Review

Retrograde axonal transport: pathways to cell death?

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Active transport along the axon is crucial to the neuron. Motor-driven transport supplies the distal synapse with newly synthesized proteins and lipids, and clears damaged or misfolded proteins. Microtubule motors also drive long-distance signaling along the axon via signaling endosomes. Although positive signaling initiated by neurotrophic factors has been well-studied, recent research has focused on stress-signaling along the axon. Here, the connections between axonal transport alterations and neurodegeneration are discussed, including evidence for defective transport of vesicles, mitochondria, degradative organelles, and signaling endosomes in models of amyotrophic lateral sclerosis, Huntington's, Parkinson's and Alzheimer's disease. Defects in transport are sufficient to induce neurodegeneration, but recent progress suggests that changes in retrograde signaling pathways correlate with rapidly progressive neuronal cell death.

Active axonal transport maintains extended neuronal processes

The unique morphology of neurons, highly polarized cells with extended axons and dendrites, makes them particularly dependent on active intracellular transport. The transport of proteins, RNA, and organelles over long distances requires molecular motors that operate along the cellular cytoskeleton (Glossary).

Two major roles for axonal transport are supply/clearance and long-distance signaling. Supply of newly synthesized proteins and lipids to the distal synapse maintains axonal activity, whereas misfolded and aggregated proteins are cleared from the axon by transport to the cell soma for efficient degradation [1]. Active transport of mitochondria also supplies local energy needs [2]. The second major role for active transport is the communication of intracellular signals from the distal axon to the soma, allowing the neuron to respond to changes in environment. While defects in either supply or clearance can readily be predicted to be deleterious to the health of the neuron, there has been a growing appreciation that the propagation of stress-signaling along the axon could be a key neurodegenerative pathway leading to cell death [3,4].

We focus here on recent progress linking defects in fast axonal transport to the pathogenesis of neurodegenerative diseases (reviewed in Table 1). Observations from cellular and animal models have provided evidence for multiple alterations in axonal transport, including impaired organelle motility, defects in degradative pathways, impaired neurotrophic signaling, and elevated stress-signaling. Whereas it is likely that several cellular pathways contribute to distal degeneration, recent progress suggests that changes in the balance of signaling along the axon, from survival to stress signaling, could be a crucial component of rapidly progressive neuronal cell death.

Mutant motors link axonal transport defects to neurodegeneration

Direct evidence implicating axonal transport defects in the pathogenesis of neurodegeneration has come from the identification of mutations in the motors that drive axonal transport. Defects in kinesin-mediated anterograde transport would be predicted to lead to either synaptic defects or axonal dieback due to inadequate supply of new proteins and lipids from the soma to the distal synapse. Relatively few degenerative diseases have been directly linked to mutations in kinesin motors [1], possibly due to functional redundancy in the extended kinesin superfamily. However, targeted disruption of kinesin function

Glossary

Microtubules: cytoskeletal filaments formed from the head-to-tail assembly of α- and β-tubulin dimers that serve as tracks for the motors that drive fast axonal transport. Microtubules are oriented in a polarized array in the axon, with their plus, or fast-growing ends, directed outward, and their minus, or slow-growing ends, directed toward the cell center. Microtubule organization is more complex in dendrites, where the mixed polarity seen in mammalian neurons could contribute to axonal-dendritic sorting and specification.

Kinesins: an extended superfamily of proteins that share homology within a conserved motor domain. Kinesin tail domains are more divergent, and this allows coupling to a diverse array of cargos. Many kinesins are microtubule-based motors, some are microtubule depolymerizers, and the function of others has yet to be explored. Kinesins known to drive anterograde axonal transport include kinesin-1 (also known as KHC or KIF5), kinesin-2 (KIF3), and kinesin-3 (KIF1).

Dynein: cytoplasmic dynein is the major minus-end-directed microtubule motor in the neuron. Dynein is a large protein complex with two heavy chains that form the two motor domains, as well as associated intermediate, light intermediate, and light chains that are involved in cargo recognition and binding specificity.

Dynactin: a large, multi-subunit complex required as an activator for most dynein functions in the cell, including retrograde axonal transport. The largest subunit of dynactin is $p150^{Glued}$, which binds directly to dynein and the microtubule. Multiple mutations in the *DCTN1* gene encoding $p150^{Glued}$ cause neurodegeneration.

Vesicle-associated motors and adaptors: vesicular cargos are transported along the axon by both kinesin and dynein motors. The activity of these cargo-bound motors is likely to be co-regulated by scaffolding proteins such as JIPs and Htt/HAP1 that can interact with either kinesin or dynein motors, or potentially with both.

