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Research report

Conventional kinesin: Biochemical heterogeneity and functional implications in health and disease

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ABSTRACT

Intracellular trafficking events powered by microtubule-based molecular motors facilitate the targeted delivery of selected molecular components to specific neuronal subdomains. Within this context, we provide a brief review of mechanisms underlying the execution of axonal transport (AT) by *conventional kinesin*, the most abundant kinesin-related motor protein in the mature nervous system. We emphasize the biochemical heterogeneity of this multi-subunit motor protein, further discussing its significance in light of recent discoveries revealing its regulation by various protein kinases. In addition, we raise issues relevant to the mode of conventional kinesin attachment to cargoes and examine recent evidence linking alterations in conventional kinesin phosphorylation to the pathogenesis of adult-onset neurodegenerative diseases.

Contents

1. Axonal transport: a specialized form of intracellular trafficking in neurons

Neurons are highly polarized cells bearing morphologically and biochemically distinct somatodendritic and axonal compartments that fulfill information-input and information-output-related functions, respectively (Caceres et al., 2012). Neuritic compartments comprise the overwhelming bulk of the total cell volume of neurons, and some axons may reach lengths of over a meter in humans. The development and life-long maintenance of this unique cellular architecture of neurons involve numerous specializations of the cytoskeleton and the secretory pathway. Together, these specializations facilitate the continuous transport and delivery of molecular components from their place of synthesis and packaging in the neuronal cell body to specialized subdomains within dendrites and axons (Bradke and Dotti, 2000; Higgins et al., 1997; Maeder et al., 2014; Morfini et al., 2001).

Intracellular directional transport of membrane-bounded organelles (MBOs) is driven by molecular motors, mechanochemical proteins that utilize energy derived from ATP hydrolysis to translocate their cargoes along specific filamentous components of the neuronal cytoskeleton (Hirokawa et al., 2010). Short-range

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transport of MBOs within actin filament-rich cellular domains, including growth cones, pre- and post-synaptic terminals, is mainly powered by the *myosin* family of motor proteins (Kneussel and Wagner, 2013). On the other hand, long-range transport of MBOs from their site of assembly and packaging (*i.e.*, the *trans* Golgi network) to specific dendritic and axonal compartments is mediated by microtubule-based molecular motors (Hirokawa et al., 2009).

2. Microtubule-based motor proteins power axonal transport

Microtubules are intrinsically polarized, with beta-tubulin being present at the plus-end and alpha-tubulin at the minus-end (Baas et al., 2016). The intrinsic polarity of microtubules is recognized by molecular motor proteins, and allows for directional transport of cargoes along the microtubule surface. Within axons, microtubules are mostly uniformly oriented, with their plus ends directed towards the presynaptic terminals. This microtubule organization within axons allows for transport of MBOs in the retrograde (from the cell periphery towards the cell soma) and anterograde (away from the neuronal soma) directions (Black, 2016; Morfini et al., 2012). The former mainly depends on the large multisubunit motor protein *cytoplasmic dynein*, whereas anterograde AT is executed by the kinesin superfamily of motor proteins (KIFs) (Hirokawa and Noda, 2008). Unlike axons, microtubules in vertebrate dendrites display a non-uniform (mixed) orientation. Accordingly, unidirectional motor proteins could, in principle, move cargoes away and towards the neuronal soma within this subcompartment (Baas et al., 2016).

Microtubule motor-based intracellular trafficking of molecular components within axons represents a cellular process collectively referred to as *axonal transport* (AT) (Black, 2016). AT involves the delivery of components synthesized in the neuronal soma to specific axonal subdomains, the removal of old and damaged cellular components from these domains, and the sustained maintenance of neurotrophic support [reviewed in (Black, 2016; Morfini et al., 2012)]. As such, AT is regarded as a cellular process critical for the appropriate maintenance of neuronal architecture and connectivity throughout the long lifetime of neurons (Brady and Morfini, 2010; Morfini et al., 2009a).

In mammals, the KIF superfamily of motors comprises 45 different genes, of which 38 are expressed in nerve tissue (Miki et al., 2003). Based on phylogenetic analysis and sequence homology, KIF members have been classified into 15 KIF subfamilies, termed kinesin-1 to kinesin-14B (Lawrence et al., 2004). Closer sequence similarities within members of each KIF subfamily have long been thought to reflect related functionalities, but the specific function of most KIFs has yet to be established. While a possibility exists that each MBO type is transported by a unique KIF, the number of KIFs expressed in nerve tissue largely exceeds the number of defined MBO cargoes, and only a few KIFs have been confirmed to mediate AT of specific MBOs in neurons, suggesting that some cellular activities requiring KIFs may have not yet been recognized (Brady and Sperry, 1995). Moreover, cumulative evidence also suggests functional redundancy among some KIF members on the AT of some MBOs, particularly mitochondria (Saxton and Hollenbeck, 2012). Here, we focus our review on basic aspects of *conventional kinesin*, the founding member of the KIF superfamily of proteins, and the most abundant KIF in the mature mammalian nervous system (Wagner et al., 1989).

3. Conventional kinesin: structural organization and biochemical diversity

Conventional kinesin was initially purified from mammalian brain tissue taking advantage of its unique biochemical properties,

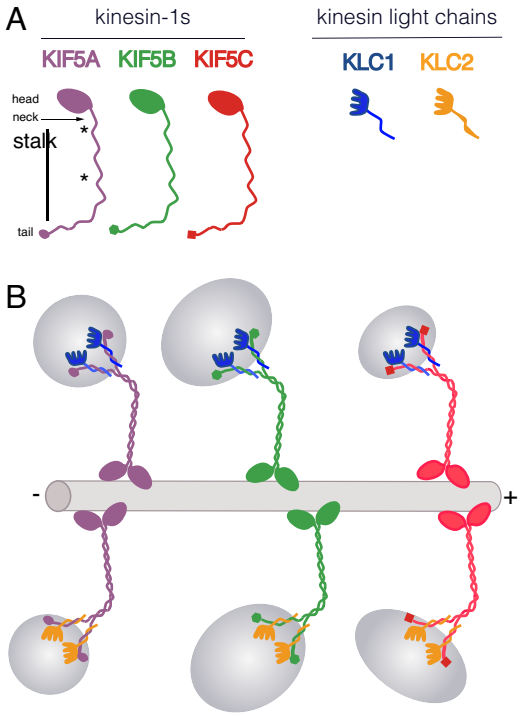

Fig. 1. Conventional kinesin subunit variants. (A) Three kinesin-1 genes are expressed in mammalian tissues, including the neuron-enriched KIF5A and KIF5C isoforms, and the ubiquitously expressed KIF5B isoform. The overall structure of KIF5s is highly conserved, involving a head domain responsible for microtubule binding and ATP hydrolysis, a neck linker region, and a long stalk mainly comprising coiled-coil and hinge domains (asterisks) involved in KIF5 homodimerization. The globular tail domain of KIF5 features the most divergent sequences among KIF5 subunits. (B) Biochemical experiments demonstrated that both KIF5s and KLCs are present as homodimers within the conventional kinesin holoenzyme. Combinations of KIF5 and KLC homodimers give rise to six conventional kinesin variants, as defined by their subunit composition. Alternative splicing of the carboxy terminal region of KLC1 further increases the complexity of these variants. Experimental evidence suggests combined roles of the tail domain of KIF5s and the carboxy terminus of KLCs on the targeting of conventional kinesin variants to MBOs of unique protein composition.

which were first revealed by pioneering microscopic observations in the isolated squid axoplasm preparation (Allen et al., 1982; Brady, 1985; Brady et al., 1983; Vale et al., 1985). To date, it is well established that this motor protein exists as a heterotetrameric complex of approximately 380 kDa, being composed of two *kinesin heavy chain* subunits of 115–130 kD, and two *kinesin light chain* (KLCs) subunits of 62–70 kD (Wagner et al., 1989) (Fig. 1).

