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Neuron
Review

Axonal Transport: Cargo-Specific Mechanisms of Motility and Regulation

Sandra Maday,[1] Alison E. Twelvetrees,[1] Armen J. Moughamian,[1] and Erika L.F. Holzbaur[1,*]
[1]Department of Physiology, Perelman School of Medicine, University of Pennsylvania, 638A Clinical Research Building, 415 Curie Boulevard, Philadelphia, PA 19104-6085 USA
*Correspondence: holzbaur@mail.med.upenn.edu
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Axonal transport is essential for neuronal function, and many neurodevelopmental and neurodegenerative diseases result from mutations in the axonal transport machinery. Anterograde transport supplies distal axons with newly synthesized proteins and lipids, including synaptic components required to maintain presynaptic activity. Retrograde transport is required to maintain homeostasis by removing aging proteins and organelles from the distal axon for degradation and recycling of components. Retrograde axonal transport also plays a major role in neurotrophic and injury response signaling. This review provides an overview of axonal transport pathways and discusses their role in neuronal function.

The active transport of organelles, proteins, and RNA along the extended axons of neurons has long fascinated scientists. The remarkable fact that the axon depends on the biosynthetic and degradative activities of the soma, located up to a meter away, highlights the importance of active transport. Genetic evidence confirms an essential role for active transport in the neuron, as defects in many of the proteins involved are sufficient to cause either neurodevelopmental or neurodegenerative disease (Table 1).

Metabolic cell-labeling experiments in the 1960s demonstrated the rapid movement of newly synthesized proteins along the axon in a process once termed "cellulifugal transport" (Weiss, 1967). Experiments with drugs that disrupt the cellular cytoskeleton demonstrated that microtubules are required for active transport along the axon (Kreutzberg, 1969). Pulse-chase labeling experiments led to the discovery of multiple phases of transport (reviewed in Griffin et al., 1976). Organelles were observed to move outward from the cell body at "fast" speeds of up to 400 mm/day, or ~1 μm/s, while cytoskeletal proteins and some soluble proteins were observed to move via "slow" transport, at speeds of <8 mm/day, or <0.1 μm/s. Outward-bound, anterograde (also known as orthograde) transport was most clearly defined by these metabolic labeling approaches. However, the retrograde transport of organelles from the distal axon back toward the cell body was also observed (Griffin et al., 1976). The development of live-cell imaging allowed the direct observation of organelle motility (Allen et al., 1982; Brady et al., 1982). These observations led to the discovery of the microtubule motor kinesin (Vale et al., 1985), now known as kinesin-1 (see Table 1); cytoplasmic dynein was discovered soon after (Paschal et al., 1987). Breakthrough experiments using nerve ligation assays identified kinesin-1 as a major motor for anterograde transport along the axon (Hirokawa et al., 1991) and dynein as the motor for retrograde transport (Hirokawa et al., 1990).

Since these initial discoveries there has been considerable progress in understanding the mechanisms regulating the transport of organelles including mitochondria, lysosomes, autophagosomes, and endosomes (Figure 1), as well as the transport mechanisms involved in neurotrophic and injury signaling. Together, these studies support a model in which the regulation of transport is compartment specific. The complement of motors, adaptors, and scaffolding proteins bound to each cargo is organelle specific, leading to distinct patterns of motility and localization along the axon. Thus, while broad themes emerge, the specific mechanisms regulating the transport of each organelle or protein complex may be unique. Further, there is increasing evidence for the localized regulation of trafficking in key zones along the axon, such as the axon initial segment or in the distal axon.

Here, we discuss both general themes and specific mechanisms involved in axonal transport. We will review recent progress and highlight some of the critical questions that remain, focusing on the mechanisms that regulate the dynamic trafficking of organelles along the axon.

Molecular Motors Drive Transport along the Neuronal Cytoskeleton

The Neuronal Cytoskeleton

Microtubules, actin filaments, and intermediate filaments all contribute to the morphology and function of neurons, but axonal transport depends almost entirely on microtubules. Microtubules are polarized tubulin polymers with fast-growing plus ends and more stable minus ends, organized in a generally radial array in the soma with plus ends directed toward the cortex. In the axon, parallel microtubules form a unipolar array with plus ends oriented outward (Burton and Paige, 1981; Stepanova et al., 2003), while in dendrites microtubule organization is more complex, with microtubules often organized in arrays with mixed polarity (Baas et al., 1988; Kleele et al., 2014; Kwan et al., 2008). In the cell body, microtubule minus ends may be rooted near the centrosome, but microtubules along axons are likely to be capped at their minus ends by a mechanism that is not yet understood (Kuijpers and Hoogenraad, 2011).

Microtubule-associated proteins, or MAPs, are bound along the length of axonal and dendritic microtubules. The canonical role for MAPs is to promote microtubule polymerization and

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Table 1. Neurodevelopmental and Neurodegenerative Diseases Caused by Mutations in the Axonal Transport Machinery

Protein(s)	Gene(s) with Known Mutation	Disease(s)	References
Motor Proteins			
Dynein	*DYNC1H1*	CMT, SMA-LED, ID, MCD (Epilepsy)	Weedon et al., 2011; Tsurusaki et al., 2012; Harms et al., 2012; Willemsen et al., 2012; Poirier et al., 2013; Fiorillo et al., 2014
Kinesin-1	*KIF5A*, *KIF5C*	HSP (SPG10), ID, MCD	Ebbing et al., 2008; de Ligt et al., 2012; Poirier et al., 2013
Kinesin-13	*KIF2A*	CDCBM3/MCD	Poirier et al., 2013
Kinesin-3	*KIF1A*, *KIF1B*, *KIF1C*	HSP (SPG30), CMT2A, HSN, MR, SPAX	Erlich et al., 2011; Zhao et al., 2001; Rivière et al., 2011; Hamdan et al., 2011; Klebe et al., 2012; Dor et al., 2014; Novarino et al., 2014
Kinesin-4	*KIF21A*	CFEOM	Yamada et al., 2003
Motor Adaptors and Regulators			
Dynactin	*DCTN1*	Perry syndrome, MND	Puls et al., 2003; Farrer et al., 2009; Caroppo et al., 2014; Araki et al., 2014
BICD2	*BICD2*	SMA, HSP	Neveling et al., 2013; Peeters et al., 2013; Oates et al., 2013
Huntingtin	*HTT*	HD	HDCRG, 1993
Lis-1	*PAFAH1B1*	Lissencephaly	Dobyns et al., 1993; Reiner et al., 1993
NDE1	*NDE1*	Microcephaly, MHAC	Alkuraya et al., 2011; Bakircioglu et al., 2011; Paciorkowski et al., 2013
Rab7	*RAB7A*	CMT2B	Verhoeven et al., 2003
Cytoskeleton and Associated Proteins (e.g., MAPs)			
CLIP-170	*CLIP1*	ARID	Larti et al., 2014
Doublecortin	*DCX*	Lissencephaly	des Portes et al., 1998a, 1998b; Gleeson et al., 1998
Microtubules	*TUBA1A*, *TUBA8*, *TUBG1*, *TUBB3*, *TUBB2B*	Lissencephaly, MCD, microcephaly, polymicrogyria, CFEOM	Keays et al., 2007; Poirier et al., 2007, 2010, 2013; Jaglin et al., 2009; Abdollahi et al., 2009; Tischfield et al., 2010; Chew et al., 2013
Neurofilaments	*NEFL*	CMT	Mersiyanova et al., 2000
Spastin	*SPAST*	HSP (SPG4)	Hazan et al., 1999
Tau	*MAPT*	FTD, Pick disease, AD	Hutton et al., 1998; Murrell et al., 1999

Abbreviations are as follows: AD, Alzheimer's disease; ARID, autosomal recessive intellectual disability; CDCBM3, complex cortical dysplasia with other brain malformations-3; CFEOM, congenital fibrosis of the extraocular muscles; CMT, Charcot-Marie-Tooth disease; FTD, frontotemporal dementia; HD, Huntington's disease; HMN, hereditary motor neuropathy; HSN, hereditary sensory neuropathy; HSP, hereditary spastic paraplegia; ID, intellectual disability; MCD, malformations of cortical development; MHAC, microhydranencephaly; MND, motor neuron disease; MR, mental retardation; SMA, spinal muscular atrophy; SMA-LED, SMA-lower extremity dominant; and SPAX, spastic ataxia.