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Table 1. Neurodegenerative diseases linked to defects in axonal transport

Disease	Clinical Features[a]	Genetics	Proteins Implicated	Axonal Transport Disrupted?	Evidence	Ref
Amyotrophic Lateral Sclerosis	Upper[b] and Lower[c] motor neuron degeneration	Multi-factorial	SOD1	Yes	Mutant SOD1 expression inhibits axonal transport early in disease.	[3,17]
			Alsin	Not determined	Defects in endosome morphology and motility	[36–38]
Huntington's Disease	Chorea, psychiatric and cognitive dysfunction	Autosomal dominant	Huntingtin	Yes	Expression of the pathogenic Htt causes axonal transport defects in fly models. Striatal neurons are selectively vulnerable to transport defects induced by mutant Htt expression in mouse models.	[18,101]
Alzheimer's Disease	Memory impairment, dementia	Multi-factorial	Tau, amyloid-β	Yes	Axonal swellings observed in mouse and fly models. Reductions in kinesin I promote amyloid deposition.	[102]
Parkinson's Disease	Rest tremor, rigidity, bradykinesia and gait disturbance	Multi-factorial	α-synuclein	Yes	α-synuclein mutants associated with PD induce reduced transport in cultured neurons.	[21]
Hereditary Motor Neuropathy, type VIIB (HMN7B) [also known as distal Spinal and Bulbar Muscular Atrophy (dSBMA)]	Lower motor neuron degeneration (hands>feet), prominent bulbar weakness	Autosomal dominant	$p150^{Glued}$	Not significantly affected	No significant defects observed in sciatic nerve ligation assays, but organelle accumulations observed in motor neurons in mice expressing mutant $p150^{Glued}$.	[13,15]
Perry Syndrome	Parkinsonism, weight loss, hypoventilation, depression	Autosomal dominant	$p150^{Glued}$	Not determined	Mutations recently characterized	[16]
Charcot –Marie-Tooth, type 2B	Length-dependent sensory and motor axonal neuropathy	Autosomal dominant	Rab 7	Equivocal	Rab7 recruits effectors and/or motors to late endosomes/lysosomes.	[32]
Charcot–Marie-Tooth, type 2A	Length-dependent sensory and motor axonal neuropathy	Autosomal dominant	Kinesin (KIF1B)	Equivocal	Decreased synaptic vesicle proteins in sciatic nerve extracts of $KIF1B^{-/-}$ mice.	[103]
Hereditary Spastic Paraplegia, type 10	Lower extremity weakness and spasticity	Autosomal dominant	Kinesin (KIF5A)	Equivocal	Slower cargo velocity *in-vitro*	[104]

[a]Represents classical disease features.
[b]Upper motor neuron symptoms include: weakness, hyperreflexia and spasticity.
[c]Lower motor neuron symptoms include: weakness, muscle atrophy and fasciculations. SOD1, superoxide dismutase-1; Htt, huntingtin.

is sufficient to induce neurodegeneration (reviewed in Ref. [5]).

In contrast, an increasing number of models link defects in components of the retrograde transport pathway to neurodegenerative disease (Figure 1). Disruption of the dynein–dynactin motor complex that drives retrograde transport leads to motor-neuron loss and muscle denervation in a transgenic mouse model [6]. Characterization of multiple lines of mice with either point mutations or a small deletion in dynein heavy chain support the hypothesis that neurons are preferentially susceptible to defects in dynein function [7,8]. Legs at odd angles (*Loa*), cramping 1 (*Cra1*), and sprawling (*Swl*) mice express mutant forms of the cytoplasmic dynein heavy chain (Figure 1). Heterozygous *Loa* ($Dync1h1^{Loa}$/+) mice exhibit impaired muscle function and motor coordination, with defects in retrograde axonal transport observed in live-cell imaging of cultured dorsal root ganglion (DRG) neurons *in vitro* and sciatic

