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An axonal stress response pathway: degenerative and regenerative signaling by DLK

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Abstract

Signaling through the dual leucine zipper-bearing kinase (DLK) is required for injured neurons to initiate new axonal growth; however, activation of this kinase also leads to neuronal degeneration and death in multiple models of injury and neurodegenerative diseases. This has spurred current consideration of DLK as a candidate therapeutic target, and raises a vital question: in what context is DLK a friend or foe to neurons? Here, we review our current understanding of DLK's function and mechanisms in regulating both regenerative and degenerative responses to axonal damage and stress in the nervous system.

Introduction

An overarching question is whether mechanisms that are required for the wiring of neuronal circuits during development can be re-utilized to stimulate repair after damage or to restore function after loss in disease. In contrast to development, the capacity to repair mature neuronal circuits following damage, and, in many circumstances, the inability to repair, is linked to the activation of damage response pathways in the nervous system. Injury response signaling mediated by the dual leucine zipper-bearing kinase (DLK) is critical for neurons to initiate new axonal growth in the peripheral nervous system (PNS). However, this same kinase enhances neuronal death and degeneration in a growing number of models for neuronal injury, stress and neurodegenerative diseases. These dichotomous responses, along with other recent observations discussed in this review, can be reconciled into a unified view in which DLK regulates and coordinates stress response signaling in neurons [1].

In particular, DLK signaling appears specifically tuned to stressors that impair or damage axons (Figures 1, 2 and Table 1). These stressors include mechanical transection (Figure 1), which leads to activation of DLK signaling in all neurons and model organisms examined thus far [2–7]. They also include more chronic forms of stress associated with genetic mutations and drugs that hinder the microtubule cytoskeleton and axonal transport within neurons (Table 1 and Figure 2). Since axons often extend over great distances, reaching lengths of over 1000 times the diameter of the neuron's cell body [8], the integrity of the axon and the ability to transport organelles and proteins within it is a point of vulnerability

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for neurons. Such impairments within an axon can effectively silence a neuron from communicating with its post-synaptic targets, so it is logical that neurons should have mechanisms to monitor the state of their axon. In this review we will discuss how DLK's signaling mechanisms and functions appear to be intimately linked to the process of axonal transport.

As a mitogen-activated protein kinase kinase kinase (MAP3K), DLK functions as an upstream regulator of MAP Kinase signaling by activating the MAP2Ks MKK7 and MKK4, and the stress activated kinases JNK and p38 [9,10] (Figure 1). In mammals, DLK (MAP3K12) has a sister kinase, MAP3K13 (LZK), which has some partially overlapping biochemical activities and roles [9,11•]. Worms (*Caenorhabditis elegans*) and flies (*Drosophila melanogaster*) each have a single orthologue of equivalent homology to both DLK and LZK, named DLK-1 and Wallenda. Since these kinases share similar functions with DLK in the nervous system, we refer to all of these related kinases as 'DLK' in this review.

Developmental roles versus stress response

Some roles in nervous system development, including developmental neuronal cell death in sensory and motor neurons, neuronal migration, axon formation, and axon outgrowth have been documented for DLK and LZK [12–16], particularly when disrupted in combination with other components of JNK signaling [16] (Table 1). More dramatic defects in developmental wiring of the nervous system have been linked to lost regulation of DLK: DLK protein is held in check by a highly conserved ubiquitin ligase, Pam/Highwire/Rpm-1 (PHR) [17–20]. This restraint appears to be important for some axon guidance decisions [17,21], axon termination at correct locations [22,23], assembly of presynaptic machinery [19,20,24••], and elaboration of dendrite branches [25]. Hence restraint verses activity of DLK appears to be important at specific time points in nervous system development.

In contrast to development, in which only mild axon outgrowth defects have been noted for loss of *dlk* function in sensory and motor axons [12–15,26], DLK becomes activated in all types of neurons and axonal damage paradigms examined thus far in multiple model organisms [2–7], and is required for both regenerative and degenerative responses to axonal damage (Table 1). Many of the developmental defects associated with unrestrained DLK regulation may actually mimic responses made by neurons to axonal injury. For instance, recent studies using the Drosophila larval neuromuscular junction (NMJ) suggest that activation of DLK signaling promotes synaptic decline [24••,27•], which also occurs at disconnected synapses following injury [28]. Another well known response to axonal injury is a reduction in the injured neuron's dendritic tree and in the synaptic inputs received by the injured neuron [29,30]. Whether DLK promotes post-developmental changes in dendrite architecture remains to be examined, however recent findings that DLK mediates a reduction in synaptic spines in a mouse model of Alzheimer's Disease [31••] suggests this possibility.