After standardization of the kinesin nomenclature (Lawrence et al., 2004), heavy chain subunits of conventional kinesin were listed as members of the *kinesin-1* subfamily of KIFs. A single kinesin-1 gene is encoded in the *Caenorhabditis elegans* (UNC-116) and *Drosophila melanogaster* genomes, with genetic deletion experiments indicating an essential role of this subunit on organism development and synaptic function (Hurd and Saxton, 1996; Siddiqui, 2002). In contrast, the mammalian kinesin-1 subfamily comprises three genes encoding the neuron-enriched *KIF5A* and *KIF5C*, and the ubiquitously expressed *KIF5B* members (Kanai et al., 2000) (Fig. 1A). Immunoelectron microscopy-based visualization of the purified conventional kinesin holoenzyme revealed kinesin-1 subunits as two 80 nm long rods, each featuring a globular head and a fan-shaped tail (Bloom et al., 1988; Hirokawa et al., 1989). A molecular basis underlying this structure was illuminated after KIF5 protein sequences became available (Kosik et al., 1990), and it is now clear that the overall protein domain organization of all KIF5 members within the kinesin-1 subfamily is highly conserved [reviewed in (Jeppesen and Hoerber, 2012)]. A head motor region,

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located at the amino-terminus, comprises microtubule binding and ATPase hydrolysis domains responsible for the mechanochemical properties of conventional klnesis. A disordered, 14 amino acid long neck-linker follows this head region, and plays an important role in motor processivity and step coordination. A single ATP hydrolysis event by a given KIF5 dimer powers an 8 nm step, which is a distance equivalent to the length of a tubulin-dimer (Gennerich and Vale, 2009). The neck-linker and head domains are followed by a long stalk region, containing hinge and long coiled-coil domains that facilitate dimerization of KIF5 subunits. Finally, the extreme C-terminal tail of KIF5s comprises a small globular domain featuring the most divergent sequence stretch among KIF5s. Interestingly, electron microscopic observations revealed 20–30 nm long rods (as opposed to 80 nm) linking transported MBOs to microtubules, suggesting that a portion of the KIF5 stalk interacts with its transported MBOs (Hirokawa, 2011). Consistent with these findings, evidence from subcellular fractionation (DeBoer et al., 2008), nerve ligation (Dahlström et al., 1991) and pulse-chase studies (Elluru et al., 1995) suggested association of specific KIF5 isoforms with selected MBOs. An initial report suggested functional redundancy among KIF5s, which resulted from heterodimerization (Kanai et al., 2000). However, subsequent co-immunoprecipitation studies using well-characterized isoform-specific anti-KIF5 antibodies demonstrated that KIF5s are exclusively organized as homodimers within the conventional kinesin holoenzyme (DeBoer et al., 2008).

KLC subunits localize to the end of the stalk domain of conventional kinesin. Two KLCs are expressed in mammalian nervous tissue (KLC1 and KLC2) (Rahman et al., 1998), which exclusively associate as homodimers within the conventional kinesin holoenzyme (DeBoer et al., 2008). At their amino terminus, KLC subunits feature a heptad repeat region that mediates their interaction with kinesin-1 subunits. In addition, the central region of KLCs features highly conserved DnaJ-like domains (Tsai et al., 2000) [also reported as Tandem Repeat domains (TRs) by some research groups (Goldstein and Gindhart, 1996)]. These domains have been shown to mediate the tight interaction of conventional kinesin with MBO cargoes and to recruit the chaperone hsc70 for removal of this motor protein from MBO surfaces. Biochemical studies indicated that KIF5 and KLC homodimers interact in all possible combinations to form at least six biochemical variants of conventional kinesin, as defined by their tetrameric subunit composition (DeBoer et al., 2008) (Fig. 1B). Further increasing the complexity of conventional kinesin subunit variants, KLC1 was found to undergo alternative splicing in its extreme carboxy-terminal sequence to generate a large number of KLC1 isoforms (Cyr et al., 1991). Along with the carboxy-terminal region of KIF5s, these isoform-specific KLC1 sequences appear to target conventional kinesin to different MBOs (DeBoer et al., 2008; Gyoeva et al., 2000; Khodjakov et al., 1998) (Fig. 1B).

4. The mode of conventional kinesin attachment to membrane-bounded organelle cargoes remains largely unknown

Mainly based on its partitioning to the soluble fraction after homogenization, conventional kinesin was originally thought to exist as a soluble protein in cells. However, subsequent ligation (Hirokawa et al., 1991) and pulse-chase radiolabeling experiments (Elluru et al., 1995; Elluru et al., 1990) indicated that, *in vivo*, the overwhelming majority of conventional kinesin moves along axons in association with MBOs as part of the fast component (FC) of AT (Black, 2016). Providing a partial explanation for these contrasting findings, it was later shown that partitioning of conventional kinesin to soluble fractions results from an active enzymatic process involving post-lysis modification of this motor (Hollenbeck, 1993; Morfini et al., 2000). Further, these studies suggested the involvement of chaperones and protein kinases in this process, which might become activated during the homogenization procedure (Morfini et al., 2001; Tsai et al., 2000).

Although a protein-based association of conventional kinesin with MBO cargoes is well established (Szodorai et al., 2009), no *bona fide* receptors for this motor protein have been identified to date and thus, the mode of attachment of conventional kinesin to its transported MBOs remains a largely unresolved issue. On the other hand, an increasingly growing number of studies have yielded a long list of candidate proteins reportedly binding to KIF5 and KLC subunits. An exhaustive discussion of these findings is beyond the scope of this review, but most KIF5-interacting proteins partners identified to date have been proposed to function as "adaptors" that would directly or indirectly bind KIF5 s to various MBO cargoes. In some cases, KIF5s have also been proposed to bind and transport non-MBO cargoes, including mRNA-containing multiprotein complexes (Fu and Holzbaur, 2014; Hackney, 2007; Hirokawa, 2006; Lin and Sheng, 2015; Loss and Stephenson, 2015; Maday et al., 2014).

Intriguingly, cargo "adaptors" binding the globular tail of KIF5s include a wide variety proteins including syntabulin (Cai et al., 2007; Su et al., 2004), glutamate receptor-interacting protein 1 (GRIP1) (Hoogenraad et al., 2005; Setou et al., 2002), fasciculation and elongation protein-ζ (FEZ1) (Gindhart et al., 2003), adaptor protein mitogen-activated protein kinase-activating death domain (DENN) (Niwa et al., 2008) and the TRAK/Milton family of proteins (Randall et al., 2013; van Spronsen et al., 2013), among many others (Maday et al., 2014). The lack of functional and/or structural relationship among these proteins raises concerns about the specificity of these interactions, especially since most supporting studies involve transient overexpression and affinity purification approaches, as well as the use of heterologous systems (most notably, yeast two-hybrid system). Further, the notion that protein adaptors would facilitate KIF5-mediated transport of cargoes in the absence of KLCs appears inconsistent with data showing co-transport of these subunits along axons *in vivo* (Elluru et al., 1995).