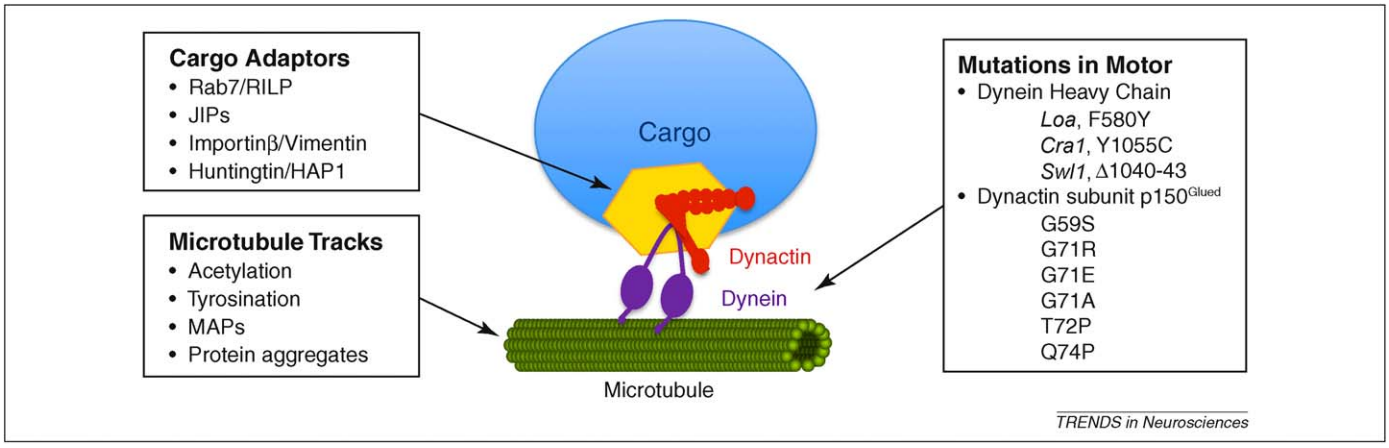

Figure 1. Retrograde axonal transport can be altered at multiple levels. Impairment of transport can arise from direct mutations in microtubule motors or their activators and adaptors. Models expressing mutations in cytoplasmic dynein heavy chain have been identified in the mouse (Loa, Cra1, and Swl), and point mutations in the p150^{Glued} subunit of dynactin have been identified in humans (G59S, G71R, G71E, G71A, T72P, and Q74P). Changes in the velocity or efficiency of retrograde transport can be induced by changes in cargo adaptors or effectors, such as Rab7/RILP or Huntingtin/HAP1, that coordinate cargo-bound motors. Transport along the axon can also be affected by changes in post-translational modifications of the microtubule track, such as changes in acetylation, tyrosination, or the complement of bound microtubule-associate proteins (MAPs). Finally, pathological changes along the axon, such as remodeling of the cellular cytoskeleton or the development of protein aggregates, could deleteriously affect retrograde axonal transport.

nerve ligation assays *in vivo* [3]. Embryonic motor neurons cultured from homozygous *Loa* mice also exhibit a significant retrograde transport defect [7]. Although the *Loa* and *Cra1* phenotypes were initially attributed to a loss of alpha motor neurons [7], more recent evidence suggests that mutations in dynein also induce sensory neuropathy [8]. The relative contributions of sensory and motor neuron degeneration to the phenotypes of *Loa*, *Cra1*, and *Swl* mice are still under debate [7–9].

Human genetic studies also demonstrate that neurons are uniquely vulnerable to disruptions in the retrograde motor complex. Mutations in the dynein-cofactor dynactin cause two distinct forms of neurodegeneration. A G59S point mutation in the *DCTN1* gene encoding the p150^{Glued} subunit of dynactin results in a late-onset, slowly progressive form of motor neuron disease termed distal hereditary motor neuropathy type VIIB (HMN7B; also known as distal spinal and bulbar muscular atrophy or dSBMA) [10]. HMN7B is an autosomal-dominant lower motor-neuron disease with prominent bulbar symptoms but no clinically apparent sensory involvement [11]. The G59S mutation in the highly conserved CAP-Gly domain inhibits the interaction of dynactin with microtubules and the microtubule plus-end protein EB1 [12]. The mutation also disrupts folding, favoring aggregation [12]; pathological inclusions of both dynactin and dynein are present in motor neurons of affected individuals [11].

These observations suggest that both loss of normal dynactin function and enhanced protein aggregation contribute to pathogenesis [12]. This hypothesis has been tested in three lines of mice modeling the G59S mutation, all of which show motor neuron degeneration reminiscent of the human disease [13–15]. The most consistent abnormalities among the three models are motor-neuron loss, decreased axon caliber, and disruption of the neuromuscular junction (NMJ). An increase in the number of degradative organelles is also observed [13–15], but it remains unclear whether this increase results directly from the accumulation of misfolded dynactin or instead from dysfunction in cellular degradative pathways that are dependent on normal dynein–dynactin function (discussed below).

More recently, distinct point-mutations within the CAP-Gly domain of p150^{Glued} were found to cause Perry syndrome [16]. This autosomal-dominant disorder presents as a constellation of symptoms including Parkinsonism, hypoventilation, depression and weight loss. Multiple point-mutations identified in 8 families with Perry syndrome localize to the same CAP-Gly domain as the previously characterized G59S mutation (Figure 1). However, the Perry mutations cluster in or near the surface-exposed microtubule-binding motif whereas the HMN7B-associated G59S mutation is buried within the folded domain. These mutations could differentially affect p150^{Glued} structure and/or function, potentially accounting for the selective vulnerability of distinct neuronal populations. Although the mechanistic basis for selective cell death remains to be determined, cumulative observations indicate that neurons are uniquely vulnerable to defects in the dynein–dynactin complex.

Axonal transport defects in neurodegenerative disease

The identification of mutations in either dynein or dynactin provides strong support for the hypothesis that defects in axonal transport are sufficient to cause neuronal degeneration. More broadly, a growing body of evidence suggests that slowing of axonal transport is an early event in the pathogenesis of a number of neurodegenerative diseases such as amylotrophic lateral sclerosis (ALS) and Huntington's disease (HD). For example, in the well-characterized superoxide dismutase SOD1^{G93A} (mSOD1) transgenic mouse model for familial ALS, a significant defect in retrograde transport is observed that is similar in magnitude to that seen in mice with specific disruption of dynein function, such as the *Loa* mouse [3]. Time-course studies indicate that this inhibition is observed well before disease onset [17], consistent with a causative or contributory role in motor neuron cell death.

Similarly, careful analysis of fast axonal transport in neurons isolated from a mouse model of HD (Htt^{150Q}) indicates significant impairment of both anterograde and retrograde transport [18]. Intriguingly, this impairment is cell-type specific: transport was found to be impaired in both striatal and hippocampal neurons but not in cortical neurons [18], consistent with the differential susceptibility of these neurons to cell death in HD patients.

The role that defective axonal transport plays in Alzheimer's disease (AD) and Parkinson's disease (PD) is less clear. Although impaired axonal transport has been shown in a number of AD models, it remains unclear whether this impairment has a causative role in triggering AD, or is a secondary defect resulting from other changes to the cellular environment [19]. As such, defects in transport could still contribute to pathology, for example by inhibiting the localization of mitochondria to the synapse [20]. The possible role for axonal transport impairment in PD has been less well studied. Although mutations in α-synuclein affect the slow axonal transport of this protein in a heterologous expression system [21], current research is focusing on defects in mitochondrial dynamics and function (discussed below).

