

# One axon, many kinesins: What's the logic?

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## Summary

A large number of membrane-bounded organelles, protein complexes, and mRNAs are transported along microtubules to different locations within the neuronal axon. Axonal transport in the anterograde direction is carried out by members of a superfamily of specialized motor proteins, the kinesins. All kinesins contain a conserved motor domain that hydrolyses ATP to generate movement along microtubules. Regions outside the motor domain are responsible for cargo binding and regulation of motor activity. Present in a soluble, inactive form in the cytoplasm, kinesins are activated upon cargo binding. Selective targeting of different types of kinesin motors to specific cargoes is directed by amino acid sequences situated in their variable tails. Cargo proteins with specific function at their destination, bind directly to specific kinesins for transport. Whereas most kinesins move to microtubule plus-ends, a small number of them move to microtubule minus-ends, and may participate in retrograde axonal transport. Axonal transport by kinesins has a logic: Fully assembled, multisubunit, functional complexes (e.g., ion channel complexes, signaling complexes, RNA-protein complexes) are transported to their destination by kinesin motors that interact transiently (i.e., during transport only) with one of the complexes' subunits.

## Introduction

Neurons are highly polarized cells consisting of three structurally and functionally distinct compartments: the cell body, comprising the perikaryon, the dendrites with their massive arborization, and the axon. Vital cellular functions, such as protein metabolism (synthesis and degradation) and organelle biogenesis and turnover, occur in the cell body, whereas the axon transmits signals to connecting neurons, and the dendrites receive information from the presynaptic axons. This functional asymmetry is accompanied by distinct biochemical compositions of these compartments that are generated and maintained by a continuous and selective transport of material from the site of synthesis in the cell body to the appropriate destinations within the axon or the dendrites. In most neurons, axons and dendrites extend over enormous distances away from the cell body; in humans for example, some axons may exceed 1 m in length. In addition, protein and membrane renewal at the dendritic and axonal terminals of some specialized neurons, such as the photoreceptor cells in the retina, require that thousands of molecules reach the terminals every second (Besharse & Horst, 1990). These requirements impose the existence of a highly efficient machinery for a robust long-range transport of material.

A large proportion of protein and organelle transport occurs along the microtubules, which are polarized cytoskeletal structures (made of  $\alpha$  and  $\beta$  tubulin)

with a defined orientation of their plus- (i.e., fast growing) and minus- (i.e., more stable) ends within the cell. Axonal microtubules are uniformly oriented with their plus-ends pointed toward the synaptic terminal (Heidemann *et al.*, 1981), whereas dendrites contain microtubules of mixed orientation (Baas *et al.*, 1988). The many proteins and organelles that need to be conveyed to different destinations within the cell use molecular motors—kinesins and cytoplasmic dynein—that recognize the intrinsic polarity of microtubules to travel either to their plus- or minus-ends. From a mechanistic point of view, this constitutes the basis of selective targeting within neuronal cells.

This review focuses on axonal transport by the action of kinesin motors. After a brief presentation of the components that are transported in the axon, and their destinations within the axon, the review will make an inventory of the kinesin motors that have been implicated in axonal transport. Finally, the regulation of the interaction of kinesins with their cargoes will be addressed. In the instances where important results on this topic have been obtained in systems other than the axon, they will be briefly mentioned. Additional information on the structure and function of kinesins in neuronal and nonneuronal cells can be found in several recent excellent reviews (Goldstein & Philp, 1999, Goldstein & Yang, 2000, Martin & Saxton, 1999, Manning & Snyder, 2000, Klopfenstein *et al.*, 2000).

### Cargoes, destinations, roads, and carriers

Except for the synaptic terminal, axons have a simple, linear organization and a relatively uniform composition. The axonal shaft is filled with elements of the cytoskeleton—neurofilaments, microtubules, and actin filaments—running parallel to the longitudinal axis of the axon, which support a robust traffic activity. Neurofilaments regulate the caliber of the axon (Cleveland *et al.*, 1991), while microtubules and actin filaments provide the actual tracks on which a large variety of cargoes move bidirectionally. The cargoes being transported in an axon are membrane-bounded organelles, proteins, protein complexes and polymers, and mRNAs. Because axons, to a large extent, lack protein synthetic machinery and are not engaged in the *de novo* assembly of membrane compartments (Lasek & Brady, 1982, Cyr & Brady, 1992), most vesicles, protein complexes, and RNA-protein complexes in axons are fully assembled and in transit, moving primarily along microtubules between the cell body and the nerve terminals. Membrane compartments carrying synaptic vesicle precursors and components of the axonal membrane are derived from the Golgi and move in the anterograde direction, while endocytic compartments carrying trophic factors and recycling membrane proteins move in the retrograde direction (Dahlstrom *et al.*, 1992, DiStefano *et al.*, 1992, Tsukita & Ishikawa, 1980). Because axonal microtubules are oriented with their plus-ends pointed away from the cell body, anterograde and retrograde cargoes move toward microtubule plus- and minus-ends, respectively. This establishes an axonal road map in which cargoes are transported anterogradely *via* plus-end motors and retrogradely *via* minus-end motors. Transport towards microtubule minus-ends is driven primarily by cytoplasmic dynein (Paschal & Vallee, 1987, Schnapp & Reese, 1989, Schroer *et al.*, 1989), and to a lesser extent by the carboxy-terminal type kinesins (Hanlon *et al.*, 1997, Saito *et al.*, 1997). Plus-end directed transport along microtubules is driven by conventional kinesin (Vale *et al.*, 1985) (referred to as kinesin I) and numerous kinesin-related proteins (referred to, in this review, as kinesins) (Stewart *et al.*, 1991, Aizawa *et al.*, 1992). Unlike cytoplasmic dynein, which may associate with many types of cargo (reviewed in Karki & Holzbaur, 1999), the different kinesin-related motors are proposed to bind selectively to specific types of cargo (Coy & Howard, 1994, Hirokawa, 1996). This selective targeting appears to be directed by amino acid sequences that lie outside of the conserved ~350 amino acid motor domain that defines the kinesin superfamily (Stewart *et al.*, 1991, Aizawa *et al.*, 1992).