An even larger number of proposed "adaptor" proteins have been reported to interact directly with the DnaJ-like/TR domain of KLCs. The list of proteins includes, but is not limited to, APP (Kamal et al., 2000), YETI (Wisniewski et al., 2003), JIP1 (Matsuda et al., 2003), JIP3 (Koushika, 2008), Sunday Driver (Bowman et al., 2000), surface proteins in vaccinia virus (Ward and Moss, 2004), and HAP1 (McGuire et al., 2006), among many others. While DnaJ-like/TR domains may indeed mediate specific protein–protein interactions (Cyr et al., 1994), they are unlikely to provide MBO cargo binding specificity because they are highly conserved in both KLC1 and KLC2 (Tsai et al., 2000), yet these KLCs associate with different MBO subsets (Rahman et al., 1998). Regardless, how could conventional kinesin discriminate among such large number of structurally unrelated adaptor proteins that bind to the same protein domain remains largely unclear. More recently, a mechanism was proposed where KLCs would bind a bipartite WD/E motif present in several hundred unrelated proteins (Dodding et al., 2011). But again, the uneven stoichometries of KLCs and those proteins leaves unclear the issues of cargo specificity and selective delivery of those cargoes to discrete neuronal subdomains (see below).

Of note, both the tail domain of KIF5s and the DnaJ-like/TR domains of KLCs contain exposed hydrophobic surfaces, a feature already known to render such proteins extremely "sticky" in various protein–protein interaction assays (Vites et al., 2004). For example, findings of high affinity (nanomolar) interaction between the intracellular domain of APP and the DnaJ-like domain of KLCs fueled the proposal that APP acts as a receptor protein for conventional kinesin (Kamal et al., 2000), a concept bearing major implications for our understanding of Alzheimer's disease (AD)

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pathogenesis (Goldstein et al., 2003). However, subsequent studies revealed that recombinant KLCs produced in bacteria interact non-specifically with proteins as diverse as GFP, Fe65, PAT1a and the intracellular domains of APP, APLP1, and APLP2 in pull-down assays (Lazarov et al., 2005). Significantly, *in vitro*-translated KLC1, which has fewer non-specific binding characteristics, failed to bind the intracellular domain of APP (Lazarov et al., 2005). Moreover, immunoprecipitation experiments using brain tissue as starting material also failed to detect a direct interaction between APP and conventional kinesin (Lazarov et al., 2005). Similarly, and largely based on overexpression experiments, the ubiquitously expressed protein huntingtin was proposed to function as a scaffolding protein recruiting conventional kinesin and other unrelated proteins to MBOs (Colin et al., 2008). However, an interaction between huntingtin and conventional kinesin subunits could not be confirmed for endogenous proteins from nerve tissue (Morfini et al., 2009b). Collectively, these precedents highlight the importance to confirm putative interactions by multiple independent approaches, such that *bona fide* adaptors for conventional kinesin binding to MBO cargoes can be established. Despite the wealth of data, the relevance of most adaptor partners proposed for KIF5 and KLCs to date has not yet been rigorously established.

5. Functional implications of conventional kinesin subunit variants

The functional significance of conventional kinesin variants, as defined by their subunit composition, is only partially understood. Subcellular fractionation experiments showed association of KIF5s and KLCs with a broad spectrum of MBO cargoes that feature little or no overlap in membrane protein composition. Such MBOs include mitochondria, and tubulo-vesicular MBOs containing amyloid precursor protein (APP), neurotransmitter receptors, plasmalemma and synaptic vesicle precursors (Leopold et al., 1992; Szodorai et al., 2009; Takamori et al., 2006). Antisense oligonucleotide experiments in cultured neurons confirmed a major role of conventional kinesin on the AT of membrane proteins, including APP, to axons and dendrites (Ferreira et al., 1992; Rathgeber et al., 2015), but these experiments failed to reveal the issue of biochemical diversity.

Various independent observations from subcellular fractionation (DeBoer et al., 2008), nerve ligation (Dahlström et al., 1991), and pulse-chase radiolabeling experiments (Elluru et al., 1995) suggest that KIF5s play a role on the targeting of conventional kinesin subunit variants to selected MBOs. Also supporting this notion, immunoisolation experiments revealed an association of conventional kinesin variants containing KIF5C, but not KIF5A or KIF5B, with vesicles containing APP and various presynaptic components including synapsin-I, SNAP25, syntaxin-1B, VAMP2, Munc13-1, RIM2, Rab3, and Rab3Gas (Szodorai et al., 2009). Finally, differences in tissue expression profiles for KIF5s and phenotypic outcomes elicited upon their genetic deletion also provide evidence of functional specializations (Nakajima et al., 2012; Xia et al., 2003).

Further complicating the daunting transport task of neuronal cells, MBOs transported by conventional kinesin need to be precisely delivered to spatially and functionally distinct subdomains of unique protein composition within axons and dendrites. For example, synaptic vesicles precursors undergoing transport along axons from CNS neurons need to be selectively delivered to hundreds or even thousands of presynaptic terminals *en passant*. Similarly, MBOs containing specific ion channels need to be inserted at the axonal plasma membrane within nodes of Ranvier. This asymmetric organization of materials within axons implies the existence of regulatory mechanisms for the localized delivery of MBOs (Brady, 1995; Morfini et al., 2001).

As discussed above, various lines of experimental evidence indicate that conventional kinesin primarily exists as a membrane-associated protein *in vivo*, suggesting that its association with MBOs is subject to regulatory mechanisms. In support, biochemical approaches illuminated multiple pathways promoting the detachment of conventional kinesin from membranes (Morfini et al., 2000; Tsai et al., 2000). Further, cumulative data indicates that phosphorylation represents a major mechanism for the regulation of conventional kinesin-based AT (Gibbs et al., 2015; Hollenbeck, 1993; Lee and Hollenbeck, 1995). Many findings supporting this concept were initially established using isolated squid axoplasm, a model that greatly facilitates the evaluation of axon-autonomous molecular events (Kang et al., 2016; Song et al., 2016). Consistent with the heterogeneity of axonal MBOs and the need for delivering those to specific destinations, multiple kinases were found to regulate both enzymatic (*i.e.* binding to microtubules and ATPase activity) and non-enzymatic (*i.e.* attachment to transported cargoes) properties of conventional kinesin. The effect of these regulatory kinases largely depends on the specific target subunit, as well as the site modified. For example, both glycogen synthase kinase 3 (GSK3) and casein kinase 2 (CK2) phosphorylate KLCs and promote detachment of conventional kinesin from MBOs (Pigino et al., 2009). On the other hand, both c-jun amino-terminal kinase 3 (JNK3) and p38α MAP kinase (Fig. 2A) phosphorylate KIF5 subunits at residues located in close proximity to microtubule-binding domains (Morfini et al., 2013; Morfini et al., 2009b). Accordingly, these phosphorylation events were found to compromise processive movement of KIF5s along axonal microtubules (Morfini et al., 2013; Morfini et al., 2009b). In addition, other kinases (*i.e.*, CDK5) and phosphatases (*i.e.*, PP1) indirectly regulate conventional kinesin by modulating GSK3 activation (Morfini et al., 2004).