What is the mechanistic basis for transport inhibition?

One mechanism that might account for the observed transport defects in multiple models is that the well-characterized formation of protein aggregates seen in models of ALS, HD, or AD might lead to a sequestration of active motors; this depletion of motors from the axon could then result in a functional inhibition of transport. There is some evidence that both dynein and kinesin motors are recruited to aggregates of mutant SOD1 or Huntingtin protein [17,22–24]. However, these interactions appear to be generally low-affinity and occur relatively late in the course of the disease, and thus do not explain the observed early inhibition of transport [3,17].

Although it remains a possibility that transport impairment reflects direct inhibition of motor function, it is more likely that the defects arise from misregulation of trafficking along the axon. Regulation of axonal transport occurs at multiple levels including modulation of the microtubule track, cargo-specific adaptors and scaffolding proteins that coordinate cargo-bound motors (Figure 1).

Direct modification of the microtubule cytoskeleton, for example by acetylation [25] or tyrosination [26] of tubulin subunits, has been shown to affect intracellular transport. Experimental modulation of tubulin acetylation was shown to rescue some of the transport deficits seen in a cellular model of HD [25]. Other modifications to the cytoskeletal track involve alterations in MAPs (microtubule-associated proteins), which can compete with motors for binding to the microtubule surface [27,28]. Hence, regulation of MAPs allows spatiotemporal control of transport direction. Consequently, misregulation of MAPs such as the changes in tau expression and localization seen in AD has the potential to alter the steady-state distribution of organelles.

Regulation of axonal transport also involves cargo-specific adaptors, such as Rabs, small membrane-bound GTPases that actively recruit motors to organelles, including endosomes and lysosomes [29]. For example, Rab7-associated late endosomes move long distances in the cell [30], due to the interaction of Rab7 with its effector RILP (Rab-interacting lysosomal protein), which in turn recruits the dynein/dynactin motor complex [31]. Misregulation of adaptor function is associated with neurological disease. Mutant forms of Rab7 cause axonal neuropathy in Charcot–Marie–Tooth Disease Type 2B (CMT2B) [32,33]. These mutant forms of Rab7 exhibit aberrant GTP hydrolysis activity [34,35], supporting the hypothesis that misregulation of axonal trafficking can lead to neurodegeneration.

Similarly, disruption in early endosome trafficking can also induce disease because mutations affecting the Rab5 GEF (guanine-exchange factor), alsin, that facilitates the conversion of inactive Rab5-GDP to active Rab5-GTP, have been identified in juvenile-onset familial ALS [36,37]. These mutations could potentially affect motor recruitment or function, although this has not been demonstrated. Analysis of Rab5-positive endosomes in neurons cultured from alsin-null mice indicates defects in both endosome morphology and motility, resembling those seen in neurons expressing constitutively active Rab5 [38]. Alsin could function as a negative regulator of Rab5, and thus mutations in alsin could lead to a misregulation of intracellular trafficking.

Scaffold proteins represent another level of regulation of transport along the axon. Scaffolding proteins bind to both anterograde and retrograde motors, as well as to adaptors and signaling proteins [39]. Thus, scaffolding proteins have the potential to integrate signaling components with motor proteins, allowing localized regulation in response to a changing environment. For example, upon axonal injury, local activation of JNK (c-Jun N-terminal kinase) enhances the interaction of its scaffolding protein JIP (JNK-interacting protein) with dynactin, resulting in retrograde transport of the activated JNK–JIP complex [40]. Interestingly, JIP also binds kinesin [41] and associates with vesicular cargo via interactions with membrane proteins such as APP (amyloid precursor protein) [42]. JIPs may not be limited to a role in injury signaling, but may actively coordinate bidirectional transport along the axon [43]. Similarly, importin-β and vimentin have an important role in dynein-mediated retrograde injury-signaling [44–46]; these proteins could also function in a parallel role in retrograde signaling during neurodegeneration, although this requires further exploration.

Post-translational modifications of another scaffolding protein, Huntingtin (Htt), has been proposed to regulate recruitment of motors to cargo, potentially affecting directionality of transport along the axon. Htt, which is mutated by expansion of polyglutamine repeats in HD, binds directly to dynein, and also associates with kinesin via the adaptor HAP1 (huntingtin-associated protein 1) (reviewed in Ref. [39]). Phosphorylation of Htt at Ser421 enhances kinesin recruitment and promotes anterograde transport [47], whereas depletion of Htt inhibits dynein-mediated motility [48]. Htt has been proposed to function to integrate vesicular transport along the cellular cytoskeleton [39]; it is not clear to what extent disruption of this function through expansion of polyglutamine repeats contributes to pathogenesis in HD.

Because axonal transport is a tightly regulated process, deregulation through alterations in Rab activity or post-translational modifications of key adaptors and scaffolds has the potential to significantly disrupt transport. These disruptions could result from specific mutations, such as the Rab7 mutations associated with CMT2B, but they are more likely to result from perturbations in the regulatory environment of the cell. As the overall regulation of bidirectional transport along the axon is still poorly understood, further progress should enhance our understanding of disease-associated transport impairment.