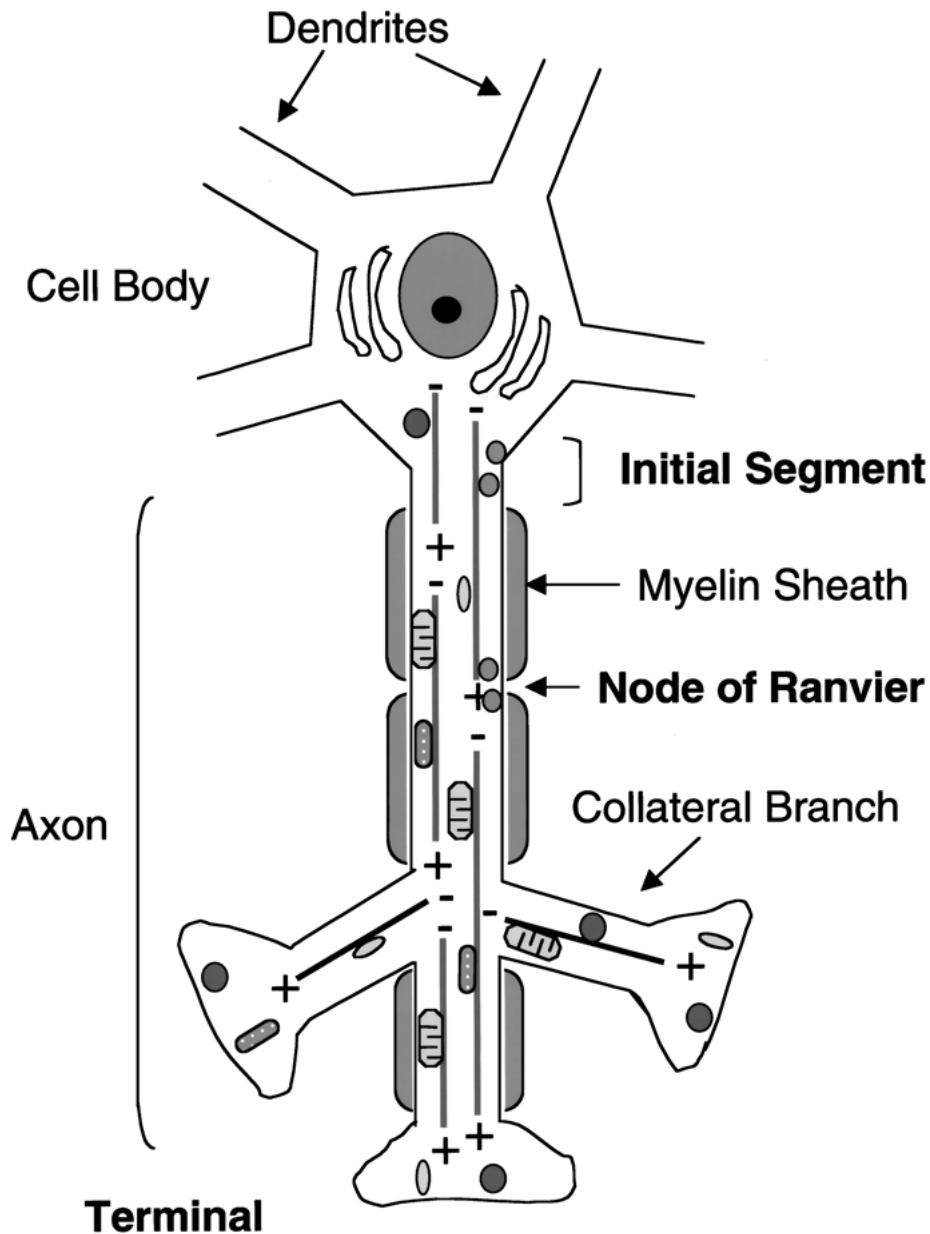
Kinesins are responsible for the transport of numerous cargoes that travel anterogradely along microtubules. Differences in their motor domains are in part responsible for the different rates at which different cargoes travel along the axon (Pierce *et al.*, 1999).

The transport of membranous organelles occurs at a rate of 50–400 mm/day and is known as fast axonal transport. Cytoskeletal proteins, polymers or small subunits, as well as other soluble protein complexes (e.g., enzymes) move at a rate of 0.2–8.0 mm/day in a process known as slow axonal transport (Lasek *et al.*, 1984, Nixon, 1992). mRNA-protein complexes appear to move at the rate of both fast and slow axonal transport (Kohrmann *et al.*, 1999, Mohr, 1999).

All anterogradely-transported cargoes follow the same route in an axon, yet they have different destinations (Fig. 1). An important anterograde destination is the synaptic terminal; precursors of synaptic vesicles and vesicles carrying proteins of the synaptic plasma membrane, as well as the machinery required for the retrograde transport, are main cargoes for this destination. The initial segment of a myelinated axon, with its specialized cytoskeleton and plasma membrane composition, is another transport destination for a specific set of proteins. A third destination is the axolemma at the nodes of Ranvier that contains clusters of ankyrin<sub>C</sub>-bound voltage-gated sodium channels and a distinctive set of adhesion proteins involved in the formation of the axo-glial junction (Bennett & Lambert, 1999). Other cargoes, such as proteins of the axonal plasma membrane or the mitochondria, are needed throughout the axon. For example, mitochondria are transported to various places along the axon, where they remain relatively stationary or make short, bidirectional excursions (Morris & Hollenbeck, 1993). During development, when axons are extended, the spectrum of the transported cargoes is different from that in mature neurons, and a special set of developmentally regulated kinesins may be required (Takemura *et al.*, 1996).

### An inventory of axonal kinesins

The most abundant plus-end motor in both vertebrate and nonvertebrate neurons is kinesin I (Brady, 1985, Vale *et al.*, 1985, Scholey *et al.*, 1985). The kinesin I holoenzyme (Fig. 2) is assembled from two identical polypeptides, the heavy chains (KHCs), each containing a globular motor domain, a central dimerization region (stalk), and a globular carboxy-terminal domain (Yang *et al.*, 1989) to which two identical accessory polypeptides, the light chains (KLCs), are attached (Hirokawa *et al.*, 1989). The motor domain contains the ATP and microtubule binding sites, and is responsible for ATP hydrolysis and force generation along microtubules (Yang *et al.*, 1990). The light chains appear to be involved in cargo binding and regulation of microtubule binding (see below). Many of the other known neuronal kinesins are multisubunit complexes formed of two motor polypeptides—identical, as in conventional kinesin, or distinct but related, as in kinesin II (see below). Occasionally, nonmotor accessory subunits,