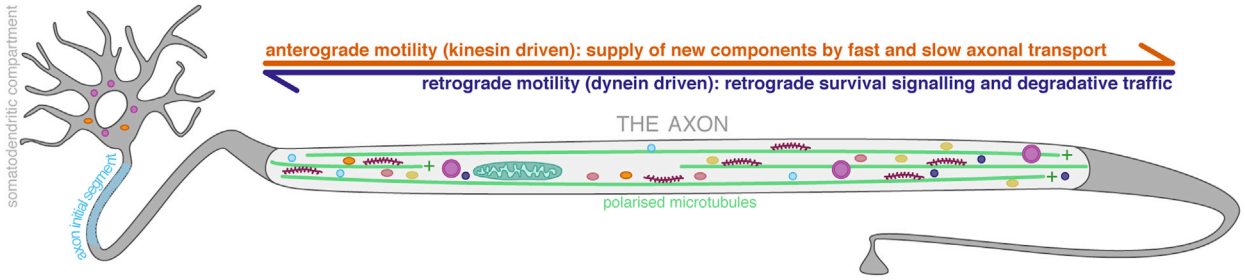
stabilization; because of the high expression levels of MAPs in neurons, microtubules are generally more stable in these cells than in other cell types. MAPs may also function to regulate transport, as in vitro studies indicate they modulate the interaction of motors with the microtubule (Dixit et al., 2008b; Vershinin et al., 2007). The discovery of a specific class of MAPs, known as plus-end-interacting proteins or +TIPs, has shown that microtubules in axons can be dynamic. Live-cell imaging with GFP-labeled +TIPs that bind selectively to actively growing microtubule plus ends has shown that axonal microtubules exhibit the parameters of dynamic instability observed in non-neuronal cells, including slow growth and rapid shortening, punctuated by catastrophe and rescue events, respectively (Stepanova et al., 2003, 2010). The +TIPS EB1 and EB3 recruit additional binding partners to microtubule ends, many of which have a role in the localized regulation of axonal transport (Moughamian et al., 2013).

Direct posttranslational modification of tubulin is widespread in neurons (Janke and Bulinski, 2011). Microtubule modifications directly modulate the activities of motor proteins (Sirajuddin et al., 2014), potentially contributing to the polarized trafficking of motors into axons (Hammond et al., 2010; Jacobson et al., 2006; Konishi and Setou, 2009). The nucleotide state of microtubules can also affect motor activity and contribute to polarized vesicle transport (Nakata et al., 2011).

Kinesin and Dynein Motors Drive Axonal Transport

The kinesin superfamily constitutes 45 genes in the human genome, 38 of which are expressed in brain (Miki et al., 2001). The neuronal motor proteome is more complex than that expressed in most other cell types, likely reflecting the enhanced importance of regulated and specific intracellular transport in neurons with their highly polarized morphology (Kuta et al., 2010; Silverman et al., 2010). A standardized nomenclature (Lawrence et al., 2004) groups kinesin genes into 14 subfamilies that share structural and functional similarities; motors from the kinesin-1, kinesin-2, and kinesin-3 families all contribute to axonal transport dynamics.

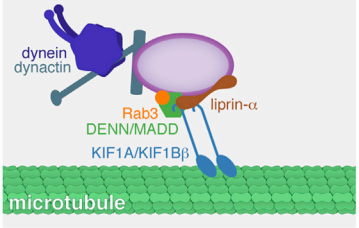
Members of the kinesin-1 family drive the transport of a wide range of cargos along the axon at velocities of ~0.5–1 μm/s, including vesicles, organelles, proteins, and RNA particles



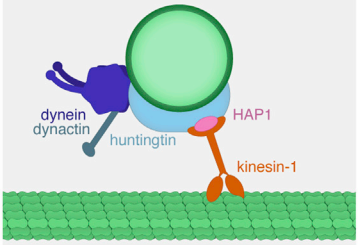
fast axonal transport

anterograde

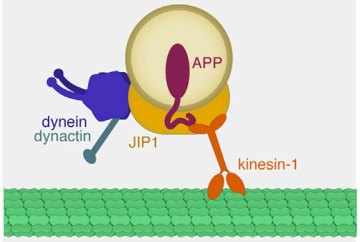
SYNAPTIC VESICLE PRECURSORS & DENSE CORE VESICLES



BDNF VESICLES

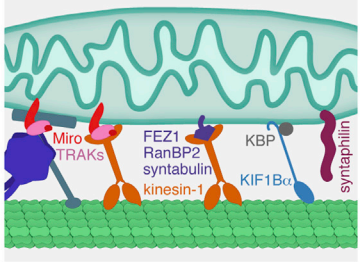


APP

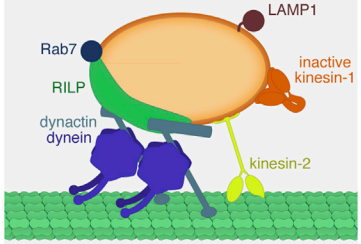


bi-directional

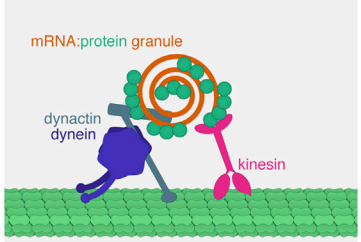
MITOCHONDRIA



LATE ENDOSOMES & LYSOSOMES

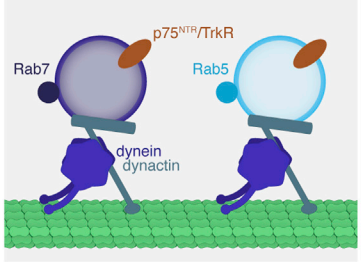


mRNA

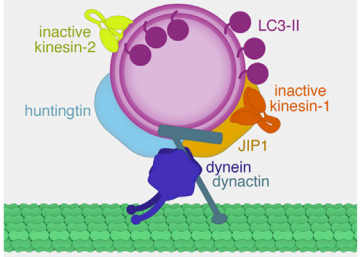


retrograde

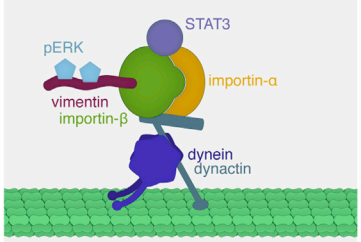
SIGNALLING ENDOSOMES



AUTOPHAGOSOMES

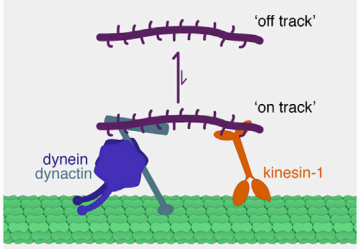


INJURY SIGNALLING

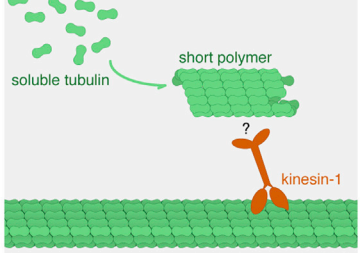


slow anterograde axonal transport

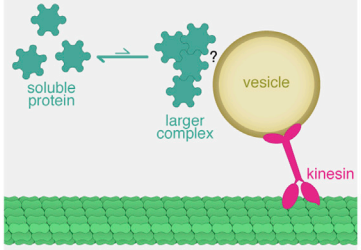
NEUROFILAMENTS (SCa)



TUBULIN (SCa)



CYTOSOLIC PROTEIN (SCb)



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(Hirokawa et al., 2010) (Figure 1). Active kinesin-1 motors are formed from a dimer of kinesin heavy chains (encoded by three mammalian genes, *KIF5A*, *KIF5B*, and *KIF5C*); a dimer of kinesin light chains (KLCs) is often but not always part of the complex (Sun et al., 2011) and contributes to the autoinhibitory mechanism of the motor.