From slowed transport to neuronal cell death

Defects in either motor proteins or the regulatory pathways modulating intracellular transport can lead to neurodegeneration, but what is the proximal cause of cell death in affected neurons? The most obvious possibility is that inhibition of transport leads to defects in the localization or delivery of essential cargos (Figure 2). For example, *failure to deliver mitochondria* to areas of need could induce cell death through energy deprivation. Or, *disruption of lysosomal and/or autophagosome motility* could lead to the toxic buildup of aggregated proteins or defective organelles. Another hypothesis is that the key defect in axonal transport is not a disruption in bulk supply/clearance, but instead is an alteration in *cell signaling* (Figure 3). Evidence for each of these possibilities will be reviewed.

Death by starvation?

Mitochondrial functions, including aerobic production of ATP and calcium buffering, are vital to the health of the neuron, and therefore neurons must have a proper intracellular distribution of mitochondria. Mitochondria are actively transported to areas of high metabolic demand by the motors kinesin and dynein [2,49–52] in a calcium-regulated process involving the protein Milton and the GTPase Miro [53–55].

Defects in mitochondrial transport would lead to altered distribution of mitochondria along the axon, in turn leading to an inability to meet local ATP demands and/or toxic changes in calcium buffering. Indeed, defects in mitochondrial transport along the axon have been implicated in several disease models. For example, distal depletion of mitochondria could be of significance for the synaptic deficits seen in AD [20].

Recently, Pink1, a mitochondrial protein that is mutated in familial PD, was suggested to play a role in mitochondrial transport when it was found to be complexed with Milton and Miro [56]. Furthermore, in neurons expressing the mutant form of mitofusin found in CMT2A, mitochondrial mobility was decreased dramatically, resulting in a redistribution of mitochondria to the soma and the proximal axon [57]. Primary motor neurons from a mouse model of familial ALS expressing mutant SOD1 also exhibit an aberrant distribution of mitochondria, with a decrease in both the frequency and velocity of mitochondrial transport [58].