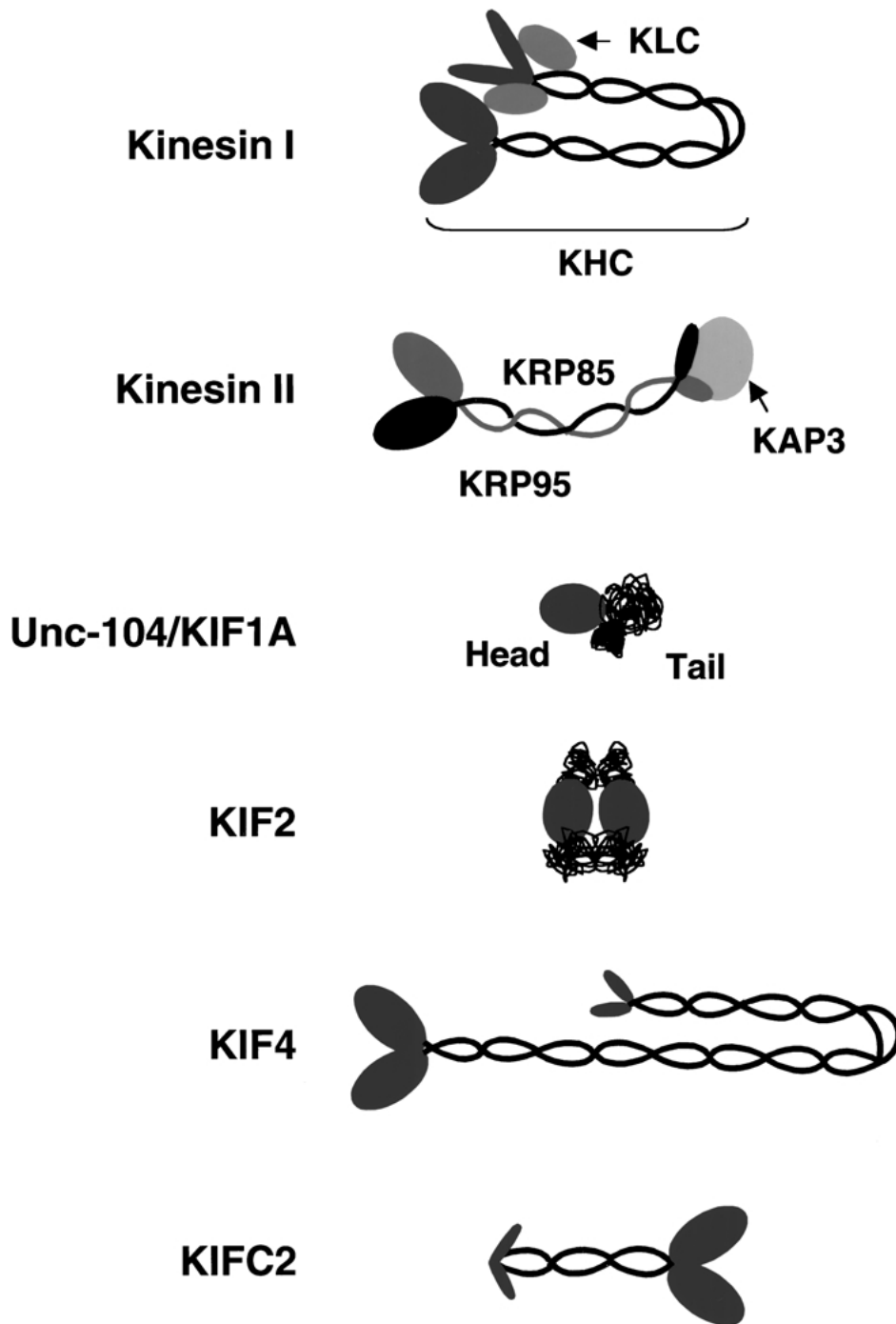


**Fig. 1.** Diagram showing the organization of axonal transport, and cargo destinations in a motor neuron. The myelin sheath on the collateral branches is not shown. Microtubule polarity is indicated. Cargo destinations are shown in bold.

topologically corresponding to the light chains in kinesin I, may associate with the motor polypeptides (Wedaman *et al.*, 1996). A region adjacent to the motor domain of kinesins, called neck, is essential for directionality of kinesin movement (Endow, 1999). Interestingly, the position of the globular motor domain in the motor polypeptide appears to be indicative of the direction of movement along microtubules (Endow, 1999). In most kinesin families, the motor domain is situated at the amino terminus of the molecule, and these move plus end-directed. Other kinesins, those which move minus end-directed, contain the motor domain at the carboxy terminus of the molecule (Fig. 2). A few kinesins have a central motor domain, and appear to move plus end-directed or not at all.

In *Drosophila* and *C. elegans*, the two model systems with sequenced genomes, there are 24 and 22 genes, respectively, encoding proteins with putative kinesin motor domains (Rubin *et al.*, 2000, Goldstein & Gunawardena, 2000). In mammals, about 50 kinesins (grouped in several families) have been discovered so far, many of them being expressed in the brain. Surprisingly, the human genome appears to contain only slightly more kinesin genes than those already known (Pollard, 2001). To date, about nine kinesin families have been characterized in mammalian neurons (Table 1), and many of these kinesins are also present in axons.

There is evidence that several kinesins play active roles in anterograde axonal transport, and that these



**Fig. 2.** Subunit organization of several kinesin motors involved in axonal transport. Drawings are based on electron microscopy studies (Kim & Endow, 2000).

may be involved in the transport of both membrane-bound and proteinaceous cargoes. These include members of the kinesin I, kinesin II, Unc104/KIF1A, KIF2, and KIF4 families (see below). Other kinesins found in axons are KIF21A (Marszalek *et al.*, 1999), and the carboxy-terminal motor domain kinesins, KIFC2 (Hanlon *et al.*, 1997, Saito *et al.*, 1997) and KIFC3 (Hoang *et al.*, 1999, Yang *et al.*, 1997, Yang *et al.*, 2001), the latter two probably functioning in retrograde axonal

transport. Several neuronal kinesin motors (e.g., KIF21B, KIFC2, KIF17, CHO/MKLP1) are localized primarily to cell bodies or dendrites and may thus have cell body- and dendrite-specific functions (Niclas *et al.*, 1994, Sharp *et al.*, 1997, Marszalek *et al.*, 1999, Saito *et al.*, 1997, Setou *et al.*, 2000). Interestingly, no kinesin has yet been found to be localized exclusively to axons, although KIF4 and KIF1A were reported to be enriched in axons (Okada *et al.*, 1995b, Peretti *et al.*, 2000). This

**Table 1.** Neuronal kinesins and their axonal cargoes.

<i>Kinesin family</i>	<i>Holoenzyme structure of various members</i>	<i>Presumed axonal cargo</i>	<i>Interacting partner on presumed axonal cargo</i>	<i>Observations</i>
Kinesin I/KIF5	(KHC) <sub>2</sub> /(KLC) <sub>2</sub>	Vesicles Mitochondria, lysosomes Tubulin oligomers, neurofilaments	Sunday driver, APP, JIPs  Tubulin, neurofilament proteins	May participate in both fast and slow axonal transport
Kinesin II/KIF3	KIF3A/KIF3B/KAP3  KIF3A/KIF3C/KAP3	Vesicles Choline acetyltransferase Vesicles	$\alpha$ Fodrin	KIF3A is localized at ribbon synapses in the retina KIF3C may also form homodimers
UNC104/KIF1A	KIF1A  KIF1B KIF1C	Synaptic vesicle precursors Mitochondria Vesicles (?)	Membrane lipids (?)  14-3-3 protein	The KIF1A monomer may be processive Multiple splice variants Low expression level in brain
KIF13	KIF13A	M6PR-containing vesicles	AP-1 adaptor complex	Transports vesicles from the TGN to the plasma membrane
	GAKIN (KIF13B?)	Vesicles (?)	hDlg	Interacts also with PSD95
KIF2	(KIF2) <sub>2</sub>	Vesicles	$\beta$ subunit of an IGF-1 receptor variant	May also induce microtubule depolymerization
KIF4	(KIF4) <sub>2</sub>	Vesicles	Adhesion molecule L1	May also have role in mitosis
KIF17	KIF17			Dendritic motor for NMDA receptor complex; interacts with mLin10
KIF21	KIF21A  KIF21B	Large protein complexes		Tail contains WD-40 repeats Localized primarily to dendrites
MKLP1	(MKLP1/CHO1) <sub>2</sub>			Involved in dendrite formation
Carboxy-terminal motor type	(KIFC2) <sub>2</sub>  (KIFC3) <sub>2</sub>	Retrograde vesicles		Present at low levels in axons Localized at ribbon synapses in the retina

implies that transport from the cell body to the axon is performed by kinesin motors which also function in somato-dendritic transport. The following is a brief examination of what is known about the function of various kinesins in axons.