Interestingly, and directly relevant to the biochemical diversity of conventional kinesin, some physiologically relevant phosphorylation sites are not conserved among KIF5 and KLC isoforms (Fig. 2A). Based on these observations, it is conceivable that specific conventional kinesin subunit variants are assembled in a way that facilitates kinase-mediated delivery of specific MBOs at selected subcellular domains (Fig. 2B). Such notion is supported by recent studies demonstrating a role of protein kinases on the delivery of MBOs containing presynaptic proteins at newly formed synapses of developing neurons (Easley-Neal et al., 2013). Further, removal of conventional kinesin from MBOs by hsc70, an abundant and ubiquitously expressed chaperone, could also be spatially restricted by localized activation of kinases targeting KLCs. In support, removal of conventional kinesin from purified MBOs was found to correlate with KLC2 phosphorylation (Morfini et al., 2002b; Morfini et al., 2001).

6. Alterations in conventional kinesin-based AT and neurodegenerative disease pathogenesis

A few familiar forms of neurodegenerative diseases have been linked to mutations in genes encoding conventional kinesin subunits. For example, loss-of-function mutations in KIF5A result in a subset of hereditary form of spastic paraplegia (HSP), SPG10-HSP (Reid et al., 2002). HSP is a disease characterized by progressive dysfunction and *dying back* degeneration of upper motor neurons (Solowska and Baas, 2015). The increased vulnerability of upper motor neurons observed in HSP appears consistent with a specialized role of KIF5A-containing conventional kinesin variants on these cells. However, specific MBOs whose transport is compromised in SPG10-HSP have not been identified, and whether KIF5A powers AT of the same MBOs in all neuronal cell types has not been addressed. The late onset characteristic of HSP indicates that reductions in KIF5A-related conventional kinesin-based AT

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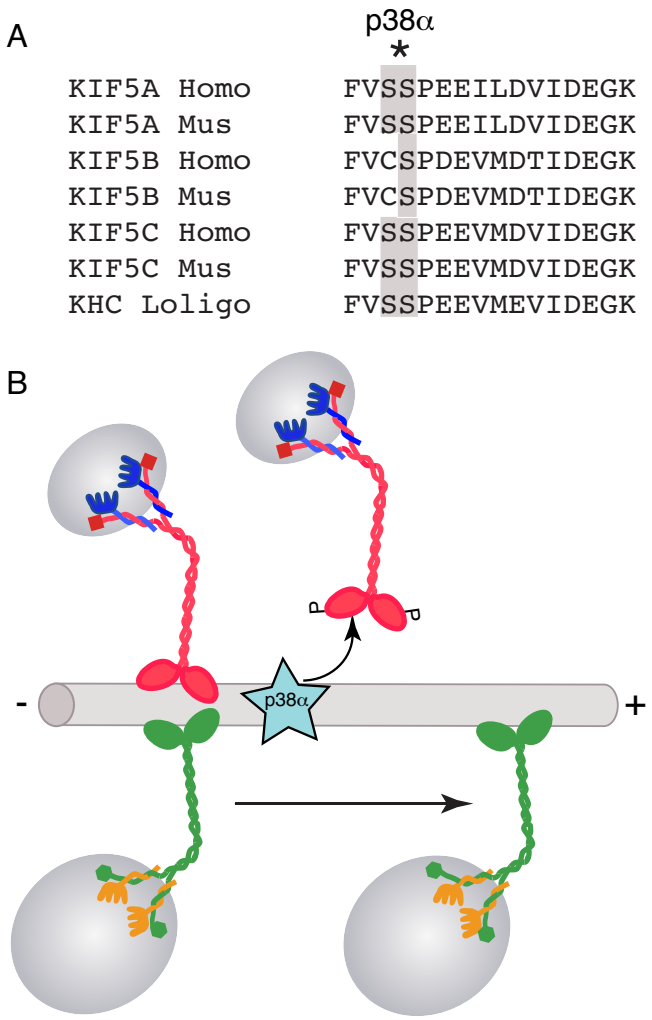

Fig. 2. Conventional kinesin subunit variants and phosphorylation-mediated delivery of MBO cargoes at discrete subcellular domains. (A) Serines 175/176 of KIF5C, which are conserved in squid kinesin-1 (*Loligo*), are directly phosphorylated by p38α. Consistent with the location of these residues within the head domain of KIF5s, phosphorylation of these residues dramatically impairs the translocation of KIF5C along axonal microtubules (Bosco et al., 2010; Morfini et al., 2013). Interestingly, serines 175/176 are conserved in KIF5A, but not KIF5B. (B) Schematic depicting a model where localized activation of kinases would promote delivery of MBOs transported by specific conventional kinesin subunit variants. In this case, localized p38 activation would allow the delivery of MBOs transported by conventional kinesin variants containing KIF5A and KIF5C, but not KIF5B subunits (Shi et al., 2010). Similarly, localized activation of the protein kinase GSK3 would promote the delivery of MBOs transported by KLC2-containing conventional kinesin variants. Such model would have important implications for multiple neurodegenerative diseases, which feature pathological activation of specific kinase pathways.

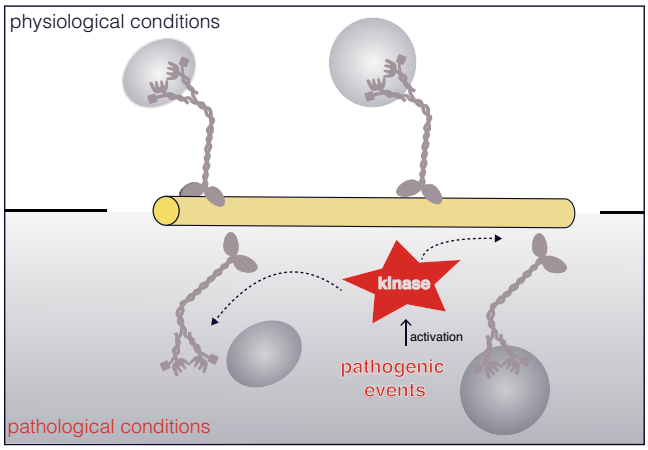

Fig. 3. Model of altered kinesin activity under pathological conditions. Pathogenic events (*e.g.* exposure to Aβ peptides) in the course of neurodegenerative diseases cause cellular stress responses affecting the balance of phosphatase/kinase activity. Early consequences of these alterations might be cargo release and/or inhibition of kinesin motor activity resulting in axonal stalling. Isoform-specific phosphorylation of conventional kinesin subunits may explain selective vulnerability of specific neuronal cell types to different disease conditions.

do not suffice to compromise the survival of upper motor neurons during development. Given that AT efficiency significantly declines with aging (McQuarrie et al., 1989), the negative impact of KIF5A mutations on AT would likely be higher in aged neurons. An illumination of MBO cargoes transported by KIF5A-containing conventional kinesin variants should provide novel insights on mechanisms underlying the differential vulnerability of specific neuronal cell types observed in SPG10-HSP.