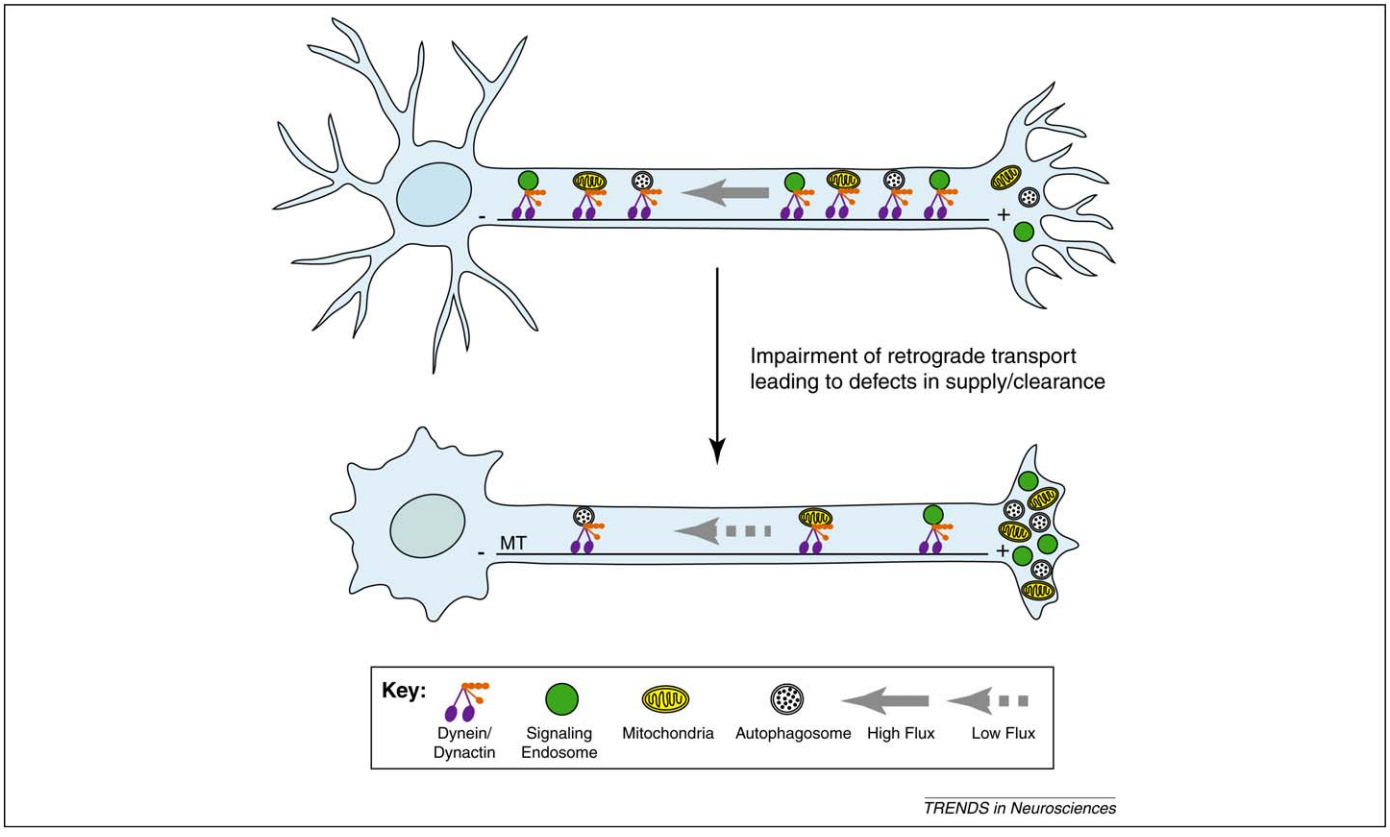

Figure 2. Changes in retrograde flux along the axon can lead to defects in supply and clearance. *Above,* neuronal function and survival depend on retrograde axonal transport driven by the microtubule motor protein dynein and its activator dynactin. Cargos that are actively transported along the axon include transport vesicles, mitochondria, lysosomes, autophagosomes, and signaling endosomes. *Below,* a significant slowing of retrograde axonal transport is observed at early stages of disease in several neurodegenerative models, consistent with a pathogenic role. This slowed transport leads to decreased flux, and potentially to defects in supply and clearance. MT, microtubules oriented along the axon with plus (+) ends distal and minus (−) ends proximal to the cell body.

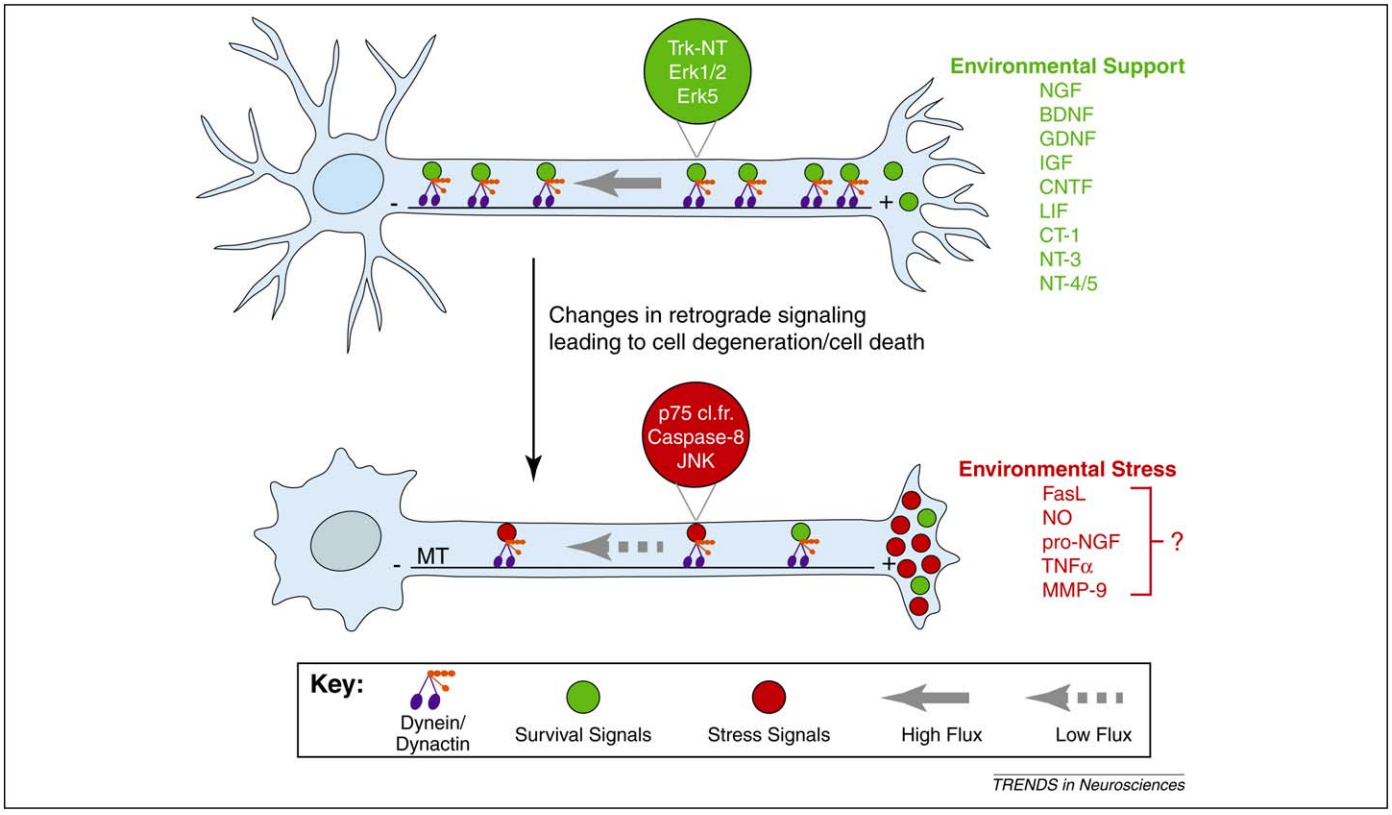

Figure 3. Changes in retrograde signaling lead to neurodegeneration and cell death. *Above,* in a healthy neuron, pro-survival signals (green) associated with signaling endosomes are actively transported from the cell periphery to the nucleus to promote neuron survival. Neurotrophic factors activate downstream effectors such as Trk receptors and are transported to the soma via a retrograde signaling endosome. During neurodegeneration, *below,* activation of retrograde death pathways (red) in a non-cell autonomous process can activate cell stress pathways and lead to cell death; decreased retrograde flux might also contribute. For instance, p75 cleavage-fragment, activated caspase8 and p-JNK are transported to the cell soma to initiate cell stress/death responses in a mouse model of familial ALS [3]. The specific identity of the environmental stress ligands, as well as the specific combinatorial role of the receptors and co-receptors that regulate survival/death pathways, remain to be determined. Examples of possible pro-survival ligands present in a supportive environment are listed in green. Examples of possible pro-death ligands secreted in a stressful environment are listed in red. NT, neurotrophins; p75 cl.fr., p75 cleavage fragment; MT, microtubules.