Kinesin-2 and kinesin-3 motors are also critical for normal axonal transport (Figure 1). Kinesin-2 members can assemble into either homodimeric or heterotrimeric motors (Scholey, 2013), while kinesin-3 motors undergo cargo-mediated dimerization resulting in the formation of highly processive motors when bound to intracellular organelles (Soppina et al., 2014). Kinesin-2 motors drive the anterograde motility of fodrin-positive plasma membrane precursors (Takeda et al., 2000), N-cadherin and β-catenin (Teng et al., 2005), and choline acetyltransferase (Ray et al., 1999), and are also associated with Rab7-positive late endosome-lysosome compartments in the neuron (Castle et al., 2014; Hendricks et al., 2010). Kinesin-3 motors drive the motility of synaptic vesicle precursors (SVPs) and dense core vesicles (DCVs) (Hall and Hedgecock, 1991; Lo et al., 2011; Okada et al., 1995).

Cytoplasmic dynein is the major motor driving retrograde transport. In contrast to the diversity of the kinesin superfamily, the motor subunit of cytoplasmic dynein is encoded by a single gene (reviewed in Roberts et al., 2013). Two dynein heavy chains (DHCs) dimerize by their N-terminal tail domains; additional intermediate chains, light intermediate chains, and light chains associate with the tails of the heavy chains to form a cargo-binding domain. Together, these proteins serve as the binding site for many of the proteins regulating dynein function in the cell. While there is a single gene encoding the motor domain of cytoplasmic dynein, there is more diversity in the other subunits of the dynein complex—for example, there are two genes encoding dynein intermediate chains, one of which is neuron specific (*DYNC1I1*), and two genes encoding dynein light intermediate chains (DLICs) (Kuta et al., 2010). There is evidence that these subunits can either coassemble (Zhang et al., 2013) or alternatively assemble into distinct complexes with specialized functions (Mitchell et al., 2012; Salata et al., 2001), which may allow for organelle-specific recruitment or regulation.

Most dynein functions in the cell require the dynein activator, dynactin. Dynactin is a highly conserved multiprotein complex (Schroer, 2004) that is essential for normal neuronal function (LaMonte et al., 2002; Moughamian and Holzbaur, 2012). The base of dynactin is formed from a 37 nm-long actin-like polymer; both the Arp1 subunit that forms this polymer and additional dynactin subunits including p25 and p27 have been implicated in cargo binding (Holleran et al., 1996; Yeh et al., 2012; Zhang et al., 2011). Projecting from this base is a dimer of the subunit $p150^{Glued}$ (Holzbaur et al., 1991). This subunit binds directly to dynein intermediate chain (Karki and Holzbaur, 1995; Vaughan and Vallee, 1995), and also binds directly to microtubules via a cytoskeletal associated protein-glycine-rich (CAP-Gly) domain (Waterman-Storer et al., 1995) and a lower-affinity basic domain found in neuronal isoforms of $p150^{Glued}$ (Culver-Hanlon et al., 2006; Dixit et al., 2008a). In vitro assays demonstrate that these independent microtubule-binding domains increase the processivity of the dynein-dynactin motor complex (King and Schroer, 2000; Ross et al., 2006) by enhancing the association of the motor with the microtubule (Ayloo et al., 2014). In neurons, the CAP-Gly domain of dynactin has a key role in the initiation of retrograde transport in the distal axon (Lloyd et al., 2012; Moughamian and Holzbaur, 2012).

The properties of kinesin and dynein motors have been explored in vitro at the single-molecule level. Kinesin-1 motors move in a highly processive manner toward the plus end of the microtubule, taking 8 nm steps in a straight path along a single protofilament. A single kinesin-1 motor has a stall force of 5–6 pN (Svoboda and Block, 1994), sufficient to move an organelle through the cytoplasm. Kinesin-2 motors also drive organelle motility along axons, and have a stall force of similar magnitude (5 pN). However, kinesin-2 exhibits force-dependent detachment from the microtubule (Schroeder et al., 2012), indicating that this motor may be less likely to win a tug-of-war interaction with an opposing motor such as dynein. Stall forces of kinesin-3 motors have not yet been determined. However, recent work has shown that kinesin-3 motors become superprocessive following cargo-mediated dimerization (Soppina et al., 2014).

Studies with purified mammalian dynein indicate that dynein is a fast motor, with velocities from 0.5 to 1 μm/s. Unlike the highly processive unidirectional motility of kinesin-1, kinesin-2, and kinesin-3 motors, single mammalian dynein motors take frequent back and side steps during movement along the microtubule (Mallik et al., 2005; Ross et al., 2006). However, either the coordinated activities of multiple dynein motors (Mallik et al., 2005) or the binding of activators such as BICD2 (McKenney et al., 2014; Schlager et al., 2014) converts dynein to a unidirectional and highly processive motor. Dynein is a much weaker motor than kinesin-1 or kinesin-2; there is general although not complete consensus that the stall force for mammalian cytoplasmic dynein is ~1 pN (Mallik et al., 2004; Schroeder et al., 2010).

While these observations might suggest that dynein is a less effective motor than kinesin, both the flexible nature of dynein and its ability to move backward and sideways along a microtubule may allow the motor to function effectively in teams (Mallik et al., 2013), and to navigate around obstacles along its path (Dixit et al., 2008b). In contrast, kinesin-1 motors are much less capable of effectively working in teams (Mallik et al., 2013). Kinesin-1 motors are also more likely than dynein to detach from the microtubule track upon encountering obstacles (Dixit et al., 2008b; Vershinin et al., 2007), although recent work has shown that kinesin-2 motors are more robust (Hoeprich et al., 2014).

Figure 1. Molecular Mechanisms of Axonal Transport
Microtubule motor proteins kinesin and dynein drive the movement of organelles, vesicles, RNA granules, and proteins along the axon. Kinesins drive anterograde transport outward from the soma, and dynein drives retrograde transport back from distal axon. However, most cargos have both motor types bound simultaneously. Cargo-bound motors are regulated by organelle-specific complements of scaffolding and adaptor proteins. To avoid either distal accumulation or distal depletion of cellular components, anterograde and retrograde axonal transport must be in balance.

Opposing Motors Bind Simultaneously to Cargos along the Axon

Many axonal cargos have multiple motor types bound simultaneously (Figure 1). For example, late endosomes/lysosomes copurify with kinesin-1, kinesin-2, and dynein motors (Hendricks et al., 2010). Similarly, kinesin-1 and dynein colocalize on single prion-positive vesicles undergoing transport along the axon (Encalada et al., 2011). Even cargos that move processively in a single direction over long distances, such as autophagosomes, copurify with opposing dynein and kinesin motors (Maday et al., 2012). Quantitative analyses and live-cell trapping experiments suggest that 1–2 kinesins and 6–12 dyneins may act together to move a single organelle along the microtubule (Hendricks et al., 2010, 2012; Rai et al., 2013).

Thus, it is essential to consider how multiple motors, and multiple types of motors, may interact either cooperatively or competitively to yield effective motility. Multiple models have been put forth (Fu and Holzbaur, 2014; Gross, 2004; Gross et al., 2007; Müller et al., 2008; Welte, 2004). The simplest model posits an unregulated tug-of-war between opposing kinesin and dynein motors. In a contrasting model, motors are coordinately regulated so that only a single motor type is active at any given time. Intermediate models suggest that one motor, such as kinesin, might be tightly regulated while the activity of dynein might be less carefully controlled; as dynein is a weaker motor than kinesin-1, it might simply be overpowered in situations where both motors are active simultaneously.