Considering DLK's major role in damage responses, and that its most striking requirement during development is for programmed neuron cell death [14], one may speculate that DLK's function and restraint is relevant for developmental transitions in which neurons

inherently experience conditions of cellular stress. For instance, limited levels of neurotrophic factors, or major rearrangements in neuronal cytoskeleton required for neuronal migration, may be considered ‘stressful’ for neurons. Also, Li *et al.* found that DLK signaling restrains the expression levels of presynaptic proteins to match the timing of synaptic maturation and growth [24••]. Premature expression of these abundant structural components of the synapse fully ready to transport and implement these molecules may also result in cellular stress.

DLK regulates retrograde responses to axonal damage and trophic factor withdrawal

A large body of work supports a unified view that DLK regulates an axon-to-nucleus signaling cascade that monitors the state of the axon and becomes activated in response to axonal damage. Endogenous DLK associates with vesicles [3], and live imaging studies of GFP-DLK transgenes suggest these vesicles are transported both anterogradely and retrogradely in axons [3,32]. DLK function is required cell autonomously for nuclear responses induced by axonal injury, including the activation of specific transcription factors [2,4,5,7,11•,14,33••]. These include phosphorylated STAT3, which is thought to be retrogradely transported in peripheral nerves from axons to the nucleus [5], and also transcriptional reporters for JNK signaling [3]. Mutations that disrupt retrograde axonal transport, including mutations in dynein and dynactin [3] and a known cargo for retrograde transport, JNK interacting protein JIP3, inhibit cell body responses downstream of DLK [14,34]. Importantly, DLK’s actions and signaling mechanisms appear specifically tuned to axonal damage and not dendrite damage: in contrast to axonal regeneration, DLK is not required for the regrowth of dendrites following injury [35,36•]. In addition, certain cell body responses to axonal injury induced by DLK are not induced by dendritic injury [37–39].

DLK was first discovered to play an essential role in the ability of axons to initiate new axonal growth following injury in the PNS [2,3,5,6,40]. However, following CNS injury in the optic nerve, DLK signaling initiates a cell death program [4,7]. Death downstream of DLK can be induced by other signals, including trophic factor withdrawal [14], which is known to rely upon retrograde transport and whose response can be probed specifically in axons using compartmentalized cultures [42,43]. Strikingly, DLK is essential for this classic form of developmental apoptosis in embryonic dorsal root ganglion (eDRG) neurons [14]. Moreover, DLK signaling can originate from the axonal compartment following NGF withdrawal: biochemical indications of DLK and JNK activation can be detected in extracts isolated from axons [44•], and inhibition of DLK and/or JNK solely in the axonal compartment can inhibit the appearance of downstream signaling markers in the cell body [14,44•]. These studies demonstrate compellingly DLK’s ability to initiate compartmentalized signaling within axons.

Links between DLK signaling, cytoskeleton and axonal transport

Intracellular transport within axons becomes acutely blocked at sites of axonal damage, and it can also become impaired or diminished in the presence of cellular stressors (Figure 2),

such as chemotherapeutic agents that disrupt the cytoskeleton [45] or accumulations of misfolded proteins in neurodegenerative disease models [46]. There is a striking correlation between conditions that impair axonal transport and conditions that activate DLK signaling: DLK signaling becomes activated in invertebrate and vertebrate PNS neurons that are treated with cytoskeletal destabilizing agents [47,48•,49,50], or with genetic mutations in the cytoskeletal components spectroplakin, TCP1, Tau, or spectrin [6,47,51•]. Activation also occurs in mutations that impair the kinesin Unc-104 (homologous to Kif1A), which is a major carrier of synaptic vesicle precursors in axons [24••]. Mutations that inhibit DLK signaling rescue the synaptic defects associated with mutations in the kinesin *unc-104* [24••]. Other genetic interaction studies in invertebrate peripheral neurons suggest that DLK mediates changes in neuronal morphology caused by mutations that impair cytoskeletal structure [47,52–55]. Hence DLK signaling appears responsible for both neuronal plasticity and for major pathologies associated with defects in cytoskeleton and axonal transport.