Together, these data implicate alterations in mitochondrial localization, mobility, and/or function as crucial factors in neuronal degeneration in a number of diseases. What remains unclear is whether these defects are a causal factor in the onset of further pathology, or a downstream response to pathogenic changes in the cellular environment.

Is active transport required for efficient degradation?

Defects in the transport and distribution of degradative organelles have also been observed in neurons from mouse models of neurodegenerative disease [13,15]. These defects are of particular interest due to the frequent correlation between the development of protein aggregates and the onset and/or progression of neurodegeneration that is seen in a wide range of diseases including ALS, HD, and AD. This correlation suggests that clearance of aggregates via cellular degradative pathways could be defective in these diseases.

Macroautophagy (hereafter referred to as autophagy) is a lysosomal degradation process that eliminates damaged and long-lived proteins, organelles and protein aggregates. Autophagy is generally considered to be a non-selective, bulk degradation process, although recent reports have uncovered signals that specifically target mutant proteins and impaired mitochondria for degradation [59,60]. Autophagy initiates when a portion of the cytoplasm is enclosed within a double-membrane organelle termed an autophagosome [61]. These organelles then fuse with degradative compartments in the endosomal/lysosomal pathway. Autophagosomes are formed throughout the cell, but are transported to the perinuclear region for efficient fusion with lysosomes [62,63]. This centripetal movement is dependent on microtubules and dynein [62,63]. Although the precise events underlying autophagosome biogenesis in neurons remain unclear, evidence suggests that autophagosomes can be generated locally within the axon [64,65]. They are then transported in a retrograde direction along the axon towards the cell body for fusion with lysosomes.

Autophagy serves as a quality control to maintain homeostasis and prevent accumulation of toxic material within the cell. Post-mitotic cells, such as neurons, are particularly sensitive to this toxic accumulation. Neuron-specific ablation of either *Atg5* or *Atg7*, genes required for autophagosome formation, results in protein aggregation and neuronal cell death [66,67]. Furthermore, autophagy is deregulated in ALS, AD, HD, and PD. An increase in autophagic vacuoles has been observed in patients and/or animal models of AD, HD, PD and ALS [68,69]; reviewed in Refs [70–72].

It remains unclear whether the autophagosome accumulation observed during neurodegeneration is due to activation of autophagy or, rather, due to inhibition of basal autophagy as a result of defective retrograde transport and/or lysosome fusion. In patients with AD, autophagic

vacuoles accumulate within neurites of dystrophic cortical neurons [73]; this distal accumulation could be due to defective retrograde transport. In the mSOD1 model of ALS, autophagosomes accumulate in the soma of motor neurons [68,69]; autophagic activity within the axon remains to be investigated.

In HD, it has been proposed that autophagy is activated due to sequestration of mTOR (mammalian target of rapamycin), a negative regulator of autophagy, by Htt aggregates [74]. One cannot exclude the possibility, however, that defective transport could also contribute to the buildup of autophagosomes in HD. For example, mutations in dynein lead to an accumulation of autophagosomes and enhanced protein aggregation and toxicity in a model of HD [75].

In PD, autophagy can be activated as a secondary response to a primary block in substrate-specific chaperone-mediated autophagy by mutant alpha-synuclein [76]. More directly, a pathway involving the proteins PINK1 and Parkin has been shown to selectively target impaired mitochondria for degradation by autophagy [77]. Because mutations affecting either PINK1 or Parkin lead to early-onset PD, there is now substantial evidence implicating defects in the autophagic clearance of damaged mitochondria to pathogenesis in this disease.

Long-distance signaling along the axon

Although the inhibition of organelle transport is a common feature in many models of neurodegenerative disease, it remains unclear if this altered organelle distribution is in itself pathogenic. Alternatively, changes in intracellular signaling could play a more significant role. The soma must receive and integrate precise and timely information from the cell periphery and from neighboring cells in order to maintain neuronal function and viability [78]. The transmission of vital information along the axon to the soma can signal either neuronal survival or cell death [79]. These signals must be accurate, specific and tightly controlled. Either the loss of a positive signal (such as a neurotrophic factor) or the gain of a negative signal (such as the activation of stress kinases) could explain the observed links between alterations in axonal transport and neurodegeneration.

Neuronal viability depends on diverse survival factors whose inhibition can activate apoptosis and cell death. The best-studied survival factors are members of the neurotrophin family. Neurotrophins such as NGF and BDNF bind to members of the Trk receptor family as well as the p75 neurotrophic receptor ($p75^{NTR}$) [80]. Ligand binding induces Trk dimerization, internalization, autophosphorylation and the recruitment of downstream effectors for activation of a signal-transduction cascade. The signals are retrogradely transported to the cell body by dynein via signaling endosomes [81] and promote survival of target-dependent neurons [78,82–85].