#### KINESIN I/ KIF5 FAMILY

The first kinesin motor to be discovered, kinesin I, is also the most investigated kinesin. Much has been learned in recent years about its structure and biophysics

of its motility (see, for example, Vale & Fletterick, 1997). Kinesin is processive, which means that it is able to move over long distances without falling off its microtubule. This processivity is due at least in part to its two heads moving alternately and coordinately. Kinesin moves on microtubules in 8 nm steps (Svoboda *et al.*, 1993), hydrolyzing one ATP molecule per step (Coy *et al.*, 1999b). Although invertebrate kinesin I subunits (i.e., KHCs and KLCs) appear to be encoded by single-copy genes, multiple isoforms of

heavy and light chains are generated by posttranslational modifications and alternative splicing, even in a single cell. In mammals, there are three genes encoding for heavy chains (KIF5A, KIF5B, and KIF5C) (Kanai *et al.*, 2000), and three genes encoding for the light chains (KLC1, KLC2, and KLC3) (Rahman *et al.*, 1998). While KIF5B is ubiquitously expressed, KIF5A and KIF5C are neuron-specific (Niclas *et al.*, 1994, Kanai *et al.*, 2000). Combinatorial associations between the heavy and light chains may generate different kinesin I motors (Goldstein & Yang, 2000). It is likely that different kinesin I motors are used in different transport events within cells, but there may also be functional redundancy, which make it difficult to interpret studies investigating the roles of these motors. A recent study has shown that the three mammalian KHC gene products, believed to only form homodimers, may also form heterodimers, and may have overlapping functions (Kanai *et al.*, 2000).

Studies done in *Drosophila*, *C. elegans*, and mice showed that kinesin I is essential for the viability of organisms (reviewed, for example, in Martin & Saxton, 1999). The function of kinesin I was studied in both neuronal and nonneuronal cells. In nonneuronal cells, there is strong evidence for a role for kinesin I in mitochondrial (Khodjakov *et al.*, 1998, Tanaka *et al.*, 1998) and lysosomal (Hollenbeck & Swanson, 1990, Nakata & Hirokawa, 1995, Tanaka *et al.*, 1998) motility. In neurons, kinesin I is considered to be one of the motors used in axonal transport. Many lines of evidence support this hypothesis. First, when axonal transport is blocked by axon ligation or crushing, kinesin I accumulates at the proximal side, together with material transported towards the synaptic terminal (Hirokawa *et al.*, 1991, Dahlstrom *et al.*, 1991). Second, mutants lacking KHC or KLC in *C. elegans* and *Drosophila* have profound neuronal defects (Patel *et al.*, 1993, Hurd & Saxton, 1996, Hurd *et al.*, 1996, Gindhart *et al.*, 1998). At microscopic level, accumulations of membranous material in large axonal swellings are detected (Hurd & Saxton, 1996). Third, suppression of kinesin I expression in cultured neurons and in the rabbit optic nerve *in vivo* inhibits transport of several vesicle-associated axonal proteins, including synapsin I and amyloid precursor protein (APP) (Ferreira *et al.*, 1992, Amaratunga *et al.*, 1993, Amaratunga *et al.*, 1995). In cultured neurons, neurite outgrowth is also affected (Ferreira *et al.*, 1992). Fourth, overexpression of kinesin I dominant negative constructs in neuronal like cells in culture abolishes proper localization of scaffolding proteins for the c-Jun N-terminal kinase (JNK) signaling pathway (Verhey *et al.*, 2001). Finally, antibodies to KHC and KLC inhibit vesicle movement in axoplasm extruded from the squid giant axon (Brady *et al.*, 1990). Some of these observations are consistent with a general block of axonal transport. However, they are most probably the consequence of an indirect disruption of many differ-

ent transport pathways caused by a block in the transport of a limited number of cargoes normally moved by kinesin I.

The nature of the axonal cargoes transported by kinesin I is under intense investigation. Since kinesin I is by far the most abundant kinesin motor in axons ( $\sim 0.5 \mu\text{M}$  concentration in squid axoplasm), with a molar ratio to tubulin of 1:8 (Brady *et al.*, 1990), it certainly transports either a very abundant cargo, or many different cargoes. Recent studies have shown that kinesin I transports vesicles carrying APP (Kamal *et al.*, 2000) and JNK signaling complexes (Verhey *et al.*, 2001). However, reports on how much kinesin I is associated with axonal membrane-bounded organelles are contradictory. Some studies have found that, in the rat optic nerve, most if not all kinesin I is membrane-bound (Elluru *et al.*, 1995). Also, in a recent report, a large proportion of the kinesin I present in the mouse sciatic nerve was associated with vesicles carrying APP (Kamal *et al.*, 2000). Others have found that only a small percentage of kinesin I cofractionates with vesicles from homogenized squid axoplasm (Schnapp *et al.*, 1992, Muresan *et al.*, 1996). In addition, an antibody highly specific for squid kinesin I labels only a small population of vesicular compartments *in situ*, with over 90% of the labeling appearing free in the axoplasm. Such a distribution is consistent with the proposal that kinesin I may play a role in the slow axonal transport of some cytoskeletal proteins, such as neurofilament proteins (Yabe *et al.*, 1999) and tubulin oligomers (Galbraith *et al.*, 1999, Terada *et al.*, 2000). The transport of these cytoskeletal elements certainly would require a very abundant motor, such as kinesin I. In conclusion, it is likely that kinesin I motors transport a variety of cargoes in axons—soluble and membranous—being thus involved in both fast and slow axonal transport.