Consistent with the dying back pattern of degeneration characteristic of most adult onset neurodegenerative diseases, AT deficits have been documented in multiple animal models of such diseases, including Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), Hereditary Spastic paraplegias, and polyglutamine-expansion diseases [reviewed in (Morfini et al., 2009a; Roy et al., 2005)]. However, these diseases are not associated with mutations in conventional kinesin or other KIFs, so other mechanisms are thought to underlie these deficits. Interestingly, abnormal activation of protein kinases and aberrant patterns of protein phosphorylation represent pathogenic hallmarks common to most neurodegenerative diseases (Gibbs et al., 2015; Wagey and Krieger, 1998), and many kinases deregulated in these diseases have been implicated in the regulation of conventional kinesin-based AT. In the context of HD, mutant huntingtin has been shown to inhibit AT through a mechanism involving JNK3 activation and phosphorylation of KIF5s (Morfini et al., 2009a). Pathogenic forms of tau and β-Amyloid, major AD protein hallmarks, were also found to inhibit conventional kinesin-based AT. In the case of Aβ, this toxic effect appears to involve several pathways including activation of the protein kinases CK2 (Moreno et al., 2009; Pigino et al., 2009) and GSK3 (Decker et al., 2010; Takach et al., 2015; Tang et al., 2012). Extending these findings, pathogenic forms of tau associated with AD and other human tauopathies were shown to inhibit AT by activating a PP1-GSK3 pathway (Kanaan et al., 2011; Lapointe et al., 2009; Morfini et al., 2007). Further, AT deficits induced by AD-related mutations in the APP-processing secretase presenilin-1 were associated with GSK3 activation (Lazarov et al., 2007; Morfini et al., 2002a; Pigino et al., 2003). Finally, both familial and sporadic ALS-related forms of the protein SOD1 were shown to inhibit AT by promoting activation of the protein kinase p38 (Bosco et al., 2010; Morfini et al., 2013). Based on these precedents, AT deficits resulting from aberrant phosphorylation of conventional kinesin could represent an important pathogenic event common to several unrelated neurodegenerative diseases (Morfini et al., 2009a) (Fig. 3). An illumination of pathologically-relevant protein kinases deregulated in each disease would facilitate the development of disease-specific therapeutic strategies aimed to prevent the loss of neuritic connectivity associated with alterations in conventional kinesin-based AT. Such strategies would also prevent additional pathogenic events associated with deregulated kinases.