Impairments in Trk-mediated signaling have been observed in mouse models with impaired dynein function [3], potentially supporting the hypothesis that neurotrophic-factor deprivation contributes to neuronal degeneration. However, the observed disruptions in neurotrophic signaling do not correlate with the extent of neuronal loss, because similar levels of disruption were observed in both slowly-progressive and rapidly progressive mouse models (*Loa* and mSOD1, respectively) [3]. Thus, in the mature CNS, loss of ongoing trophic factor support could be less important than the activation of stress-factor signaling pathways, as described below.

Activation of retrograde death signals

Although neurotrophins are positive factors that are transported along the axon, there is also evidence for the active transport of negative factors by dynein (Figure 3). Activation of axonal signaling factors such as $p75^{NTR}$ can initiate cell death [86]. Retrograde transport of growth-inhibitory signals could be part of the normal neuronal maturation pathway during development. For example, the retrograde transport of Nogo-A endosomes initiates growth-cone collapse and inhibits neurite outgrowth [87]; this signaling could be essential for blocking unwanted outgrowth and branching during myelination. Similarly, retrograde signaling, both positive and negative, has been found to play a profound role in neuronal injury response [88].

Several stress/death signaling pathways that lead to neurodegeneration have been identified. For example, NGF deprivation induces a retrograde signal that activates the pro-apoptotic transcription factor, c-Jun [89]. In another neuronal self-destruction pathway, binding of a cleaved fragment of APP to death receptor 6 (DR6) triggers a caspase-dependent degeneration process [90]. Furthermore, the Fas/p38 ER stress-signaling pathway activates caspase-8 leading to the degeneration of motor-neuron subpopulations in mSOD1 mice at an early stage of disease [91]. Caspase-8 has been shown to interact directly with the $p150^{Glued}$ subunit of dynactin [92], potentially linking this process to retrograde axonal signaling. In an unbiased proteomic screen for dynein-mediated retrograde signaling in mSOD1 mice, p-JNK, $p75^{NTR}$ cleavage fragments, and activated caspase-8 were all shown to be retrogradely transported along the axon, leading to activation of c-Jun and subsequent cell death [3]. Inhibition of this signaling is sufficient to rescue cell death [3].

Neurotrophin signaling is subject to combinatorial regulation. For example, differential signaling cascades involving the Trk and $p75^{NTR}$ receptors can lead to either survival or death [79]. Proteolytic cleavage of proneurotrophins could also be a mechanism to regulate cell fate; whereas mature neurotrophins bind with high affinity to Trk receptors (and with low affinity to $p75^{NTR}$) and signal for survival, proneurotrophins bind with high affinity to $p75^{NTR}$ and induce cell death [93]. Finally, alterations in the cellular environment can change prosurvival signals to proapoptotic signals [94,95], so it is clear that context matters.

It is also likely that a set of signaling factors rather than a single pathway is altered in neurodegenerative diseases leading to cell death. This could explain the limited effects observed when crossing mSOD1 mice with mice null for genes implicated in cell death-inducing pathways, including $p75^{NTR}$ [96], $FasL^{-/-}$ [97] or $Bax^{-/-}$ [98]. In contrast, crossing $SOD1^{G93A}$ mice with *Loa* mice led to an extension in lifespan [99] that could be attributed to the delayed transport of stress/death signals to the soma by mutant dynein.

Changes in the balance of retrograde signaling, from neuroprotective/survival signals to apoptosis/stress signaling could be a crucial switch in pathogenesis [3]. Many neurodegenerative diseases are not cell-autonomous, but instead involve interactive signaling with neighboring non-neuronal cells [100]. Further studies on retrograde axonal signaling of neurons in context is needed to develop a more comprehensive understanding of how the physiological environment contributes to neuronal cell death [4]

Conclusions: how do we get there from here?

Neurons are uniquely dependent on active intracellular transport, so it is not surprising that defects in transport lead to neuronal stress and cell death. Multiple mechanisms are likely to be involved, including disruptions in energy metabolism, degradative pathways, trophic factor signaling, and stress signaling. Studies across disease models suggest that differing aspects of axonal transport can be more centrally involved in one disease process or another, and that axonal transport defects can be either a proximal cause or a downstream consequence of disease progression. Causality will need to be assessed for each case.

Further, our current level of understanding does not provide insight into the basis for the cell type-specificity characteristic of many neurodegenerative diseases. ALS, HD, PD, and AD all preferentially affect one or a few neuronal subclasses, at least initially. Of the mechanisms discussed here, perhaps the possibility that disease-induced changes in the cellular signaling program can lead to cell death has the highest potential to explain why one type of neuron, for example motor or striatal, might be selectively affected during disease progression. One can easily envisage that changes in the full complement of positive and negative signals actively transported along the axon might selectively affect neurons in a cell-type-specific and context-specific manner, but this needs to be demonstrated more directly.

Together, these observations suggest that a multi-pronged approach will be needed to effectively intervene in diseases in which axonal transport is affected. For example, strategies that include compensation for decreased neurotrophic-factor transport as well as inhibition of stress-signaling pathways are likely to be more successful than approaches directed toward a single target. Further research is required to actively transport us to a more thorough understanding of the biology involved and will allow more thoughtfully designed therapeutic interventions in future.

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