The motility of some axonal cargos, such as late endosomes/lysosomes, can be effectively modeled, at least to a first approximation, as a tug-of-war between opposing kinesin and dynein motors (Hendricks et al., 2010; Müller et al., 2008). In contrast, the motility of other cargos in the degradative pathway such as autophagosomes exhibit strongly unidirectional motility, indicating that kinesin motor activity can be effectively downregulated (Fu et al., 2014; Maday et al., 2012). Growing evidence suggests that the activities of opposing motors bound to the same cargo are regulated by scaffolding proteins (reviewed in Fu and Holzbaur, 2014).

The autoinhibition of kinesin-1 is key to this regulation. The binding of kinesin tail to the motor domain blocks motor function (Kaan et al., 2011); inhibition is relieved by specific binding partners such as the scaffolding proteins JIP1 and JIP3 (Blasius et al., 2007; Fu and Holzbaur, 2013; Sun et al., 2011). In the mechanisms explored in detail to date, tight regulation of kinesin-1 activation by scaffolding proteins allows for sustained axonal transport of organelles in either the anterograde or retrograde directions. The regulation of other kinesin subfamilies is less well studied.

Regulation of dynein motors is also important to maintain axonal transport, but the mechanisms involved are not as well understood. Lis1 is a critical and conserved effector of dynein function. Structural studies indicate that Lis1 binds directly to the dynein motor domain and uncouples ATP hydrolysis from force production, leading to sustained attachment of the motor to the microtubule (Huang et al., 2012). While induction of tight binding might be expected to block effective transport, instead it has been found that depletion of Lis1 inhibits the dynein-driven transport of late endosomes and lysosomes along the axon (Moughamian et al., 2013; Pandey and Smith, 2011), as well as mitochondrial motility in axons (Shao et al., 2013). Nde1 (also known as NudE) and Ndel1 (also known as NudE-like or NudEL) form a complex with Lis1 and are similarly required for normal axonal transport of at least some dynein cargos (Pandey and Smith, 2011; Shao et al., 2013).

The Bicaudal D homolog (BICD) proteins are also key dynein effectors. BICD1 and BICD2 recruit dynein-dynactin to Rab6-positive Golgi and cytoplasmic vesicles (Matanis et al., 2002) as well as mRNAs including Fragile X mental retardation protein (FMRP; Bianco et al., 2010). Recently BICD1 was shown to control the trafficking of activated neurotrophin receptors to degradation routes in order to balance the neuronal response to neurotrophin stimulation (Terenzio et al., 2014). In vitro studies have shown that an N-terminal fragment of BICD2 induces highly processive dynein motility (McKenney et al., 2014; Schlager et al., 2014).

Multiple additional mechanisms have been proposed to regulate motor activity on cargos moving along the axon. Rab GTPases have been shown to regulate motor recruitment to several cargos (reviewed in Akhmanova and Hammer, 2010). Scaffolding proteins are also key: huntingtin is involved in the regulation of BDNF-positive vesicles (Gauthier et al., 2004) and autophagosomes (Wong and Holzbaur, 2014); JIP1 is involved in the regulation of APP-positive vesicles and autophagosomes (Fu and Holzbaur, 2013; Fu et al., 2014); JIP3 regulates the injury-signaling pathway in mammalian cells (Cavalli et al., 2005) and lysosomal motility in zebrafish (Drerup and Nechiporuk, 2013); and the Miro/TRAK complex regulates motors bound to mitochondria (Macaskill et al., 2009b; Wang and Schwarz, 2009). Finally, there is clear evidence implicating upstream kinases in the regulation of transport including Cdk5, JNK, and p38MAPK (Fu and Holzbaur, 2013; Horiuchi et al., 2007; Morfini et al., 2013; Pandey and Smith, 2011), but the mechanisms involved have not yet been fully elucidated.

Both Common Themes and Cargo-Specific Mechanisms Operate in the Axonal Transport of Diverse Axonal Cargos

Live-cell and in vivo imaging of fluorescently tagged organelles moving along axons has revealed a surprising diversity in the movement of specific populations, indicating that the regulation of the motors that drive transport likely occurs primarily at the level of the organelle, rather than reflecting an overall regulatory environment within the axon. While the observed patterns of motility are diverse, some common themes are emerging:

(1) Motors remain stably associated with a cargo during transport along the axon, even when they are inactive.
(2) Only a small complement of motors is necessary to effectively move even large (>1 μm) organelles along the microtubule. These motors function in groups that usually include opposing motor activities.
(3) Motors are regulated by mechanisms that may include Rab-specific recruitment, upstream regulation by kinases and phosphatases, and scaffolding proteins that control motor activity.
(4) Mutations in motors, their adaptors, or their regulators can lead to neurodegeneration or neuronal cell death (Table 1), consistent with an essential role for axonal transport in maintaining neuronal homeostasis.

Despite these common themes, accumulating evidence suggests that the motility of each cargo actively transported along the axon is regulated by a distinct mechanism.

Fast Anterograde Transport: Axonal Proteins and Synaptic Components

APP-Positive Vesicles

APP-positive vesicles are a canonical cargo of kinesin-1 motors (Kamal et al., 2000). APP-positive vesicles are transported in a highly processive manner at rapid speeds (~1 μm/s), primarily in the anterograde direction, although rapid retrograde motility is also observed (Falzone et al., 2009; Kaether et al., 2000). APP binds to the scaffolding protein JIP1 (Matsuda et al., 2001; Scheinfeld et al., 2002). JIP1 is a JNK-binding scaffolding protein implicated in the regulation of constitutive axonal transport in *Drosophila* (Horiuchi et al., 2005). The C terminus of JIP1 binds to KLC (Verhey et al., 2001), and this binding contributes to the regulation of the kinesin-1 motor in concert with FEZ1 (Blasius et al., 2007). JIP1 also binds directly to kinesin-1 heavy chain (KHC) and the $p150^{Glued}$ subunit of dynactin (Fu and Holzbaur, 2013). JIP1 binding to KHC activates the motor by relieving autoinhibition, while the binding of JIP1 to dynactin competitively blocks this activation (Fu and Holzbaur, 2013).

In the neuron, the relative affinity of JIP1 for kinesin-1 or dynactin is controlled by a JNK-dependent phosphorylation site, which acts as a molecular switch to control the directionality of APP transport—when S421 in JIP1 is phosphorylated, anterograde transport of APP is favored, while dephosphorylation of S421 favors the retrograde motility of JIP1 (Fu and Holzbaur, 2013). Regulation of this activation is likely to involve JNK, and possibly upstream kinases such as Wallenda/DLK (Horiuchi et al., 2007).

Synaptic Vesicle Precursors and Dense Core Vesicles

A large fraction of vesicular organelles in the axon are components destined for the presynapse, namely SVPs and DCVs packed with neuropeptides and neurotrophins.

Anterograde transport of SVPs is driven by motors from the kinesin-3 family, Unc-104 in *C. elegans* and KIF1A in mammals (Hall and Hedgecock, 1991; Okada et al., 1995). Neurons from *unc-104* mutants and KIF1A knockout mice (Yonekawa et al., 1998) fail to develop normal synapses; synaptic precursors accumulate in the soma, consistent with a transport defect. Conversely, overexpression of KIF1A promotes the formation of presynaptic boutons (Kondo et al., 2012). Kinesin-3 motors undergo cargo-mediated dimerization, which leads to the formation of highly processive anterograde motors to drive efficient delivery of synaptic components (Klopfenstein and Vale, 2004; Soppina et al., 2014).

