrowth in the PNS. This hypothesis is supported by the fact that multiple lesions along the nerve stump increase the axonal regeneration rate (Brown et al. 1994). However, this is a less intensely explored field and it would be interesting to see if, in light of these new findings, it is also possible to enhance functional axonal regeneration in a more intact tissue protected from degeneration.

Recent technical advances have now made it feasible to study axonal regeneration in genetically tractable organisms such as C. elegans (Yanik et al. 2004). In worms, a laser microbeam can be used to snip individual axons of green fluorescent protein-labeled neurons, and the axonal regeneration pattern can be observed. Despite the absence of myelin, the restricted number of glial cells (about 50), and the overall simplicity of the system, some axons do regenerate whereas others do not (Yanik et al. 2004, 2006; Wu et al. 2007; Gabel et al. 2008). These differences offer enormous opportunities to understand how neuronal intrinsic regenerative potential is established. In C. elegans, when individual processes of the anterior and posterior lateral mechanosensory neurons (ALM and PLM respectively) are axotomized, their proximal fragments will regrow toward their distal fragments. If the regenerating proximal axon makes contact with the distal fragment, the distal fragment is protected and survives; otherwise it invariably undergoes Wallerian degeneration (Yanik et al. 2006). In this case, time is of the essence to shift the balance toward a fully successful regeneration rather than towards a degenerative condition. Developmental stage affects axonal regeneration, with older animals being less successful in regenerating their neuronal processes (Wu et al. 2007). Using a candidate gene approach and the posterior lateral mechanosensory neuron as a model, Wu et al. have shown that ephrin signals influence the guidance of regrowing axons. In ephrin or Eph receptor mutants, the regenerating axonal process grows straighter than in wild-type animals. In a similar set of experiments using a different anterior ventral mechanosensory neuron (AVM), Gabel et al. (2008) have shown that
MIG-10/Lamellipodin, UNC-34/Enabled, and CED-10/Rac are necessary for correct axonal regrowth.

It appears that *C. elegans* genetics has not yet attained its full power in this field, one reason being the time-consuming surgery step (about 10 min/animal). Recent engineering applications, based on the development of microfluidic devices designed to trap one or more individual worms into small chambers, have addressed this issue and reduced by a factor of 10 the time required for the surgery (Guo et al. 2008). Importantly, these novel tools allow immobilization of the worm without the use of anesthetics. This has already revealed the interesting finding that the regeneration process occurs on a much faster time scale (in the first hour after surgery) than previously thought, and that the distal fragment of a severed axon is also able to undergo active regrowth (Guo et al. 2008). These essential technical advances mean unbiased genetic screens and pharmacological screens are now a realistic possibility (Rohde et al. 2007; Guo et al. 2008).

Another recent important discovery is the identification and characterization of a *C. elegans* mutant strain with a defect in the gene unc-70, encoding for β-spectrin (Hammarlund et al. 2000, 2007; Moorthy et al. 2000). β-Spectrin forms part of the membrane skeleton of most cells, including neurons (Bennett and Baines 2001). In unc-70 mutants, the axons of the GABAergic motor neurons continuously break and attempt to regenerate (Hammarlund et al. 2007). These animals therefore provide an excellent genetic tool to study axonal degeneration and regeneration in great detail.

It is foreseeable that in the coming years new essential molecules and mechanisms involved in these crucial processes will be discovered, possibly contributing to the development of more effective therapies.

**Conclusion**

Like two sides of the same coin, axonal degeneration and regeneration are crucial processes regulating normal development as well as pathological conditions of the nervous system. We have acquired some knowledge of the neuronal intrinsic and extrinsic factors underlying axonal degeneration and regeneration as distinct processes, although we are just starting to understand how they are connected and how they can influence each other. In some cases, as in vertebrates, a certain level of degeneration appears to be necessary for axonal regeneration to occur; in other cases, as in invertebrates, successful axonal regeneration seems independent of degeneration or even functionally improved if degeneration does not take place. Research aimed at understanding the molecular and cellular basis underlying these mechanistic differences might reveal important elements necessary for the development of more effective therapies for neurodegenerative conditions and nerve injuries. The substantial improvement of imaging techniques to visualize these dynamic processes in higher organisms, together with the development of genetic animal model systems suitable to address these biological questions, are now providing high hopes that key discoveries will occur in this frontier field of neurobiology.

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