Many previous studies have suggested that JNK signaling may directly regulate kinesin and dynein motors and their cargos [56,57]. However, Li et al. found that DLK signaling tunes the expression levels of presynaptic proteins, which are major cargoes for transport in axons by the Unc-104 kinesin [24••]. The restraint of presynaptic protein levels by DLK signaling when axonal transport is impaired may function as a negative feedback loop to reduce stress by decreasing the amount of cargo for transport, thereby minimizing build-up. These findings suggest that DLK can function as both a sensor and effector to regulate intracellular transport within axons.

DLK signaling contributes to neurodegenerative disease

The degenerative responses induced by DLK are gaining increased attention for their roles in a growing number of neurodegenerative diseases. These include glaucoma, where functional genomic screens have identified DLK and LZK as key mediators of retinal ganglion cell (RGC) death [7,11•]. In addition, recent studies have suggested that DLK knockout or inhibition can delay pathology in multiple models of Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD) [31••,58]. DLK inhibition is also protective in other models of neuronal death, including models of subarachnoid hemorrhage [59], 6-OHDA-induced dopaminergic cell death [60] and excitotoxicity [61], further increasing interest in DLK as a potential therapeutic target.

These findings imply that DLK signaling can be activated in contexts beyond simple axonal injury. It is also now apparent that the fundamental role of DLK signaling is not simply to increase axonal regeneration, despite its importance in regeneration paradigms. The dichotomous roles in regeneration and degeneration may be unified into an underlying biological function to stimulate pathways that allow the nervous system to react to axonal damage and cellular stress. Similar to other stress pathways (including ER stress and DNA damage) transient activation of stress pathways enables recovery, however chronic activation leads to cell death [62,63].

DLK signaling influences axonal integrity

An overarching theme for DLK signaling roles relates to the integrity of axons and trafficking within axons. It is striking that the multiple scenarios of DLK signaling summarized in Figures 1 and 2 also share a common resulting phenotype of axonal degeneration. Disruption of DLK together with other components of MAPK signaling leads to strong inhibition of axonal degeneration following axotomy [64,65], trophic factor withdrawal [14,41,66•] and chemotherapy-induced axon degeneration [64,67]. We therefore consider here our current understanding of the mechanistic relationships between DLK signaling and axonal degeneration.

Since DLK signaling may be initiated locally in axons and can regulate global (transcriptional/translational) responses in neurons, its influence upon axonal integrity and degeneration is likely multi-pronged, involving both local mechanisms in axons and global mechanisms downstream of retrograde signaling [68]. The ‘global’ responses downstream of retrograde signaling are simplest to consider first. Following trophic factor withdrawal in mouse DRGs, DLK and downstream MAPK signaling induce the expression of pro-apoptotic proteins Bax, Puma and caspases, some of which stimulate axonal degeneration following their induction in the cell body [66•]. A strikingly opposite protective response has been observed in fly motoneurons, where activation of DLK, either by ectopic expression or axonal injury, leads to a global response that increases the resiliency of both axons and dendrites to degenerate in subsequent injuries [38,69]. These responses may serve a biological purpose for neurons that have been injured to have increased resiliency to subsequent damage. In contrast, the pro-degenerative actions downstream of trophic factor deprivation may allow for pruning of axonal branches.

Together with downstream MAPK signaling effectors, DLK signaling also acts locally in distal axons to influence axonal degeneration. This may be most clearly considered for Wallerian degeneration of distal axons that become separated from cell bodies following acute axonal injury (pictured in Figure 1). Wallerian degeneration involves cell autonomous ‘self-destruction’ events that occur locally in axons independent of classical cell death machinery [70,71]. Acute inhibition of JNK in axotomized axons is sufficient to delay axonal degeneration [64], suggesting a local role for DLK/JNK signaling in promoting axon destruction.