Two adaptors have been proposed to couple kinesin-3 motors to SVPs, liprin-α and DENN/MADD. Liprin-α is a multifunctional scaffolding protein that binds directly to KIF1A and many other neuronal scaffolding proteins (Shin et al., 2003); mutations in liprin-α perturb SVP transport (Miller et al., 2005). The protein DENN/MADD is required for the transport of SVPs and binds directly to the stalk domain of kinesin-3 motors (Niwa et al., 2008). DENN/MADD can differentiate between GTP and GDP forms of Rab3, a marker for SVPs, suggesting a mechanism for regulation of motor recruitment.

Once delivered to the presynaptic site, SVPs can be recycled locally. However, DCVs can only be packaged in the soma and must be continuously supplied, targeted to axons and/or dendrites depending on their content. DCV transport is also dependent on Unc-104/KIF1A motors, suggesting the mechanisms involved are similar to those driving SVP transport (Lo et al., 2011). Upstream regulation of kinesin-3 transport is regulated by Cdk5, which promotes the Unc-104-dependent transport of DCVs into axons and inhibits the dynein-dependent transport of these vesicles into dendrites (Goodwin et al., 2012).

The current exception to the paradigm of kinesin-3-dependent transport of DCVs is BDNF transport. The neurotrophin BDNF is stored in DCVs and trafficked within axons to the presynaptic site (Altar et al., 1997; Dieni et al., 2012). However, the axonal transport of BDNF is regulated by huntingtin (Gauthier et al., 2004), which scaffolds both kinesin-1 and dynein motors (Caviston and Holzbaur, 2009). The phosphorylation of huntingtin through the IGF-1/Akt pathway acts as a molecular switch to regulate the transport of BDNF-containing vesicles in axons (Colin et al., 2008; Zala et al., 2008). Phosphorylation of huntingtin at S421 promotes anterograde transport, while dephosphorylation of huntingtin promotes retrograde transport (Colin et al., 2008). Biochemical studies indicate that phosphorylation of S421 enhances the recruitment of kinesin-1 to BDNF transport vesicles and enhances the association of kinesin-1 motors with microtubules, leading to increased anterograde flux and BDNF release (Colin et al., 2008).

Fast Retrograde Transport: Signaling Endosomes and Autophagosomes

Signaling Endosomes

The balance between neuronal survival and death is regulated by neurotrophin secretion from target tissues to modulate the connection with innervating neurons (Chowdary et al., 2012; Harrington and Ginty, 2013). Neurotrophins bind to receptors on the presynaptic membrane and are transported from the distal axon toward the cell soma to effect changes in gene expression. Since these signals must be relayed over distances of up to 1 m, robust mechanisms must exist to preserve the fidelity of information being carried.

Neurotrophins (NGF, BDNF, NT3/4) bind to and activate neurotrophin receptors (TrkA, TrkB, TrkC, $p75^{NTR}$). Following receptor-mediated endocytosis, these receptor-ligand complexes are sorted into compartments called signaling endosomes for transport toward the cell soma (Chowdary et al., 2012; Harrington and Ginty, 2013). There is evidence for an early endosomal lineage for signaling endosomes, since these organelles are positive for EEA1 and Rab5B (Cui et al., 2007; Deinhardt et al., 2006; Delcroix et al., 2003), but they may mature to Rab7-positive compartments (Deinhardt et al., 2006; Sandow et al., 2000). Ligand-receptor complexes can be sustained during transport, resulting in activated Trk receptors (pTrks) and downstream signaling molecules (e.g., pERK1/2, B-Raf, and p-p38) in both the axon and cell body (Bhattacharyya et al., 2002; Cui et al., 2007; Delcroix et al., 2003; Grimes et al., 1997).

To relay information from the distal axon to the cell soma, signaling endosomes undergo robust retrograde transport. Ligation of the sciatic nerve results in the accumulation of activated

neurotrophin receptors and signaling molecules distal to the ligation site, demonstrating a robust retrograde flux of signaling endosomes along the axon (Bhattacharyya et al., 2002; Delcroix et al., 2003; Ehlers et al., 1995). Precise spatial and temporal resolution of signaling endosome dynamics was revealed with NGF-coated quantum dots, which exhibited pronounced unidirectional motility toward the cell soma interspersed with frequent pauses; average speeds ranged from 0.2 μm/s to 3 μm/s (Cui et al., 2007). This retrograde transport depends on dynein-dynactin, as inhibition of this motor complex prevents activated neurotrophin receptors from exiting the distal axon, thereby decreasing neuron viability (Heerssen et al., 2004).

Autophagosomes

Maintaining protein and organelle quality across the extended distance of the axon poses a unique challenge to the neuronal degradation machinery. Autophagy is an essential lysosomal degradation pathway in neurons (Hara et al., 2006; Komatsu et al., 2006, 2007), required to maintain cellular homeostasis. Autophagosomes are preferentially generated in the distal axon (Hollenbeck, 1993; Maday and Holzbaur, 2014; Maday et al., 2012). For a short period after the compartment is formed, autophagosomes exhibit bidirectional motility, likely driven by both kinesin-1 and dynein motors, but they soon switch to robust retrograde transport along the length of the axon (Maday et al., 2012). Both live imaging and biochemical analysis have shown that dynein and kinesin-1 motors remain tightly bound to autophagosomes during retrograde movement along the axon, despite primarily unidirectional movement with few reversals and pauses (Maday et al., 2012). Two scaffolding proteins, JIP1 and huntingtin, regulate autophagosome motility by interacting with both kinesin-1 and the retrograde dynein-dynactin motor complex (Fu et al., 2014; Wong and Holzbaur, 2014). JIP1 binding to LC3 is required to effectively block the activation of kinesin-1 on these organelles, leading to the robust retrograde motility of autophagosomes along the axon (Fu et al., 2014).

As autophagosomes transit along the axon, they undergo maturation to form autolysosomes (Lee et al., 2011; Maday et al., 2012). Initial fusion with late endosomes occurs upon exit from the distal region of the axon, but full acidification occurs as they approach the soma (Maday et al., 2012), consistent with a gradient of degradative function along the axon (Lee et al., 2011). Transport along the axon likely facilitates additional fusion events with lysosomes encountered en route to the cell soma, as inhibition of transport leads to defective acidification and accumulation of undigested contents within the lumen of the autolysosome (Fu et al., 2014; Wong and Holzbaur, 2014).

While some degradation may occur locally within the axon (Ashrafi et al., 2014), >80% of axonal autophagosomes formed by constitutive autophagy travel toward the cell soma (Maday et al., 2012), indicating a dependence on long-range axonal transport for clearance pathways. Delivery of autophagosomes to the cell soma may ensure efficient recycling of amino acids to primary sites of protein synthesis. The pronounced retrograde motility characteristic of constitutive autophagy in neurons could also balance the net outward flow of organelles and proteins via fast and slow anterograde transport (Maday and Holzbaur, 2014).

Bidirectional Transport: Mitochondria and Lysosomes

Mitochondria

Localized regions within the neuron such as growth cones and synapses experience significant energetic demands. This requirement for ATP cannot be sustained by diffusion from the cell soma and must be handled locally within the neuron. Mitochondria, the organelles responsible for ATP production and intracellular calcium buffering, are actively shuttled and positioned within the neuron to meet the localized needs of the cell. Thus mitochondrial motility facilitates a dynamic response to balance environmental demands. In axons of hippocampal neurons grown in vitro, ~20%–30% of mitochondria are motile, moving equally in both anterograde and retrograde directions; the remaining ~70%–80% are stationary (reviewed in Hollenbeck and Saxton, 2005). In vivo, axonal mitochondria are ~10% motile and exhibit a greater bias in flux in the anterograde direction as compared to in vitro studies; ~70% are anterograde and ~30% are retrograde (Misgeld et al., 2007; Pilling et al., 2006).