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References

Allen, R.D., Metuzals, J., Tasaki, I., Brady, S.T., Gilbert, S.P., 1982. Fast axonal transport in squid giant axon. Science 218, 1127–1129.
Baas, P.W., Rao, A.N., Matamoros, A.J., Leo, L., 2016. Stability properties of neuronal microtubules. Cytoskeleton (Hoboken) (Ehead of print).
Black, M.M., 2016. Axonal transport: the orderly motion of axonal structures. Methods Cell Biol. 131, 1–19.
Bloom, G.S., Wagner, M.C., Pfister, K.K., Brady, S.T., 1988. Native structure and physical properties of bovine brain kinesin and identification of the ATP-binding subunit polypeptide. Biochemistry 27, 3409–3416.
Bosco, D.A., Morfini, G., Karabacak, N.M., Song, Y., Gros-Louis, F., Pasinelli, P., Goolsby, H., Fontaine, B.A., Lemay, N., McKenna-Yasek, D., Frosch, M.P., Agar, J.N., Julien, J.P., Brady, S.T., Brown Jr., R.H., 2010. Wild-type and mutant SOD1 share an aberrant conformation and a common pathogenic pathway in ALS. Nat. Neurosci. 13, 1396–1403.
Bowman, A.B., Kamal, A., Ritchings, B.W., Philp, A.V., McGrail, M., Gindhart, J.G., Goldstein, L.S., 2000. Kinesin-dependent axonal transport is mediated by the sunday driver (SYD) protein. Cell 103, 583–594.
Bradke, F., Dotti, C.G., 2000. Establishment of neuronal polarity: lessons from cultured hippocampal neurons. Curr. Opin. Neurobiol. 10, 574–581.
Brady, S., Morfini, G., 2010. A perspective on neuronal cell death signaling and neurodegeneration. Mol. Neurobiol. 42, 25–31.
Brady, S.T., 1985. A novel brain ATPase with properties expected for the fast axonal transport motor. Nature 317, 73–75.
Brady, S.T., 1995. A kinesin medley: biochemical and functional heterogeneity. Trends Cell Biol. 5, 159–164.
Brady, S.T., Lasek, R.J., Allen, R.D., 1983. Fast axonal transport in extruded axoplasm from squid giant axon. Cell Mot. 3 (Video Supplement).
Brady, S.T., Sperry, A.O., 1995. Biochemical and functional diversity of microtubule motors in the nervous system. Curr. Opin. Neurobiol. 5, 551–558.
Caceres, A., Ye, B., Dotti, C.G., 2012. Neuronal polarity: demarcation, growth and commitment. Curr. Opin. Cell Biol. 24, 547–553.
Cai, Q., Pan, P.Y., Sheng, Z.H., 2007. Syntabulin-kinesin-1 family member 5B-mediated axonal transport contributes to activity-dependent presynaptic assembly. J. Neurosci. 27, 7284–7296.
Colin, E., Zala, D., Liot, G., Rangone, H., Borrell-Pages, M., Li, X.J., Saudou, F., Humbert, S., 2008. Huntingtin phosphorylation acts as a molecular switch for anterograde/retrograde transport in neurons. EMBO J. 27, 2124–2134.
Cyr, D.M., Langer, T., Douglas, M.G., 1994. DNAJ-like proteins: molecular chaperones and specific regulators of HSP70. Trends Biochem. Sci. 19, 176–181.
Cyr, J.L., Pfister, K.K., Bloom, G.S., Slaughter, C.A., Brady, S.T., 1991. Molecular genetics of kinesin light chains: generation of isoforms by alternative splicing. Proc. Nat. Acad. Sci. U. S. A. 88, 10114–10118.
Dahlström, A., Pfister, K.K., Brady, S.T., 1991. The axonal transport motor kinesin is bound to anterogradely transported organelles: quantitative cytofluorimetric studies of fast axonal transport in the rat. Acta Physiol. Scand. 141, 469–476.
DeBoer, S.R., You, Y., Szodorai, A., Kaminska, A., Pigino, G., Nwabuisi, E., Wang, B., Estrada-Hernandez, T., Kins, S., Brady, S.T., Morfini, G., 2008. Conventional kinesin holoenzymes are composed of heavy and light chain homodimers. Biochemistry 47, 4535–4543.
Decker, H., Lo, K.Y., Unger, S.M., Ferreira, S.T., Silverman, M.A., 2010. Amyloid-beta peptide oligomers disrupt axonal transport through an NMDA receptor-dependent mechanism that is mediated by glycogen synthase kinase 3beta in primary cultured hippocampal neurons. J. Neurosci. 30, 9166–9171.
Dodding, M.P., Mitter, R., Humphries, A.C., Way, M., 2011. A kinesin-1 binding motif in vaccinia virus that is widespread throughout the human genome. EMBO J. 30, 4523–4538.
Easley-Neal, C., Buchanan, J., Fierro Jr., J., Washbourne, P., 2013. Late recruitment of synapsin to nascent synapses is regulated by Cdk5. Cell Rep. 3, 1199–1212.
Elluru, R., Bloom, G.S., Brady, S.T., 1995. Fast axonal transport of kinesin in the rat visual system: functionality of the kinesin heavy chain isoforms. Mol. Biol. Cell 6, 21–40.
Elluru, R.G., Bloom, G.S., Brady, S.T., 1990. Axonal transport of kinesin in the rat optic nerve/tract. J. Cell Biol. 111, 417a.
Ferreira, A., Niclas, J., Vale, R.D., Banker, G., Kosik, K.S., 1992. Suppression of kinesin expression in cultured hippocampal neurons using antisense oligonucleotides. J. Cell Biol. 117, 595–606.
Fu, M.M., Holzbaur, E.L., 2014. Integrated regulation of motor-driven organelle transport by scaffolding proteins. Trends Cell Biol. 24, 564–574.
Gennerich, A., Vale, R.D., 2009. Walking the walk: how kinesin and dynein coordinate their steps. Curr. Opin. Cell Biol. 21, 59–67.
Gibbs, K.L., Greensmith, L., Schiavo, G., 2015. Regulation of axonal transport by protein kinases. Trends Biochem. Sci. 40, 597–610.
Gindhart, J.G., Chen, J., Faulkner, M., Gandhi, R., Doerner, K., Wisniewski, T., Nandlestadt, A., 2003. The kinesin-associated protein UNC-76 is required for axonal transport in the Drosophila nervous system. Mol. Biol. Cell 14, 3356–3365.
Goldstein, J.G., Gindhart Jr., L.S., 1996. Tetratrico peptide repeats are present in the kinesin light chain. Trends Biochem. Sci. 21, 52–53.
Goldstein, L., Ashford, J.W., Busciglio, J., Crutcher, K., Gouras, G., Kinoshita, J., Mandelkow, E., Sudol, M., 2003. Live discussion. From here to there: AbetaPP as an axonal transport receptor—how could this explain neurodegeneration in AD. 15 July 2002. J. Alzheimers Dis. 5, 483–489.