What is this local role in axons? A key driver of Wallerian degeneration is the TIR-domain protein Sarm1, which functions as a NADase enzyme, degrading the essential metabolite NAD+ [72,73]. Sarm1 function is antagonized by the NAD+ biosynthetic enzyme NMNAT2 [74,75•], which, due to its short half-life in axons, must be continuously transported in axons from the cell body [76]. Yang *et al.* observed that genetic inhibition of MAPK signaling could blunt degeneration induced by ectopic activation of Sarm1 in DRG explants, and proposed a role for MAPK in promoting degeneration downstream of Sarm1 [65]. However Walker *et al.* more firmly identified an upstream role with the finding that MAPK signaling enhances the stability/turnover of NMNAT2 in both mouse DRG and fly motoneurons [75•]. Connections between DLK and NMNAT2 are also noted via their shared regulation by the PHR ubiquitin ligase [18–20,69], which is discussed further below in section 8. We

acknowledge inherent challenges to distinguishing local from global effects of DLK signaling, which likely intersect to influence axonal integrity.

Stress responses regulated by DLK

Given the many cellular responses to DLK activation discussed above, surprisingly little is currently documented about the cellular pathways controlled by DLK. The known pathways thus far all share features of roles in stress response. Studies in worms have suggested that DLK signaling leads to increased mitochondrial transport and density in axons after injury [77], and that DLK signaling stimulates the expression of poly(ADP-ribose) glycohydrolases (PARGs) [78], which are linked to a growing number of genotoxic and metabolic stress signaling pathways[79].A recent study using mouse models of axonal stress in both the PNS and CNS found that DLK is a critical regulator of the Integrated Stress Response (ISR) pathway [33••]. ISR appears to influence translational responses in cells: while global translation is inhibited, genes with upstream Open Reading Frames such as ATF4 can be selectively induced. These findings are interesting in light of other data linking ISR to neuronal loss in models of neurodegenerative diseases[80,81],as well as studies linking DLK to translational mechanisms of regulation [2,82].

In addition to cell-autonomous stress responses, DLK signaling may also promote responses by non-neuronal cell types. A recent study in flies suggested that signaling downstream of DLK (via p38) may increase neuroinflammation in a TDP-43 overexpression model of neurodegenerative disease [83], while conditional knockout of DLK in a ALS mouse model reduced the appearance of activated microglia [31••]. A recent study found that DLK controls the expression of neuroinflammatory chemokines and is required for microgliosis and neuropathic pain [106•] Future studies are needed to determine whether these pathways are controlled by DLK in different cell types and model organisms and to understand their mechanisms in axonal stress responses.

Mechanisms for restraint and activation of DLK signaling

Essential for the current model that DLK gates responses to axonal stress is that its mechanism is tightly tuned to axonal damage and restrained in healthy/undamaged neurons. One important mechanism of control is at the level of protein stability and turnover. Genetic perturbations in multiple components of ubiquitin ligase complexes and deubiquitinating enzymes result in elevated DLK levels and chronically activated DLK signaling [19,20,84,85]. Moreover, overexpression of DLK in neurons, and even ectopic expression of DLK in non-neuronal cell types, is sufficient to activate downstream signaling [10,20,41]. This is thought to be mediated by its capacity to dimerize via leucine zipper domains and phosphorylate itself [9]. Once activated, downstream signaling via JNK stimulates DLK phosphorylation at additional sites and a decrease in DLK's turnover rate [41]. This feed-forward relationship may enable neurons to kick-start DLK signaling in response to a local damage event in axons. How does DLK become activated? A growing number of conditions, kinases and some phosphatases have been implicated in its regulation [23,41,84,86•,87–95], and activated DLK is heavily phosphorylated across multiple sites [41,86•]. However, the molecular mechanisms that link various stressors in axons (in Figures 1 and 2) to DLK

activation are still poorly understood. Recent work has indicated that Protein Kinase A (PKA) is an important mediator of DLK's activation following axonal injury [86•], while Ste20 Kinases MAP4K4, MINK1 and TNIK promote DLK's activation in axons following trophic factor withdrawal [44•]. Whether these different stressors use overlapping or distinct mechanisms is not yet known. C. *elegans* DLK-1 contains a domain shared with MAP3K13/LZK that gates signaling activation in response to elevated calcium [96]. However application of microtubule destabilizing agents to axons leads to activation of DLK signaling independently of calcium [48•]. Hence it is likely that multiple distinct mechanisms regulate DLK activation in neurons.