Mitochondrial transport is regulated by neuronal activity (Sajic et al., 2013). Elevated intracellular calcium levels resulting from enhanced synaptic activity arrest mitochondrial motility in a highly localized fashion, since mitochondria as little as 15 μm away from the stimulation site remain motile (Li et al., 2004; Macaskill et al., 2009b; Wang and Schwarz, 2009). Passing mitochondria become immobilized in areas of locally high [Ca^{2+}] at active synapses where demands for energy and calcium buffering are high. The distribution of mitochondria at synapses in turn affects synaptic transmission and strength. Stable positioning of mitochondria at presynaptic boutons maintains a steady release of synaptic vesicles (SVs), resulting in steady amplitudes of excitatory postsynaptic currents (EPSCs) (Sun et al., 2013).

Mitochondrial distribution is also coupled to the balance between mitochondrial fission and fusion. Mutations in the mitochondrial fission protein dynamin-related protein (DRP1) result in the accumulation of mitochondria in the soma of both *Drosophila* motor neurons (Verstreken et al., 2005) and cultured hippocampal neurons (Li et al., 2004). The resulting decrease in mitochondrial density at presynaptic terminals of the neuromuscular junction impairs SV release, a defect rescued with exogenous ATP (Verstreken et al., 2005).

The calcium-dependent arrest of mitochondrial motility is mediated by Mitochondrial Rho GTPase (Miro) (Fransson et al., 2003; Guo et al., 2005). Miro has two Ca^{2+}-binding EF-hand domains and two GTPase domains and binds the kinesin-1 adaptors, TRAK1 and TRAK2, also known as Milton in *Drosophila* (Fransson et al., 2006; MacAskill et al., 2009a). Ca^{2+} binding to Miro induces mitochondrial arrest; however, controversy still surrounds the mechanism. One model proposes that high levels of calcium promote binding of Miro1 to the motor domain of kinesin-1, thereby sterically inhibiting access to the microtubule (Wang and Schwarz, 2009). A second model posits that elevated calcium levels cause the dissociation of kinesin-1 from mitochondria and the Miro/TRAK complex (Macaskill et al., 2009b). Differences between axonal versus dendritic modes of regulation may underlie some of these observations. Syntaphilin is enriched on stationary mitochondria in the axon, and knockout mice show enhanced axonal mitochondrial motility, with no

effect observed on the motility of dendritic mitochondria (Kang et al., 2008). Calcium promotes binding of syntaphilin to both microtubules and kinesin-1, thereby decreasing the ATPase rate of kinesin-1 and acting as a brake on motility (Chen and Sheng, 2013), but only in the axon. Thus, the differing models may reflect cell-compartment-specific regulatory mechanisms for mitochondrial movement.

In addition to the Miro/TRAK complex, syntabulin (Cai et al., 2005), FEZ1 (Fujita et al., 2007; Ikuta et al., 2007), and RanBP2 (Cho et al., 2007; Patil et al., 2013) have all been shown to recruit kinesin-1 to mitochondria to regulate mitochondrial motility. Whether these proteins can interact with the Miro1 complex or act independently remains to be established. However, in the absence of kinesin-1, a small population of mitochondria are still motile (Pilling et al., 2006), indicating that other kinesins also drive mitochondrial motility. There is evidence that both KIF1Bα (Nangaku et al., 1994) and KLP6 (Tanaka et al., 2011) contribute to the intracellular transport of mitochondria.

The role of dynein in mitochondrial trafficking is less well studied. Mutations in kinesin-1 and the Ca^{2+}-dependent inactivation of kinesin-1 arrest mitochondrial motion in both anterograde and retrograde directions (Chen and Sheng, 2013; Macaskill et al., 2009b; Pilling et al., 2006; Wang and Schwarz, 2009), suggesting that the activity of oppositely directed motors is coordinated (Pilling et al., 2006). The TRAK proteins interact with the dynein/dynactin complex and may modulate this coordination (van Spronsen et al., 2013). Loss of Miro affects both anterograde and retrograde transport (Russo et al., 2009), also consistent with an integrated regulatory mechanism.

Late Endosomes and Lysosomes

Approximately half of the late endosomes/lysosomes in the axon undergo bidirectional motility characterized by frequent directional changes and pauses while the remaining half undergo either anterograde or retrograde directed transport in approximately equal proportion (Hendricks et al., 2010; Moughamian and Holzbaur, 2012).

Dynein is necessary for the proper positioning of both late endosomes and lysosomes (Harada et al., 1998). Dynein is recruited to late endosomes and lysosomes via the Rab7 effector RILP (Rab7-interacting lysosomal protein), which interacts directly with the C terminus of the $p150^{Glued}$ subunit of dynactin (Johansson et al., 2007; Jordens et al., 2001). ORP1L, another Rab7 effector, then facilitates transport by recruiting the RILP-Rab7-dynactin-dynein complex onto βIII spectrin-associated membranes via an interaction with the Arp1 subunit of dynactin (Holleran et al., 2001; Johansson et al., 2007). DLIC may also function, independently of RILP, to recruit dynein to late endosomes and lysosomes (Tan et al., 2011). Snapin has also been proposed to regulate the recruitment of dynein to late endosomes through a direct interaction with the dynein-intermediate chain (DIC); this interaction may facilitate the fusion of late endosomes and lysosomes (Cai et al., 2010).

The anterograde transport of lysosomes is mediated by SifA and kinesin-interacting protein (SKIP), which links Arl8, a mature lysosome Arf-like G protein, directly to the light chain of kinesin-1 (Rosa-Ferreira and Munro, 2011). Kinesin-2 motors are also associated with late endosomes and lysosomes (Brown et al., 2005; Castle et al., 2014; Hendricks et al., 2010), but the regulatory mechanisms that may control kinesin-2 activity, or that coordinate kinesin-2 function with the other lysosome-bound motors, remain to be determined.

Slow Axonal Transport of Cytoskeletal Polymers and Soluble Proteins

While organelles and vesicles are transported relatively rapidly along the axon, the delivery of hundreds of different types of newly synthesized cytosolic proteins and cytoskeletal polymers occurs more slowly. The slow anterograde axonal transport of protein is subdivided into two speed categories: slow component a (SCa, mainly tubulin and neurofilaments) at rates of 0.2–1 mm/day and slow component b (SCb, cytosolic proteins), which is around 10-fold faster at 1–10 mm/day (reviewed in Roy, 2014). Due in large part to the difficulty in visualizing slow axonal transport in real time, it has remained the enigmatic cousin of fast axonal transport. Advances in imaging technologies and fluorescent probes, as well as computational modeling (Li et al., 2012; Scott et al., 2011), have allowed significant conceptual advances in understanding the processes at work, although specific molecular mechanisms and often the motor proteins involved are not yet understood.

Movement of neurofilaments by slow axonal transport has been well characterized. The vast majority of neurofilament protein is transported as assembled units of oligomers (Brown, 2000; Wang et al., 2000; Yan and Brown, 2005), moving in both the forward and reverse direction by engaging kinesin-1 and dynein motors (Shah et al., 2000; Uchida et al., 2009; Wagner et al., 2004; Yabe et al., 1999). Neurofilament subunit M binds directly to dynein (Wagner et al., 2004); KIF5A appears to be the primary kinesin-1 isoform for neurofilament transport (Wang and Brown, 2010), but the mechanisms regulating the recruitment of this motor remain unknown. In a breakthrough study, Brown and colleagues determined that the overall slow net rate of transport of neurofilaments along the axon is a result of short-lived motor-driven movements punctuated by extended pauses (Wang et al., 2000). How the activities of dynein and kinesin-1 are regulated in the context of neurofilament transport to result in such a disparate rate of transport compared to vesicular motility is unknown.

The slow axonal transport of the two other key cytoskeletal families, actin and tubulin, is more ambiguous. Analysis is complicated by the rapid polymerization and depolymerization rates of the polymers. Analogous to neurofilament transport, the movement of short microtubule fragments may be driven by motor proteins (Wang and Brown, 2002), although there is also evidence for the transport of soluble tubulin dimers in a kinesin-dependent manner (Terada et al., 2000). In contrast, the slow transport of actin occurs in growth-cone like waves that support neurite growth during development (Flynn et al., 2009), but how actin is replenished in mature neurons is unknown.