Gyoeva, F.K., Bybikova, E.M., Minin, A.A., 2000. An isoform of kinesin light chain specific for the Golgi complex. J. Cell Sci. 113 (Pt. 11), 2047–2054.
Hackney, D.D., 2007. Jump-starting kinesin. J. Cell Biol. 176, 7–9.
Higgins, D., Burack, M., Lein, P., Banker, G., 1997. Mechanisms of neuronal polarity. Curr. Opin. Neurobiol. 7, 599–604.
Hirokawa, N., 2006. mRNA transport in dendrites: RNA granules, motors, and tracks. J. Neurosci. 26, 7139–7142.
Hirokawa, N., 2011. From electron microscopy to molecular cell biology, molecular genetics and structural biology: intracellular transport and kinesin superfamily proteins, KIFs: genes, structure, dynamics and functions. J. Electron Microsc. (Tokyo) 60 (Suppl. 1), S63–92.
Hirokawa, N., Niwa, S., Tanaka, Y., 2010. Molecular motors in neurons: transport mechanisms and roles in brain function, development, and disease. Neuron 68, 610–638.
Hirokawa, N., Noda, Y., 2008. Intracellular transport and kinesin superfamily proteins, KIFs: structure, function, and dynamics. Physiol. Rev. 88, 1089–1118.
Hirokawa, N., Noda, Y., Tanaka, Y., Niwa, S., 2009. Kinesin superfamily motor proteins and intracellular transport. Nat. Rev. Mol. Cell Biol. 10, 682–696.
Hirokawa, N., Pfister, K.K., Yorifuji, H., Wagner, M.C., Brady, S.T., Bloom, G.S., 1989. Submolecular domains of bovine brain kinesin identified by electron microscopy and monoclonal antibody decoration. Cell 56, 867–878.
Hirokawa, N., Sato-Yoshitake, R., Kobayashi, N., Pfister, K.K., Bloom, G.S., Brady, S.T., 1991. Kinesin associates with anterogradely transported membranous organelles in vivo. J. Cell Biol. 114, 295–302.
Hollenbeck, P.J., 1993. Phosphorylation of neuronal kinesin heavy and light chains *in vivo*. J. Neurochem. 60, 2265–2275.
Hoogenraad, C.C., Milstein, A.D., Ethell, I.M., Henkemeyer, M., Sheng, M., 2005. GRIP1 controls dendrite morphogenesis by regulating EphB receptor trafficking. Nat. Neurosci. 8, 906–915.
Hurd, D.D., Saxton, W.M., 1996. Kinesin mutations cause motor neuron disease phenotypes by disrupting fast axonal transport in Drosophila. Genetics 144, 1075–1085.
Jeppesen, G.M., Hoerber, J.K., 2012. The mechanical properties of kinesin-1: a holistic approach. Biochem. Soc. Trans. 40, 438–443.
Kamal, A., Stokin, G.B., Yang, Z., Xia, C.H., Goldstein, L.S., 2000. Axonal transport of amyloid precursor protein is mediated by direct binding to the kinesin light chain subunit of kinesin-I. Neuron 28, 449–459.
Kanaan, N.M., Morfini, G.A., LaPointe, N.E., Pigino, G.F., Patterson, K.R., Song, Y., Andreadis, A., Fu, Y., Brady, S.T., Binder, L.I., 2011. Pathogenic forms of tau inhibit kinesin-dependent axonal transport through a mechanism involving activation of axonal phosphotransferases. J. Neurosci. 31, 9858–9868.
Kanai, Y., Okada, Y., Tanaka, Y., Harada, A., Terada, S., Hirokawa, N., 2000. KIF5C, a novel neuronal kinesin enriched in motor neurons. J. Neurosci. 20, 6374–6384.
Kang, M., Baker, L., Song, Y., Brady, S.T., Morfini, G., 2016. Biochemical analysis of axon-specific phosphorylation events using isolated squid axoplasms. Methods Cell Biol. 131, 199–216.
Khodjakov, A., Lizunova, E.M., Minin, A.A., Koonce, M.P., Gyoeva, F.K., 1998. A specific light chain of kinesin associates with mitochondria in cultured cells. Mol. Biol. Cell 9, 333–343.
Kneussel, M., Wagner, W., 2013. Myosin motors at neuronal synapses: drivers of membrane transport and actin dynamics. Nat. Rev. Neurosci. 14, 233–247.
Kosik, K.S., Orecchio, L.D., Schnapp, B., Inouye, H., Neve, R.L., 1990. The primary structure and analysis of the squid kinesin heavy chain. J. Biol. Chem. 265, 3278–3283.
Koushika, S.P., 2008. JIPing along the axon: the complex roles of JIPs in axonal transport. Bioessays 30, 10–14.
Lapointe, N.E., Morfini, G., Pigino, G., Gaisina, I.N., Kozikowski, A.P., Binder, L.I., Brady, S.T., 2009. The amino terminus of tau inhibits kinesin-dependent axonal transport: implications for filament toxicity. J. Neurosci. Res. 97, 440–451.
Lawrence, C.J., Dawe, R.K., Christie, K.R., Cleveland, D.W., Dawson, S.C., Endow, S.A., Goldstein, L.S., Goodson, H.V., Hirokawa, N., Howard, J., Malmberg, R.L., McIntosh, J.R., Miki, H., Mitchison, T.J., Okada, Y., Reddy, A.S., Saxton, W.M., Schliwa, M., Scholey, J.M., Vale, R.D., Walczak, C.E., Wordeman, L., 2004. A standardized kinesin nomenclature. J. Cell Biol. 167, 19–22.
Lazarov, O., Morfini, G.A., Lee, E.B., Farah, M.H., Szodorai, A., DeBoer, S.R., Koliatsos, V.E., Kins, S., Lee, V.M., Wong, P.C., Price, D.L., Brady, S.T., Sisodia, S.S., 2005. Axonal transport, amyloid precursor protein, kinesin-1, and the processing apparatus: revisited. J. Neurosci. 25, 2386–2395.
Lazarov, O., Morfini, G.A., Pigino, G., Gadadhar, A., Chen, X., Robinson, J., Ho, H., Brady, S.T., Sisodia, S.S., 2007. Impairments in fast axonal transport and motor neuron deficits in transgenic mice expressing familial Alzheimer's disease-linked mutant presenilin 1. J. Neurosci. 27, 7011–7020.
Lee, K.-D., Hollenbeck, P.J., 1995. Phosphorylation of kinesin *in vivo* correlates with organelle association and neurite outgrowth. J. Biol. Chem. 270, 5600–5605.
Leopold, P.L., McDowall, A.W., Pfister, K.K., Bloom, G.S., Brady, S.T., 1992. Association of kinesin with characterized membrane-bounded organelles. Cell Motil. Cytoskeleton 23, 19–33.
Lin, M.Y., Sheng, Z.H., 2015. Regulation of mitochondrial transport in neurons. Exp. Cell Res. 334, 35–44.
Loss, O., Stephenson, F.A., 2015. Localization of the kinesin adaptor proteins trafficking kinesin proteins 1 and 2 in primary cultures of hippocampal pyramidal and cortical neurons. J. Neurosci. Res. 93, 1056–1066.