DLK's retrograde signaling functions require that DLK is physically present to become activated in axons. A conserved site for palmitoylation allows DLK to associate with vesicles that are transported in axons, and palmitoylation is essential for DLK's signaling ability [97]. Since defects in axonal transport and the cytoskeleton lead to DLK activation, is DLK transport directly linked to its activation mechanism? It is intriguing that a major negative regulator of DLK, the PHR ubiquitin ligase, localizes to presynaptic terminals [98–100], hence may promote destruction of DLK at synapses (Figure 3). It is also intriguing that PHR regulates axonal degeneration via an additional target, the protective enzyme NMNAT2 [18,101] and Figure 2). PHR's regulation of DLK is best documented in the context of synapse development, where PHR's regulation of DLK becomes apparent with a timing that coincides with termination of axonal outgrowth and the initiation of synaptogenesis [20,102]. Since axonal damage inherently disrupts synaptic connections in axons, whether PHR influences DLK's activation mechanisms following axonal damage remains an interesting future question.

Conclusion

We propose that a higher order function for DLK signaling may be to promote a damage-response state in neurons that enables plasticity in neuronal circuits. In this state, the ultimate response may be strongly influenced by the circumstance of the damage. In some contexts, such as PNS injury, neurons may be supported for growth and inhibited for death. However in other contexts, in order to incur the least damage or the best adaptation within a neuronal circuit, it may be more advantageous for the damaged neuron to degenerate and be removed. As an evolutionarily conserved sensor of axonal stress and injury, DLK's regulation and modes of action are tightly coordinated with the integrity of the axonal cytoskeleton and transport machinery. As a critical mediator of injury responses and neurodegeneration pathways, future work is needed to understand the cellular responses that DLK regulates and the mechanisms that control its activation in the nervous system.

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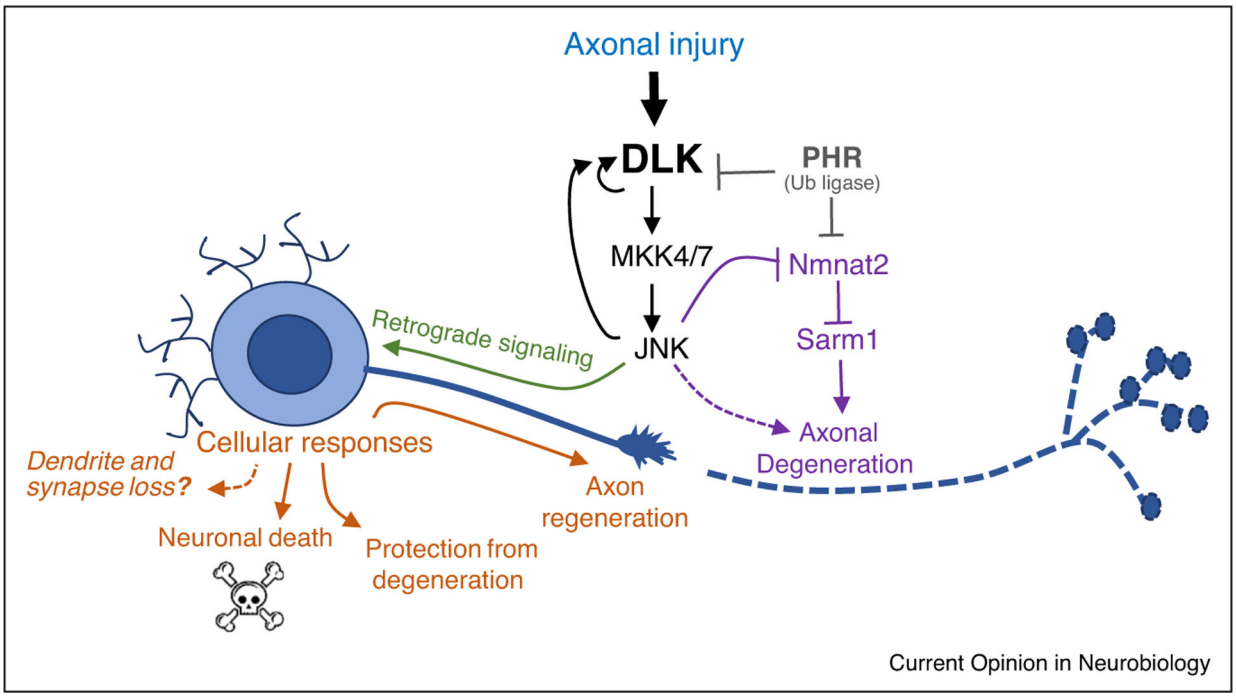

Figure 1.