Slow axonal transport also carries a large and diverse pool of cytosolic proteins, with more than 200 distinct components, although the complete proteome is unknown (Roy, 2014). A handful of examples have been studied so far. Current models suggest that proteins in this pool, such as synapsin, form spontaneously aggregated complexes (Scott et al., 2011)

that undergo "dynamic recruitment" to allow short bursts of anterograde transport by hitching a ride on passing vesicles (Tang et al., 2013).

Both the dynamic recruitment model for soluble proteins and the stop-and-go model for neurofilament transport (Brown and Jung, 2013; Roy, 2014) rely on the same microtubule motors that power fast axonal transport. The major differences in transport rates observed arise from differences in the time spent actively engaged in transport. Thus, slow axonal transport is a balance between long pauses and short bouts of motility. Despite the apparent inefficiency of this mechanism, it is worth stating that the amount of protein delivered to the presynapse by slow axonal transport outweighs that of fast axonal transport by at least 3 to 1 (Garner and Mahler, 1987; McEwen and Grafstein, 1968; Roy, 2014). The persistent and constitutive delivery of new material to the axon terminal by slow transport is critical to synapse survival.

An important outcome of slow axonal transport as it relates to neuronal function is the age of proteins conveyed by this method. Proteins that reach the axon terminus of a 1 m axon could be anywhere from 4 to 12 months old and might persist for as long as another 100 days (Garner and Mahler, 1987). Recent work suggests that mitochondria are also aged in distal neurites (Ferree et al., 2013). This fact highlights the specific axonal requirement for distal quality control (Maday and Holzbaur, 2014) and for chaperones (Song et al., 2013; Terada et al., 2010) that maintain the integrity of the proteome in the distal axon.

Regional Specificity of Axonal Transport

Axonal transport is not uniform along the axon, as cargos exhibit different motility patterns within distinct regions of the axon. Both the axon initial segment and the distal axon are key sites for regulatory control. Site-specific organization of the microtubule cytoskeleton may provide a structural basis for the motility differences observed.

The Axon Initial Segment

The AIS has a highly specialized cytoskeletal architecture. Microtubules are stabilized at the AIS by +TIPS EB1 and EB3 interacting with ankyrin G (Leterrier et al., 2011). The AIS has been proposed to act as a selective filter to exclude somatodendritic vesicular cargos from entering the axon. Live imaging studies indicate that axonal cargos move from cell body to axon with no change in velocity, while dendritic cargos that enter the base of the axon are specifically arrested at the start of the AIS (Petersen et al., 2014). Multiple mechanisms have been proposed to explain the underlying mechanism. One model posits that a dense actin meshwork at the AIS is key (Song et al., 2009; Watanabe et al., 2012), although neither polarized actin arrays nor dense actin meshworks were seen in recent platinum replica EM analysis (Jones et al., 2014) or by superresolution imaging (Xu et al., 2013). Alternatively, differences in the microtubule cytoskeleton may be critical in mediating axonal/dendritic sorting. It has been proposed that the mixed microtubule polarity of dendrites may be sufficient to allow dynein motors to selectively steer dendritic cargos to this compartment (Kapitein et al., 2010). Or, posttranslational modifications to the microtubule cytoskeleton may contribute to the regulation of axonal versus dendritic cargo sorting (Hammond et al., 2010; Nakata and Hirokawa, 2003; Setou et al., 2002). The recent observation that axo-dendritic selectivity precedes the establishment of both the AIS and mixed microtubule polarity in dendrites (Petersen et al., 2014) favors the interpretation that kinesin motors driving axonal cargos are responding to microtubule-based cues (Jacobson et al., 2006), but more work is required to fully establish this model.

Intriguingly, there is some evidence that the AIS also affects retrograde transport, as DCVs in *Drosophila* circulating through the axon reverse at both the distal and the proximal axon, further implicating these regions of the axon as specialized zones for transport regulation (Wong et al., 2012).

Distal Initiation of Retrograde Transport

Cargos undergoing retrograde transport often initiate motility very far from the soma, in the distal axon. Microtubules in the distal axon display enhanced dynamicity, with an enriched population of actively growing microtubule plus ends (Moughamian et al., 2013). Efficient initiation of retrograde transport from the distal axon requires a set of microtubule plus-end-interacting proteins, or +TIPs (Lloyd et al., 2012; Moughamian and Holzbaur, 2012; Moughamian et al., 2013). The CAP-Gly domain of the $p150^{Glued}$ subunit of dynactin interacts with additional +TIP proteins, CLIP-170 and the end-binding proteins EB1 and EB3. Ordered recruitment of these plus-end binding proteins has been proposed to facilitate the active loading of the dynein-dynactin motor complex onto dynamic microtubule ends (Moughamian et al., 2013). This mechanism enhances retrograde transport initiation for multiple cargos, including early endosomes, late endosomes and lysosomes, and mitochondria (Moughamian et al., 2013).

The dynein-binding protein Lis1 is also a +TIP, and has been proposed to act as an initiation factor for dynein-mediated transport in fungi (Lenz et al., 2006). In neurons, however, Lis1 is required for transport all along the axon, not just in regions of increased microtubule dynamicity (Moughamian et al., 2013; Pandey and Smith, 2011). Lis1 likely acts directly on dynein, priming the motor for transport (Huang et al., 2012) and/or recruiting the dynein/dynactin complex onto certain cargos (Dix et al., 2013). In sensory neurons, the spectraplakin BPAG1n4 and the endosomal protein retrolinkin have also been reported to be required for sustained retrograde transport along the axon, in a mechanism that also depends on dynamic microtubule plus ends (Kapur et al., 2014).

mRNA Transport, Local Protein Synthesis, and Injury Signaling

To carry out domain-specific tasks, neurons can locally regulate the proteome in response to dynamic changes in the environment. Local translation of mRNAs has been well characterized in dendrites (Holt and Schuman, 2013), but local translation in the axon is less well understood. Some direct evidence for this process comes from metabolic labeling studies to measure newly synthesized protein from severed axons (Merianda et al., 2009; Willis et al., 2005).

Sequences within the 5′ and 3′ UTR of mRNAs are recognized by RNA-binding proteins and direct transport to either dendrites or the axon (Holt and Schuman, 2013; Merianda et al., 2013).

mRNA is transported as translationally repressed RNA granules along with RNA-binding proteins and ribosomes (Kanai et al., 2004; Knowles et al., 1996; Krichevsky and Kosik, 2001). These RNA granules exhibit bidirectional as well as confined oscillatory movement dependent on plus- and minus-end-directed microtubule-based motors (Alami et al., 2014; Davidovic et al., 2007; Gumy et al., 2014; Kanai et al., 2004; Ling et al., 2004; Zhang et al., 2001). While mechanistic details are lacking, motor recruitment may be regulated by 3′ UTR localization signals (Amrute-Nayak and Bullock, 2012; Serano and Cohen, 1995).

Two prominent mechanisms initiate mRNA transport and local translation in the axon: axonal injury and chemotrophic signals. Injury in the distal axon induces local translation of importin-β, which heterodimerizes with importin-α to bind dynein (Hanz et al., 2003). These α/β dimers have high affinity for binding to the nuclear localization signals of transcription factors (e.g., STAT3; also translated locally upon injury). Thus, injury-induced local translation of importin-β assembles a retrograde signaling complex that delivers transcription factors to the nucleus to initiate a proregenerative transcriptional program (Hanz et al., 2003; Perry et al., 2012; Rishal and Fainzilber, 2014). Conditional disruption of the axon targeting sequence within the 3′ UTR of importin-β depletes importin-β mRNA and protein from the axon, causing delayed axon regeneration in vivo (Perry et al., 2012). Local translation of vimentin links pERK to importin-β-mediated retrograde signaling to further modulate the transcriptional program (Perlson et al., 2005).