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Maday, S., Twelvetrees, A.E., Moughamian, A.J., Holzbaur, E.L., 2014. Axonal transport: cargo-specific mechanisms of motility and regulation. Neuron 84, 292–309.
Maeder, C.I., Shen, K., Hoogenraad, C.C., 2014. Axon and dendritic trafficking. Curr. Opin. Neurobiol. 27, 165–170.
Matsuda, S., Matsuda, Y., D'Adamio, L., 2003. Amyloid beta protein precursor (AbetaPP) but not AbetaPP-like protein 2, is bridged to the kinesin light chain by the scaffold protein JNK-interacting protein 1. J. Biol. Chem. 278, 38601–38606.
McGuire, J.R., Rong, J., Li, S.H., Li, X.J., 2006. Interaction of huntingtin-associated protein-1 with kinesin light chain: implications in intracellular trafficking in neurons. J. Biol. Chem. 281, 3552–3559.
McQuarrie, I.G., Brady, S.T., Lasek, R.J., 1989. Retardation in axonal transport of cytoskeletal elements during maturation and aging. Neurobiol. Aging 10, 359–365.
Miki, H., Setou, M., Hirokawa, N., Group, R.G., Members, G.S.L., 2003. Kinesin superfamily proteins (KIFs) in the mouse transcriptome. Genome Res. 13, 1455–1465.
Moreno, H., Yu, E., Pigino, G., Hernandez, A.I., Kim, N., Moreira, J.E., Sugimori, M., Llinas, R.R., 2009. Synaptic transmission block by presynaptic injection of oligomeric amyloid beta. Proc. Natl. Acad. Sci. U. S. A. 106, 5901–5906.
Morfini, G., Pigino, G., Beffert, U., Busciglio, J., Brady, S.T., 2002a. Fast axonal transport misregulation and Alzheimer's disease. Neuromol. Med. 2, 89–99.
Morfini, G., Pigino, G., Mizuno, N., Kikkawa, M., Brady, S.T., 2007. Tau binding to microtubules does not directly affect microtubule-based vesicle motility. J. Neurosci. Res. 85, 2620–2630.
Morfini, G., Burns, M.R., Stenoien, D., Brady, S.T., 2012. Axonal transport. In: Brady, S.T., Siegel, G., Albers, R.W., Price, D. (Eds.), Basic Neurochemistry: Principles of Molecular, Cellular and Medical Neurobiology. , 8th Ed. Elsevier, Boston, pp. 146–164.
Morfini, G., Szebenyi, G., Brown, H., Pant, H.C., Pigino, G., DeBoer, S., Beffert, U., Brady, S.T., 2004. A novel CDK5-dependent pathway for regulating GSK3 activity and kinesin-driven motility in neurons. EMBO J. 23, 2235–2245.
Morfini, G., Szebenyi, G., Elluru, R., Ratner, N., Brady, S.T., 2002b. Glycogen synthase kinase 3 phosphorylates kinesin light chains and negatively regulates kinesin-based motility. EMBO J. 21, 281–293.
Morfini, G., Szebenyi, G., Richards, B., Brady, S.T., 2001. Regulation of kinesin: implications for neuronal development. Dev. Neurosci. 23, 364–376.
Morfini, G., Tsai, M., Szebenyi, G., Brady, S.T., 2000. Approaches to study interactions between kinesin motors and membranes. In: Vernos, I. (Ed.), Kinesin Protocols. Humana Press, Totowa, NJ, pp. 147–162.
Morfini, G.A., Bosco, D.A., Brown, H., Gatto, R., Kaminska, A., Song, Y., Molla, L., Baker, L., Marangoni, M.N., Berth, S., Tavassoli, E., Bagnato, C., Tiwari, A., Hayward, L.J., Pigino, G.F., Watterson, D.M., Huang, C.F., Banker, G., Brady, R.H., Brown Jr., S.T., 2013. Inhibition of fast axonal transport by pathogenic SOD1 involves activation of p38 MAP kinase. PLoS One 8, e65235.
Morfini, G.A., Burns, M., Binder, L.I., Kanaan, N.M., LaPointe, N., Bosco, D.A., Brown, R.H., Brown Jr., H., Tiwari, A., Hayward, L., Edgar, J., Nave, K.A., Garberrn, J., Atagi, Y., Song, Y., Pigino, G., Brady, S.T., 2009a. Axonal transport defects in neurodegenerative diseases. J. Neurosci. 29, 12776–12786.
Morfini, G.A., You, Y.M., Pollema, S.L., Kaminska, A., Liu, K., Yoshioka, K., Bjorkblom, B., Coffey, E.T., Bagnato, C., Han, D., Huang, C.F., Banker, G., Pigino, G., Brady, S.T., 2009b. Pathogenic huntingtin inhibits fast axonal transport by activating JNK3 and phosphorylating kinesin. Nat. Neurosci. 12, 864–871.
Nakajima, K., Yin, X., Takei, Y., Seog, D.H., Homma, N., Hirokawa, N., 2012. Molecular motor KIF5A is essential for GABA(A) receptor transport, and KIF5A deletion causes epilepsy. Neuron 76, 945–961.
Niwa, S., Tanaka, Y., Hirokawa, N., 2008. KIF1Bbeta- and KIF1A-mediated axonal transport of presynaptic regulator Rab3 occurs in a GTP-dependent manner through DENN/MADD. Nat. Cell Biol. 10, 1269–1279.
Pigino, G., Morfini, G., Atagi, Y., Deshpande, A., Yu, C., Jungbauer, L., LaDu, M., Busciglio, J., Brady, S., 2009. Disruption of fast axonal transport is a pathogenic mechanism for intraneuronal amyloid beta. Proc. Natl. Acad. Sci. U. S. A. 106, 5907–5912.
Pigino, G., Morfini, G., Mattson, M.P., Brady, S.T., Busciglio, J., 2003. Alzheimer's presenilin 1 mutations impair kinesin-based axonal transport. J. Neurosci. 23, 4499–4508.
Rahman, A., Friedman, D.S., Goldstein, L.S., 1998. Two kinesin light chain genes in mice. Identification and characterization of the encoded proteins. J. Biol. Chem. 273, 15395–15403.
Randall, T.S., Moores, C., Stephenson, F.A., 2013. Delineation of the TRAK binding regions of the kinesin-1 motor proteins. FEBS Lett. 587, 3763–3769.
Rathgeber, L., Gromova, K.V., Schaefer, I., Breiden, P., Lohr, C., Kneussel, M., 2015. GSK3 and KIF5 regulate activity-dependent sorting of gephyrin between axons and dendrites. Eur. J. Cell Biol. 94, 173–178.
Reid, E., Kloos, M., Ashley-Koch, A., Hughes, L., Bevan, S., Svenson, I.K., Graham, F.L., Gaskell, P.C., Dearlove, A., Pericak-Vance, M.A., Rubinsztein, D.C., Marchuk, D.A., 2002. A kinesin heavy chain (KIF5A) mutation in hereditary spastic paraplegia (SPG10). Am. J. Hum. Genet. 71, 1189–1194.
Roy, S., Zhang, B., Lee, V.M., Trojanowski, J.Q., 2005. Axonal transport defects: a common theme in neurodegenerative diseases. Acta Neuropathol. (Berl.) 109, 5–13.
Saxton, W.M., Hollenbeck, P.J., 2012. The axonal transport of mitochondria. J. Cell Sci. 125, 2095–2104.
Setou, M., Seog, D.H., Tanaka, Y., Kanai, Y., Takei, Y., Kawagishi, M., Hirokawa, N., 2002. Glutamate-receptor-interacting protein GRIP1 directly steers kinesin to dendrites. Nature 417, 83–87.
Shi, P., Strom, A.L., Gal, J., Zhu, H., 2010. Effects of ALS-related SOD1 mutants on dynein- and KIF5-mediated retrograde and anterograde axonal transport. Biochim. Biophys. Acta 1802, 707–716.
Siddiqui, S.S., 2002. Metazoan motor models: kinesin superfamily in C. elegans. Traffic 3, 20–28.
Solowska, J.M., Baas, P.W., 2015. Hereditary spastic paraplegia SPG4: what is known and not known about the disease. Brain 138, 2471–2484.
Song, Y., Kang, M., Morfini, G., Brady, S.T., 2016. Fast axonal transport in isolated axoplasm from the squid giant axon. Methods Cell Biol. 131, 331–348.
Su, Q., Cai, Q., Gerwin, C., Smith, C.L., Sheng, Z.H., 2004. Syntabulin is a microtubule-associated protein implicated in syntaxin transport in neurons. Nat. Cell Biol. 6, 941–953.
Szodorai, A., Kuan, Y.H., Hunzelmann, S., Engel, U., Sakane, A., Sasaki, T., Takai, Y., Kirsch, J., Muller, U., Beyreuther, K., Brady, S., Morfini, G., Kins, S., 2009. APP anterograde transport requires Rab3A GTPase activity for assembly of the transport vesicle. J. Neurosci. 29, 14534–14544.
Takach, O., Gill, T.B., Silverman, M.A., 2015. Modulation of insulin signaling rescues BDNF transport defects independent of tau in amyloid-beta oligomer-treated hippocampal neurons. Neurobiol. Aging 36, 1378–1382.
Takamori, S., Holt, M., Stenius, K., Lemke, E.A., Gronborg, M., Riedel, D., Urlaub, H., Schenck, S., Brugger, B., Ringler, P., Muller, S.A., Rammner, B., Grater, F., Hub, J.S., De Groot, B.L., Mieskes, G., Moriyama, Y., Klingauf, J., Grubmuller, H., Heuser, J., Wieland, F., Jahn, R., 2006. Molecular anatomy of a trafficking organelle. Cell 127, 831–846.
Tang, Y., Scott, D.A., Das, U., Edland, S.D., Radomski, K., Koo, E.H., Roy, S., 2012. Early and selective impairments in axonal transport kinetics of synaptic cargoes induced by soluble amyloid beta-protein oligomers. Traffic 13, 681–693.
Tsai, M.-Y., Morfini, G., Szebenyi, G., Brady, S.T., 2000. Modulation of kinesin-vesicle interactions by hsc70: implications for regulation of fast axonal transport. Mol. Biol. Cell 11, 2161–2173.
Vale, R.D., Reese, T.S., Sheetz, M.P., 1985. Identification of a novel force-generating protein kinesin, involved in microtubule-based motility. Cell 42, 39–50.
van Spronsen, M., Mikhaylova, M., Lipka, J., Schlager, M.A., van den Heuvel, D.J., Kuijpers, M., Wulf, P.S., Keijzer, N., Demmers, J., Kapitein, L.C., Jaarsma, D., Gerritsen, H.C., Akhmanova, A., Hoogenraad, C.C., 2013. TRAK/milton motor-adaptor proteins steer mitochondrial trafficking to axons and dendrites. Neuron 77, 485–502.
Vites, O., Rhee, J.S., Schwarz, M., Rosenmund, C., Jahn, R., 2004. Reinvestigation of the role of snapin in neurotransmitter release. J. Biol. Chem. 279, 26251–26256.
Wagey, R.T., Krieger, C., 1998. Abnormalities of protein kinases in neurodegenerative diseases. Prog. Drug Res. 51, 133–183.
Wagner, M.C., Pfister, K.K., Bloom, G.S., Brady, S.T., 1989. Copurification of kinesin polypeptides with microtubule-stimulated Mg-ATPase activity and kinetic analysis of enzymatic processes. Cell Motil. Cytoskeleton 12, 195–215.
Ward, B.M., Moss, B., 2004. Vaccinia virus A36R membrane protein provides a direct link between intracellular enveloped virions and the microtubule motor kinesin. J. Virol. 78, 2486–2493.
Wisniewski, T.P., Tanzi, C.L., Gindhart, J.G., 2003. The Drosophila kinesin-I associated protein YETI binds both kinesin subunits. Biol. Cell 95, 595–602.
Xia, C.H., Roberts, E.A., Her, L.S., Liu, X., Williams, D.S., Cleveland, D.W., Goldstein, L.S., 2003. Abnormal neurofilament transport caused by targeted disruption of neuronal kinesin heavy chain KIF5A. J. Cell Biol. 161, 55–66.

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