DLK regulates multiple responses to axonal damage. DLK signaling becomes activated following axonal injury and regulates multiple cellular responses (in orange): neuronal death [4,7], axonal regeneration [2,3,5,6] and/or protection from degeneration [69], depending upon the context (Table 1). Whether DLK promotes loss of dendrites and synaptic inputs is hypothesized based on discussed data [25,29,30,29–31••], but remains to be determined. The distal part of the axon, which becomes removed from the cell body undergoes Wallerian degeneration. This is also influenced by DLK signaling [64,69,103]. In addition, DLK and downstream signaling components crosstalk with other factors that influence axonal degeneration, the NMNAT enzyme and Sarm1 NADylase [18,65,75•,101].

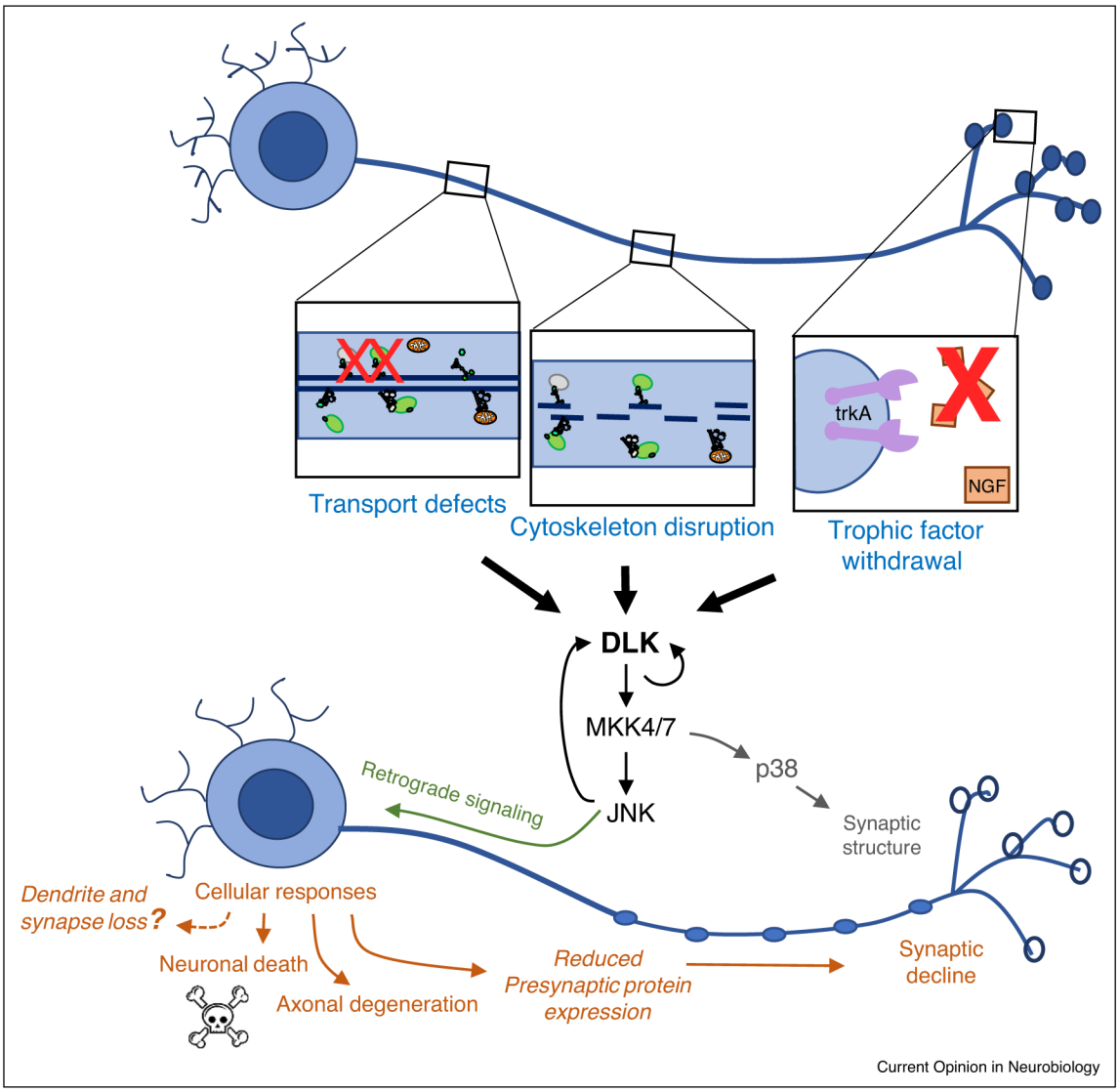

Figure 2.