Axonal injury also induces formation of the retrograde signaling complex DLK-pJNK3-JIP3-dynein/dynactin. Injury-induced calcium influx activates the mitogen-activated protein kinase kinase kinase dual leucine zipper kinase (DLK), which in turn activates c-Jun NH2-terminal kinase (JNK3) (Rishal and Fainzilber, 2014). JNK3 is linked to axonal transport vesicles via the JNK-interacting protein JIP3 (Cavalli et al., 2005). While JIP3 can interact with both kinesin and dynactin, injury induces preferential association with dynactin (Cavalli et al., 2005). Thus, upon injury, a complex is assembled of DLK-pJNK3-JIP3-dynein/dynactin that transports activated transcription factors (e.g., pSTAT3) to the nucleus to initiate axonal regeneration (Cavalli et al., 2005; Rishal and Fainzilber, 2014; Shin et al., 2012). In the absence of DLK, retrograde transport of pSTAT3 and JIP3 is blocked, resulting in delayed axonal regeneration (Shin et al., 2012).

Enhanced calcium influx at the injury site also back-propogates along the axon toward the cell soma to elicit changes in gene expression (Cho et al., 2013). Elevated intracellular calcium in the soma induces PKCμ-dependent export of HDAC5 from the nucleus, resulting in enhanced histone acetylation and activation of a proregenerative transcriptional program (Cho et al., 2013). Export of HDAC5 from the nucleus serves a dual function, as subsequent anterograde transport of HDAC5 to the injury site increases tubulin deacetylation, promoting growth cone dynamics and axon regeneration (Cho and Cavalli, 2012).

Chemotrophic signals can also induce mRNA transport and local translation in the distal axon and growth cone (reviewed in Rishal and Fainzilber, 2014). Treatment with neurotrophins localizes β-actin mRNA to the distal axon and growth cone; increased β-actin mRNA is concomitant with increased β-actin protein and forward protrusion of the growth cone (Bassell et al., 1998; Zhang et al., 2001). Interference with the 3′ UTR axonal targeting signal prevents distal accumulation of β-actin mRNA and protein, resulting in growth cone retraction (Zhang et al., 2001). Transport and translation of β-actin mRNA in the axon can be induced by NGF added exclusively to the axonal compartment, indicating an efficient relay of information from the distal axon to the cell soma and back (Willis et al., 2005). Translocation of β-actin mRNA into axons has also been observed upon axonal injury in vivo (Willis et al., 2011).

The Energy Requirements of Axonal Transport

Axonal transport is an energetically costly process as molecular motors hydrolyze ATP to carry out the work of stepping along microtubules. The conventional kinesin-1 motor consumes one molecule of ATP for every 8 nm step taken (Hackney, 1994). Measurements to date indicate a typical vesicle has one to two kinesins bound and exerting force at any one time (Encalada et al., 2011; Hendricks et al., 2010, 2012; Rai et al., 2013; Soppina et al., 2009). Taking the example of an average axon in the rat cortex, 40 mm in length, a single vesicle traversing this axon in the anterograde direction would require $\sim 5 \times 10^6$ ATP molecules to do so, assuming no tug-of-war or switch events occur, which can be frequent in vivo (Hendricks et al., 2010; Soppina et al., 2009). In the 1 m-long axons of human motor neurons, the minimum ATP consumed per anterograde transport event reaches $\sim 1.25 \times 10^8$ ATP molecules.

Unlike the consistent unidirectional stepping of kinesin-1 motors, the step size of single cytoplasmic dynein motors purified from mammalian brain ranges from 8 to 32 nm in length and can include backsteps (Mallik et al., 2004; Ross et al., 2006). However, recent in vitro and in vivo measurements show that dynein acts in teams of 6–12 motors per vesicle to produce persistent retrograde motility, and under these conditions motor teams show a step size of 8 nm (Hendricks et al., 2010; Rai et al., 2013; Soppina et al., 2009). Thus, a single vesicle traversing a human motor neuron from neuromuscular junction back to the soma would require a minimum of $\sim 7.5 \times 10^8$ ATP molecules.

Strikingly, however, the amount of ATP hydrolyzed during axonal transport is relatively inconsequential compared to the amount of ATP consumed by those same neurons to fire action potentials and maintain resting potentials. A single action potential propagated along a 40 mm-long axon would require $\sim 1 \times 10^8$ ATP molecules, and thus axonal transport likely amounts to a fraction of the 25% of energy allocated to the housekeeping budget of the gray matter (Harris and Attwell, 2012).

One mechanism proposed to specifically address the energy demands of axonal transport is based on the finding that glycolytic enzymes are bound to the surface of vesicles moving along the axon, and can serve as an independent source of ATP for the motors driving transport of these vesicles (Zala et al., 2013). The identification of an energy source independent of mitochondria that can power vesicular transport is intriguing, and may allow cargos to transit any gaps in ATP gradients between unevenly dispersed mitochondria along the axon (MacAskill and Kittler, 2010; Zala et al., 2013). However, it remains unclear whether on-board energy production by

glycolysis is required for axonal transport in vivo, as the energetic lives of glia and neurons are intimately linked (Saab et al., 2013). Glia supply neurons with lactate under conditions of glucose shortage, bypassing glycolysis in the axon. Indeed, myelinated axons can survive for extended periods with only lactate, while fast axonal transport would be predicted to stop under these conditions if solely dependent on glycolysis. Further, there are several forms of axonal transport not associated with vesicular membranes, including slow axonal transport and the movement of RNA granules. Without an onboard ATP supplier, these transport processes would experience regions of slow to no motility in the hypothesized low ATP regions. Alternatively, diffusion may be sufficient to maintain consistent levels of ATP along the axon. In either case, an onboard mechanism of glycolysis might become more relevant in situations of fast action potential firing—a high-energy task that increases local ATP demands, potentially restricting the ATP available for housekeeping tasks.

Common Themes and Outstanding Questions

The compartmentalized nature of neurons requires active mechanisms of transport to distribute organelles to localized regions of demand. The differing patterns of motility observed for distinct organelles may reflect underlying functional differences. For example, mitochondrial motility facilitates distribution to sites of need, where these organelles become tethered to supply local needs for energy production and calcium buffering. Similarly, the bidirectional movement of mRNA granules may effectively distribute these particles to sites of local synthesis. Upon arrival, mRNA granules remain poised in a translationally repressed state to rapidly respond to stimuli such as axonal injury. Other organelles, such as signaling endosomes, must relay information across the extended distance of the axon and thus undergo long journeys with highly processive, unidirectional motility to efficiently move from distal axon to cell soma. And degradative organelles such as autophagosomes must efficiently clear damaged organelles and aggregated proteins, recycling components back to the cell body for reuse.

Many major outstanding questions remain unanswered. How is organelle movement in the axon choreographed? How is the complement of motors associated with each organelle regulated? Since most organelles may have opposing motors bound simultaneously, future work will determine how oppositely directed motors are coordinated to achieve organelle-specific differences in motility patterns. Further work is also required to uncover regional-specific differences in organelle transport within the neuron. Advances in imaging technology will continue to facilitate the study of these pathways both in cells and in vivo and will provide insights into the alteration of these pathways in stress and disease. A growing number of human diseases, both neurodevelopmental and neurodegenerative, are caused by mutations in the axonal transport machinery (Table 1). Further, axonal transport is misregulated in many of the major neurodegenerative diseases affecting human populations, including ALS and Alzheimer's, Huntington's, and Parkinson's diseases (Millecamps and Julien, 2013). Thus, continued research into the molecular mechanisms involved in axonal transport and its regulation should provide new insights pointing toward development of novel therapeutic approaches in the future.

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