#### KINESIN II/KIF3 FAMILY

The first member of this heteromeric kinesin family was discovered in sea urchin (Cole *et al.*, 1993) and, based on the similarity of its subunit organization with kinesin I, was named kinesin II (Scholey, 1996). It is composed of two different but related motor subunits, KRP85 and KRP95 (Cole *et al.*, 1993), which dimerize, and a nonmotor subunit (called KAP3 protein) that binds at the tail of the dimer at a position that corresponds topologically to where light chains in kinesin I bind (Wedaman *et al.*, 1996) (see Fig. 2). Members of this kinesin family have been discovered in many different organisms (Cole, 1999). In mammals, at least three different kinesin II motor polypeptides—KIF3A, KIF3B, and KIF3C—have been described (Kondo *et al.*, 1994, Muresan *et al.*, 1998, Yang & Goldstein, 1998, Yamazaki *et al.*, 1995). The KIF3 polypeptides form kinesin motors by combinatorial association of two motor polypeptides and the additional nonmotor polypeptide KAP3

(Scholey, 1996, Muresan *et al.*, 1998, Yang & Goldstein, 1998). It has been shown that KIF3B and KIF3C each associate with a common KIF3A subunit, but not with each other (Muresan *et al.*, 1998, Yang & Goldstein, 1998); also, the KIF3A/KIF3B and KIF3A/KIF3C dimers appear to bind similar forms of KAP3 (Yang & Goldstein, 1998) to generate the motor holoenzyme.

Numerous functions have been attributed to these ubiquitously expressed motors: transport of components (assembled in "raft complexes") required for the construction and function of cilia and flagella (Cole *et al.*, 1998, Morris & Scholey, 1997), including the modified cilia of chemosensory neurons (Signor *et al.*, 1999) and retinal photoreceptors (Marszalek *et al.*, 2000); pigment granule movement in melanophores (Rogers *et al.*, 1997b); vesicular transport between the endoplasmic reticulum and Golgi (Le Bot *et al.*, 1998); and chromosome movement during mitosis (Shimizu *et al.*, 1998). In neurons, members of the kinesin II family participate in the axonal transport of vesicular organelles and, possibly, of some protein complexes (Marszalek & Goldstein, 2000). In rodents and squid, KIF3A, KIF3B, and KIF3C copurify with unidentified vesicles from brain (Kondo *et al.*, 1994, Muresan *et al.*, 1998, Yang & Goldstein, 1998, Yamazaki *et al.*, 1995). Also, a mouse KIF3A/KIF3B motor, which copurifies with fodrin-containing vesicles collected from large bundles of axons, is important for neurite extension in cultured neurons (Takeda *et al.*, 2000). In cholinergic neurons from *Drosophila*, the homologue of KIF3A, KLP64D, is required for the transport of choline acetyltransferase (Ray *et al.*, 1999). Finally, KIF3A associates with vesicles, but also with the proteinaceous ribbons, at the synaptic terminal of retinal photoreceptors and bipolar cells (Muresan *et al.*, 1999). Since kinesin II also carries proteinaceous "raft complexes" required for the assembly of cilia and flagella (see above), it is likely that this motor transports large protein complexes in addition to membrane-bounded organelles.

#### UNC104/KIF1A FAMILY

The kinesin polypeptide UNC104 was discovered in a screen for uncoordinated mutations in *C. elegans* (Hall & Hedgecock, 1991). The mammalian members of this family of monomeric kinesins (see Fig. 2) include KIF1A, many splice variants of KIF1B, KIF1C, and KIF1D (Nangaku *et al.*, 1994, Okada *et al.*, 1995b, Dorner *et al.*, 1998, Rogers *et al.*, 1997a, Conforti *et al.*, 1999, Gong *et al.*, 1999). The motor domains of some of these kinesins contain a cluster of lysines (K-loop), which was proposed to interact electrostatically with negative charges on microtubules throughout the mechanochemical cycle, thus enabling their processive movement (Okada & Hirokawa, 2000, Kikkawa *et al.*, 2000). Some members of this family contain a pleck-

strin homology (PH) domain at their carboxy termini, which may mediate interactions with other proteins or membrane lipids (Rameh *et al.*, 1997). All KIF1 kinesins contain a forkhead associated domain (FHA), following the motor domain (Westerholm-Parvinen *et al.*, 2000), in a region that contains short stretches of putative coiled-coil-forming domains. This FHA domain is contained within a larger region of AF6/cno homology (Ponting, 1995). FHA domains have been implicated in interactions with phosphorylated threonine containing polypeptides (Durocher *et al.*, 1999), in a manner similar to the interaction of SH<sub>2</sub> domains with polypeptides containing phosphorylated tyrosine. FHA domains are also present in members of the KIF13 family. Phylogenetic analysis shows that the KIF13 kinesins are related to UNC104/KIF1A kinesins.

Biochemical and genetic evidence strongly suggests that KIF1A and its homologue in *C. elegans*, UNC104, are neuron-specific motors involved in the axonal transport of some synaptic vesicle precursors (Hall & Hedgecock, 1991, Okada *et al.*, 1995b, Yonekawa *et al.*, 1998). Thus, neurons from UNC104 null mutant worms have few synaptic vesicles, and make only a few small synapses (Hall & Hedgecock, 1991). Mice lacking KIF1A die within a day after birth, and show motor and sensory defects, accompanied by a decrease in synaptic vesicle density, and an accumulation of vesicles in the neuronal cell body (Yonekawa *et al.*, 1998). In subcellular fractionation experiments, KIF1A associates with vesicles containing synaptotagmin, synaptophysin, and Rab3A (Okada *et al.*, 1995b). Whether KIF1A is a processive motor is still controversial (Pierce *et al.*, 1999), but its velocity, higher than 1  $\mu\text{m/s}$  (Okada *et al.*, 1995b), is comparable to the velocities of anterogradely moving organelles in axons *in vivo*. Certainly, UNC104/KIF1A is a good candidate for a major axonal vesicle motor.

KIF1B, expressed in many tissues, is abundant in differentiated nerve cells. The motor is likely involved in the transport of mitochondria, since it colocalizes with mitochondria in cultured cells, copurifies with mitochondria from brain, and promotes motility of mitochondria *in vitro* (Nangaku *et al.*, 1994). The function of KIF1C in brain, where it is expressed at relatively low levels, is less clear. Since it appears to function in vesicle transport from the Golgi to the endoplasmic reticulum in fibroblasts (Dorner *et al.*, 1998), it may be a vesicle motor in neurons too. Interestingly, KIF1C interacts with the protein 14-3-3 (Dorner *et al.*, 1999), a scaffolding protein involved in signal transduction events (Yaffe *et al.*, 1997).

The mouse kinesin motor KIF13A, expressed throughout the nervous system and also present in axons, may transport trans-Golgi-derived, mannose-6-phosphate receptor-containing vesicles to the plasma

membrane (Nakagawa *et al.*, 2000). The probable human homologue of KIF13B, GAKIN, also expressed at high levels in brain, interacts with the human homologue of the *Drosophila* discs large protein (hDlg) and with PSD95, two scaffolding proteins necessary for the assembly and organization of protein complexes at specialized membrane sites, including synapses (Hanada *et al.*, 2000). A close relative of GAKIN, the *Drosophila* kinesin-73, becomes restricted to the central and peripheral nervous systems at late stages during embryonic development (Li *et al.*, 1997).