Examples of axonal stress that lead to activation of DLK. Defects in axonal transport [24••], disruption of cytoskeleton within axons [47–49], and inhibition of trophic factor signaling [14,41,44•] all result in the activation of DLK signaling. Downstream responses (in orange) include reduced expression levels of presynaptic proteins [24••] and yet unknown signals that impair postsynaptic receptor function and synaptic homeostasis mechanisms [27•]. Over time these responses are expected to promote synaptic decline and loss.

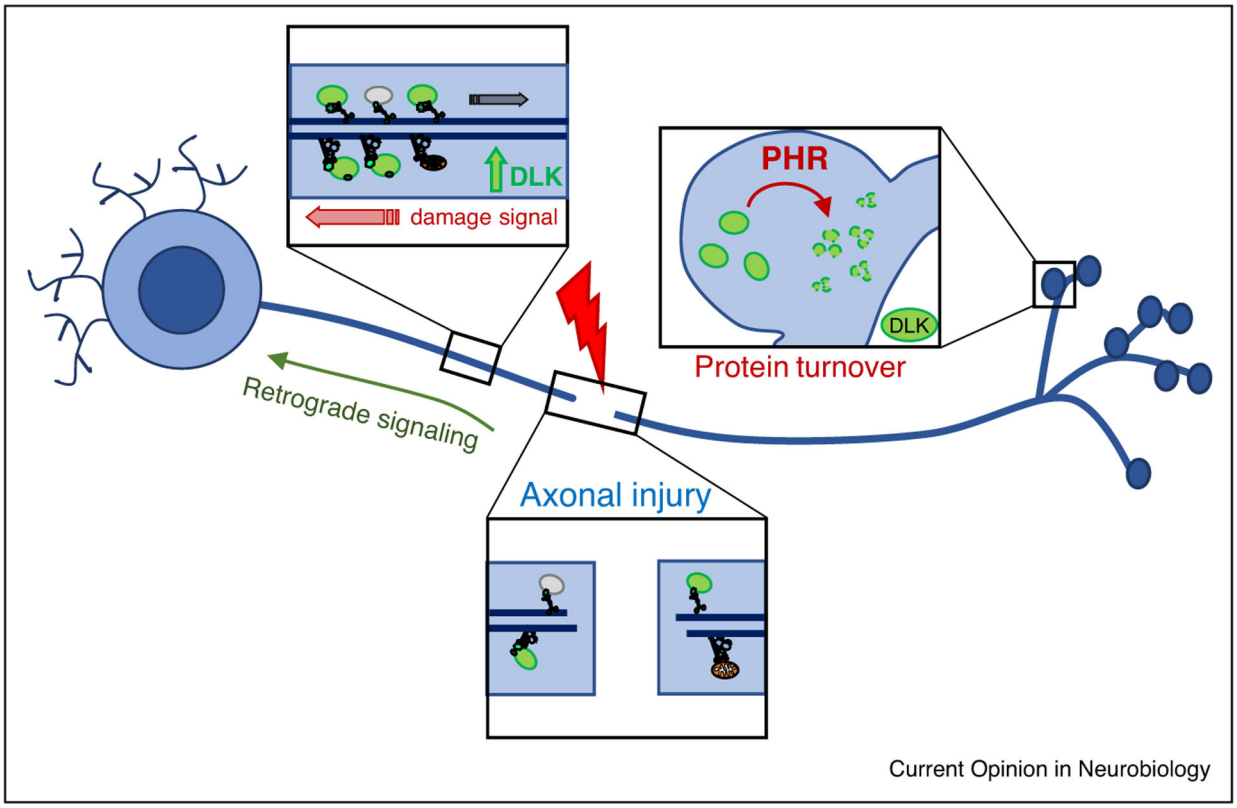

Figure 3.

Regulation of DLK. DLK associates with vesicles that are transported in axons (indicated in green) [3,32]. DLK protein is regulated by ubiquitin ligases, including the highly conserved synaptic protein PHR (Pam/Highwire/Rpm-1), which regulates DLK during synaptic development [19,20].

Table 1

Functions ascribed to DLK signaling in different paradigms and model systems

Function	Context
Axonal regeneration in PNS	DLK is required for axonal regeneration following laser axotomy in *C. elegans* GABA motoneurons [6] and ALM and PLM touch neurons [2,95], and in *D. melanogaster* larval motoneuron [3] and sensory neurons [35]. Following sciatic nerve injury in mice, DLK is required in motoneurons for reinnervation of motoneuron endplates [5]. DRG neurons deleted for DLK fail to undergo enhanced regeneration stimulated by a conditioning injury [5,104].
Axonal regeneration in CNS	DLK is required for *PTEN−/−* induced regeneration is the mouse optic nerve [4].
Wallerian degeneration of injured axons	Modest defects in Wallerian degeneration have been observed for *DLK* mutants in *D. melanogaster* olfactory neurons [64], cultured embryonic DRGs [64,65], and in the mouse sciatic nerve [64]. Combined knockout of DLK with other components of MAPK signaling leads to a strong inhibition of Wallerian degeneration of RGC axons in the optic nerve [65]).
Chemotherapy-induced axonal degeneration	DLK-deficient mouse DRG axons are protected after vincristine exposure [64]. Loss of DLK in taxol treated Drosophila axons prevents degeneration [67].
Resistance to axonal degeneration	DLK activation following a conditioning lesion in larval PNS motoneurons protects axons from degeneration following subsequent injuries [69].
Neuronal remodeling in response to cytoskeletal stress	Growth of *C. elegans* in the presence of microtubule destabilizing agent colchicine causes changes in the levels of many touch receptor proteins via DLK-1 signaling [50]. Genetic perturbations in microtubules causes synaptic remodeling of *C. elegans* GABA dorsal D-Type (DD) neurons via DLK-1 signaling [55]. *D. melanogaster* mutations in alpha-spectrin and ankyrin, which should chronically impair cytoskeleton, cause retraction and loss of presynaptic boutons; genetic manipulations in upstream and downstream components of the DLK signaling pathway modify these phenotypes [49].
Neuronal death	Mouse embryonic DRGs deleted for DLK fail to undergo cell death following trophic factor withdrawal [14,44•]. Mouse retinal ganglion cells (RGCs) deleted for DLK fail to undergo cell death following optic nerve injury [4,7,105] and in a cellular model of stress/glaucoma [7,]. DLK inhibition in adult mice is also protective against cell death in models of excitoxicity[61], subarachnoid hemorrhage [59], and 6-OHDA-induced dopaminergic cell death [60].
Neural degeneration in disease models	In two different mouse models of Alzheimer's Disease (AD) and a mouse model of ALS, conditional deletion of DLK in the adult nervous system shows neuroprotective phenotypes [31••]. These include reduced loss of axons and NMJ synapses and reduced inflammation in the spinal cord of $SOD1^{G93A}$ mice; reduced memory impairment and dendritic spine loss in PS2APP mice, and reduced neuron loss in Tau^{P301L} mice. Neither A-beta nor Tau pathology was affected by DLK knockout, suggesting a downstream role for DLK in promoting degeneration [31••]. In *D. melanogaster*, heterozygous mutations in DLK/Wnd rescue premature lethality in a TDP-43 overexpression model of ALS, however homozygous mutations enhances lethality in this model [83].
Synaptic decline	DLK activation in both *C. elegans* and *D. melanogaster* leads to defects in the structure of presynaptic terminals [19,20]. Electrophysiology recordings at *D. melanogaster* NMJ synapses indicate that DLK signaling activation in motoneurons induces both presynaptic reductions in synaptic vesicle release and post-synaptic responses to neurotransmitter [24••,27•].
Developmental axonal outgrowth and neuronal migration	DLK-deficient mice show defects in neocortical radial migration and reduced axon tracts in the anterior commissure, internal capsule, and corpus callosum [12]. Dissociated cortical neurons knocked down for DLK have reduced axonal growth [13]. Double mutants of DLK with JNK1 have severe defects in axon formation [16].
Neuroinflammation	Inhibition of DLK leads to reduced microglial responses in a mouse model of neuropathic pain [106•] and in a mouse model of ALS [31••]

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