#### KIF2

The central motor domain kinesin, KIF2 (see Fig. 2), was cloned from mouse brain and proposed to be an anterograde motor participating in the transport of some vesicles, distinct from synaptic vesicle precursors, in developing axons (Noda *et al.*, 1995). Consistent with this proposal, KIF2 is concentrated in growth cones of developing neurites in NGF stimulated PC12 cells, and appears to be needed for neurite extension and transport of the  $\beta$  subunit of an IGF-1 receptor variant (Morfini *et al.*, 1997). Since this motor is expressed at much higher levels in the developing brain compared to the adult tissue, it is unlikely that it transports an abundant cargo in mature axons. Some questions have been recently raised with regard to KIF2 being a motor at all, since close relatives of this motor in *Xenopus*, XKIF2 and XKCM1, were found not to promote microtubule motility, but to induce microtubule depolymerization *in vitro* (Desai *et al.*, 1999, Walczak *et al.*, 1996). While a role in neurite extension could be explained by the regulation of microtubule dynamics, the preferential association of KIF2 with a membrane fraction (Noda *et al.*, 1995) still argues for a role of KIF2 as axonal vesicle motor in the developing murine brain.

#### KIF4

Another kinesin motor with probable function in axonal transport is KIF4. This homodimeric motor (see Fig. 2) is expressed preferentially in developing tissues (Sekine *et al.*, 1994), and may have multiple functions. Based on its similarity with several vertebrate mitotic motors, e.g., chromokinesin and XKLP1, KIF4 is likely to play a role in mitosis (Wang & Adler, 1995, Vernos *et al.*, 1995). Indeed, KIF4 contains a DNA binding domain, is localized in part to the mitotic apparatus in mitotic cells, and is present in nuclei in interphase cells (Sekine *et al.*, 1994). In cultured neurons, KIF4 predominantly localizes to the axonal shaft and its growth cone, and is associated with vesicles containing the cell adhesion molecule L1, a glycoprotein implicated in axonal elongation (Peretti *et al.*, 2000). Suppression of KIF4 with antisense oligonucleotides prevents both localization of L1 to growth cones and L1-enhanced axonal elongation. Taken together with its enrichment in ax-

ons *versus* cell body and dendrites (Peretti *et al.*, 2000), it is likely that KIF4 plays a role in the generation of neuronal polarity.

#### CARBOXY-TERMINAL MOTOR FAMILY

Members of this family move minus-end directed on microtubules, and most of them have functions in mitosis and meiosis. Two of them, however, KIFC2 and KIFC3, appear to be involved in intracellular transport processes in adult neurons, including a possible participation, besides cytoplasmic dynein, in retrograde axonal transport. The homodimeric kinesin, KIFC2, primarily a motor for dendritic transport of a new type of organelle (Saito *et al.*, 1997), is present in axons only at low levels. Consistent with a proposed role in retrograde axonal transport, it accumulates at both sides of an axonal ligation (Hanlon *et al.*, 1997). KIFC3, presumed to be also a minus-end motor, has been localized to the synapse of retinal photoreceptor cells, suggesting a role at the ribbon synapse (Hoang *et al.*, 1999).

#### Fitting kinesins to cargoes

There is some evidence that membrane proteins destined for different axonal subdomains are transported in different transport carriers (Hirokawa, 1998, Kaether *et al.*, 2000). Based on this assumption, it was hypothesized that specific receptors on the different types of cargo vesicles select for the correct motor used in any particular transport process (Vallee & Sheetz, 1996, Hirokawa, 1996). In this model, different kinesin motors would be localized to different populations of vesicles. Based on structural considerations, kinesins are presumed to interact with their cargoes *via* regions outside their motor domain. In the case of kinesins with terminal motor domains and elongated structure, such as kinesin I and kinesin II, the cargo binding sites most likely reside in their tails. The tails of these kinesins include the carboxy termini of the motor polypeptides, as well as the associated nonmotor polypeptides (i.e., KLC or KAP3), which could both be involved in the interaction with the cargo. In one study, binding of KHC to membranes *in vitro* occurred in the absence of KLCs (Skoufias *et al.*, 1994). Such interactions have been shown to occur *in vivo*, and may link kinesin I to a membrane-associated myosin V motor (Huang *et al.*, 1999, Prekeris & Terrian, 1997). Other studies have implicated the KLCs in binding of kinesin I to mitochondria (Khodjakov *et al.*, 1998), the Golgi (Gyoeva *et al.*, 2000), and squid axonal vesicles *in vivo* (Stenoien & Brady, 1997), and suggested a role for the tetratricopeptide repeat (TPR) domains in this interaction (Stenoien & Brady, 1997). More recent results have indeed demonstrated interactions between the TPR domains of KLCs and several putative cargo-linking proteins, such as the Sunday driver protein (Bowman *et al.*, 2000), the

APP (Kamal *et al.*, 2000), or the scaffolding proteins of the JNK interacting protein (JIP) family (Verhey *et al.*, 2001). Numerous isoforms of KLCs, differing in their carboxy-terminal domains, are generated by alternative splicing (Cyr *et al.*, 1991, Beushausen *et al.*, 1993, Fan & Amos, 1994). Many of them are present in a single cell line (Gyoeva *et al.*, 2000) or even in a single axon (i.e., the squid giant axon). Therefore, it is likely that the light chains are involved in cargo selection, and their highly variable carboxy-terminal domains may determine specificity. Indeed, only one out of five KLC isoforms present in cultured fibroblasts associates with mitochondria (Khodjakov *et al.*, 1998); another isoform associates with the Golgi (Gyoeva *et al.*, 2000).

Like kinesin I motors, kinesin II motors have diverse functions and are presumed to associate with a large number of different cargoes (see above). Again, cargo selection and binding appear to be mediated *via* their tails, and the KAP3 subunit is presumed to have an important role. There is evidence that the KAP3 protein may serve as binding site for cargoes and regulators of the kinesin II motor. Pull-down experiments and two-hybrid screens showed interactions between KAP3 and a variety of proteins: a regulator of a small GTPase (Smg GDS) (Shimizu *et al.*, 1996), a mixed lineage serine/threonine kinase (MLK2) (Nagata *et al.*, 1998), and  $\alpha$  fodrin (Takeda *et al.*, 2000). It is not known whether these interactions, identified in different cell types, involve different isoforms (Yamazaki *et al.*, 1996) of the KAP3 protein.

In the case of kinesins with globular shapes, such as the monomeric kinesin polypeptides of the UNC104/KIF1A family, the position of the cargo-binding site in the molecule is less obvious, and may be situated anywhere outside the motor domain. KIF1C has been shown to interact with 14-3-3 proteins *via* a short domain situated at its very carboxy-terminal end (Dorner *et al.*, 1999). Since 14-3-3 proteins also associate with intracellular membrane compartments (Roth *et al.*, 1994, Jones *et al.*, 1995), one can speculate that they may act as adapters for KIF1C to its vesicular cargo. KIF13A also interacts with the AP-1 complex on cargo vesicles *via* its tail domain (Nakagawa *et al.*, 2000). By contrast, the related kinesin motor, GAKIN, was found to interact with the scaffolding proteins, hDlg and PSD95, *via* a region in close vicinity to the motor domain that may include the FHA domain (Hanada *et al.*, 2000). Again, these proteins may act as adapters of GAKIN to some vesicular cargo.

A growing number of published reports investigate in some detail the interaction of kinesins with their vesicular cargoes. The dendritic motor, KIF17, transports vesicles containing a preassembled NMDA receptor 2B complex to the postsynaptic terminal (Setou *et al.*, 2000). The motor polypeptide binds to the vesicle by a direct interaction of its tail with a PDZ domain of the scaffolding protein, mLin10, which is

a constituent of the NMDA receptor complex. In axons, a kinesin II motor (i.e., KIF3A/KIF3B/KAP3) that transports fodrin-containing vesicles binds *via* an interaction between KAP3 and  $\alpha$ -fodrin (Takeda *et al.*, 2000). Interestingly, fodrin forms a structural scaffold around transport vesicles that also serves as anchoring site for the minus-end motor, cytoplasmic dynein (Muresan *et al.*, 2001). KIF13A interacts with  $\beta$ 1-adaptin of the AP-1 adaptor protein complex, which itself mediates the interaction with vesicles containing the mannose-6-phosphate receptor (M6PR) (Nakagawa *et al.*, 2000). Kinesin I interacts directly with the tail of myosin V (Huang *et al.*, 1999), which itself binds to a complex of the integral membrane proteins synaptobrevin 2 and synaptophysin (Prekeris & Terrian, 1997). Finally, kinesin I also interacts with JIP scaffolding proteins, which themselves bind to the Reelin receptor, ApoER2 (Verhey *et al.*, 2001).

### Regulation of cargo binding and activation of kinesins

Transport of any cargo along the axon to its destination depends on the *recruitment* and *activation* of the correct kinesin motor. How these two regulatory processes are achieved is still largely unknown. Also unknown is whether the same motor molecules remain attached to the cargo, being used until destination is reached, and whether activity of the cargo-associated motors is modulated during transport.

The prevalent view is that kinesins are cytosolic proteins that become attached to their specific cargoes in a regulated manner. Most cargoes to be transported into the axon, whether vesicles, soluble protein complexes, or RNA-protein complexes, are synthesized and assembled in the cell body. Therefore, it is expected that motors responsible for transport become attached to their cargo in the neural soma. Since the vast majority of membranous cargoes are post-Golgi vesicles, kinesins are probably recruited to the nascent vesicle at the time of its formation in the trans-Golgi compartment or shortly thereafter. Similarly, nonvesicular cargoes, such as protein complexes or RNA-protein complexes are expected to recruit the kinesin motor once they are fully assembled. What triggers the recruitment of the specific kinesin to the cargo, once it is ready for transport, is not known. One possibility is that modifications of the cargo or of some of its components, such as the phosphorylation of a vesicle protein or a modification in the lipid composition of a nascent vesicle, may expose binding sites for the motor. Alternatively, events causing a posttranslational modification or a shape change of the kinesin molecule may induce both its binding to a component of the cargo and its activation.

With regard to axonal transport, there are indications that changes in calcium concentration (Breuer *et al.*, 1992, Kanje *et al.*, 1981), small GTPases (Bloom *et al.*,

1993), and the activation of certain protein kinase pathways (Okada *et al.*, 1995a), including cyclin-dependent kinases (Ratner *et al.*, 1998), may modulate rate and direction of vesicle movement. As shown below, these factors appear to regulate kinesin activity and its attachment to the cargo.

#### PHOSPHORYLATION

Both heavy and light chains of kinesin I are phosphorylated *in vivo* on serine residues, and phosphorylation correlates with changes in ATPase activity *in vitro* (Lindesmith *et al.*, 1997), and in motor association with membranes, including synaptic vesicles (Sato-Yoshitake *et al.*, 1992, Lee & Hollenbeck, 1995). Kinesin I copurifies from cultured cells with an unidentified kinase and phosphatase (Lindesmith *et al.*, 1997). Other kinesins also interact with protein kinases and phosphatases. For example, the kinesin motor KIF1C interacts with the protein-tyrosine phosphatase PTPD1, and is phosphorylated *in vivo* on both tyrosine and serine residues (Dorner *et al.*, 1998, Dorner *et al.*, 1999). The signaling pathways leading to regulation of kinesin-mediated transport processes by phosphorylation are still ill defined, and may be triggered by intracellular and extracellular stimuli. An interesting study, investigating kinesin I-dependent mitochondrial motility in L929 cells, finds hyperphosphorylation of KLC and inhibition of kinesin I activity *via* cytokine receptor signaling pathways (De Vos *et al.*, 2000).

#### SMALL GTPASES

Recent studies have indicated that kinesin motors are potential effectors of Rab proteins. Thus, the Golgi-associated kinesin, Rabkinesin-6, interacts with the GTP-bound form of Rab6, and this interaction is required for the effect of Rab6-GTP on intracellular transport (Echard *et al.*, 1998). This is in line with the involvement of small GTPases, at a variety of steps, in the regulation of membrane traffic. One possibility is that small GTPases are involved in membrane priming for kinesin recruitment, similar to their involvement in the recruitment of various "coat proteins" to organelles (Schimmoller *et al.*, 1997, Springer *et al.*, 1999). Alternatively, small GTPases may serve as anchors for kinesins to membranes.

#### ION CONCENTRATION

Several kinesin motors, including kinesin I, have been shown to bind calmodulin in a calcium-dependent manner; calcium, through calmodulin, appears to negatively regulate microtubule binding and ATPase activity (Matthies *et al.*, 1993, Rogers *et al.*, 1999, Day *et al.*, 2000). Also, small changes towards lower pH values trigger activation of kinesin I *in vitro*, but this effect could be indirect (Verhey *et al.*, 1998).

#### ACTIVATION BY CARGO BINDING

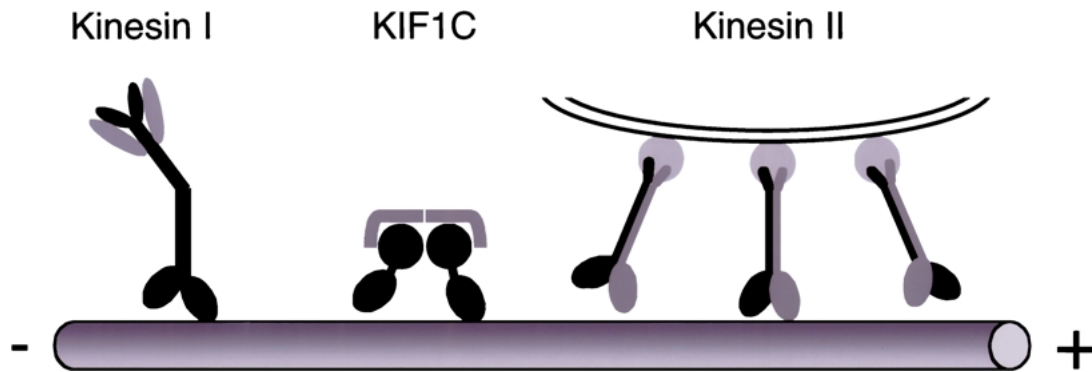
Detailed studies on kinesin I have indicated that the inactive form of the motor observed *in vivo* (Verhey *et al.*, 1998) corresponds to a folded conformation—observed *in vitro*—stabilized by an interaction between head and tail (Hackney *et al.*, 1992). It has been proposed that the light chains have a role in keeping kinesin I in an inactive ground state (Verhey *et al.*, 1998), and that the interaction of the tail domain of the motor with the cargo induces a conformational change that activates the motor (Coy *et al.*, 1999a, Friedman & Vale, 1999). Activation of kinesin II may similarly involve a conformational change, since this motor, like kinesin I (Hackney *et al.*, 1992), undergoes a salt-dependent change between a folded and an extended state (Wedaman *et al.*, 1996). As for kinesin I, this conformational change may be caused by interaction with the cargo.

#### REGULATION OF PROCESSIVITY OF MOTILITY

Cargo binding may not only activate a motor but also increase its processivity. Processivity is defined as the distance travelled or number of steps made by the motor before it diffuses away from the microtubule, and is a prerequisite for efficient transport of cargoes to their destination. The two-headed kinesin I is highly processive because of the alternate binding of the two heads to the microtubule (Hackney, 1994, Hancock & Howard, 1998). Since one of the kinesin I heads is always attached to the microtubule, this two-headed kinesin does not diffuse away from the microtubule during movement. Monomeric kinesin motors, such as those of the KIF1 family, need to rely on a different mechanism to achieve processive movement. One possibility is to generate dimers from monomers, allowing them to operate in a manner similar to the double-headed kinesin I. In the case of KIF1C, such a dimerization could be induced by association with the scaffolding protein, 14-3-3, a process which may occur simultaneously with the attachment of the KIF1C motor to the cargo (Dorner *et al.*, 1999). In a similar way, other nonprocessive motors may generate processive movement of the cargo by clustering in patches on the cargo surface (Pierce *et al.*, 1999) (Fig. 3).

#### REGULATION OF TRAFFIC BY MODIFYING MICROTUBULE TRACKS

Another way to regulate transport along microtubules is by using so-called "smart" motors (Shah & Goldstein, 2000, Burack *et al.*, 2000) capable of translocating on some microtubules but not on others. Differences between microtubules certainly exist in neurons, generated either by posttranslational modification in the tubulin subunits (Laferriere *et al.*, 1997) or by association of microtubules with different microtubule-associated proteins (MAPs) (Hirokawa, 1994). Kinesin



**Fig. 3.** Diagram showing different ways for achieving processive motion by kinesin motors. Kinesin I is highly processive *per se*. The monomeric motor, KIF1C, may become processive by interacting with a protein (e.g., the 14-3-3 dimer) that facilitates its dimerization (Dorner *et al.*, 1999). Kinesin II motors of low processivity (Pierce *et al.*, 1999) may generate processive movement by clustering on the cargo surface.

I binds with higher affinity to microtubules containing deetyrosinated tubulin (Liao & Gunderson, 1998, Kreitzer *et al.*, 1999). Also, MAPs have been shown to affect microtubule-dependent vesicle trafficking (Sato-Harada *et al.*, 1996, Hirokawa *et al.*, 1996, Trinczek *et al.*, 1999) and to interfere with the motility of kinesin I and, possibly, other motors (Lopez & Sheetz, 1993, Ebner *et al.*, 1998). Since different sets of MAPs are localized to axons versus dendrites (Hirokawa, 1994), it is likely that at least some transport to the axon and dendrites may use motors which recognize the intrinsic, neurite-specific modifications of microtubules. While preferential transport of dendritic proteins, such as the transferrin receptor, has been recently described (Burack *et al.*, 2000), selective transport to the axon has not yet been reported.

Microtubules with distinct properties may also exist within the axon itself. Observations done many years ago indicated that, while motility in extruded but otherwise undisturbed squid axoplasm was bidirectional, it appeared unidirectional on every single microtubule, after gentle dissociation of the axoplasm (Allen *et al.*, 1985, Schnapp *et al.*, 1985). This suggested that vesicle transport was entirely plus-end directed on some microtubules, and entirely minus-end directed on others. If this reflects the *in vivo* situation, then plus-end and minus-end vesicle motility would occur on different sets of microtubules.

Minus-end kinesins, eventually required for retrograde transport, need to be transported to the synaptic terminal in an inactive form. How these are recruited to their cargoes in the presynaptic region and activated is not known.

Regulation of axonal traffic certainly implies more than regulation of kinesin motors. Many studies have shown that anterogradely transported cargoes also contain associated cytoplasmic dynein (Hirokawa *et al.*, 1990, Muresan *et al.*, 1996) and myosins (Kuznetsov *et al.*, 1992, Langford, 1995), motors required for retro-

grade transport on microtubules and transport on actin filaments, respectively. These motors are likely to be transported in an inactive form, and regulated in coordination with kinesins (Reese & Haimo, 2000). Alternatively, kinesin motors may override dynein, presumed to be less processive, during transport (Muresan *et al.*, 1996).

#### Unloading the cargo

Once the destination is reached, the kinesins used during transport are no longer needed. The fate of these motors is not known. One possibility is that they become inactivated and are transported back to the cell body for recycling or degradation. However, ligation experiments have failed to detect significant amounts of kinesin I (Dahlstrom *et al.*, 1991, Hirokawa *et al.*, 1991), kinesin II (Yang & Goldstein, 1998), KIF1A (Okada *et al.*, 1995b), or KIF2 (Noda *et al.*, 1995) at the distal side of the ligation, indicating that axonal kinesins may not be recycled. This also shows that they are probably detached from their cargo and degraded at the axon terminal. Uncoupling of kinesins may be caused by a posttranslational modification or a shape change of either the kinesin motor or a component of the cargo. In the case of kinesin I, two mechanisms have been proposed. The first takes into consideration the presence of a PEST region in all KLCs, which has been associated with proteins highly susceptible to protein degradation (Beushausen *et al.*, 1993). These PEST regions could serve as selective sites for degradative removal of the motor from its cargo. The other mechanism is based on the observation that the molecular chaperone, hsc70, interacts with the KLCs and releases kinesin I from a membrane fraction (Tsai *et al.*, 2000). It was proposed that the availability of a large soluble pool of hsc70 in presynaptic terminals would automatically release kinesin I from its cargo.

### Unconventional cargoes and functions

While the major role of kinesins in an axon is to transport cargoes over long distances to a remote destination, it is likely that they also have local functions at some specialized synapses. In one example, the plus-end kinesin KIF3A and the minus-end kinesin KIFC3 have been localized at the ribbon synapse of retinal photoreceptors (Muresan *et al.*, 1999, Hoang *et al.*, 1999). It has been proposed that synaptic vesicles, docked at the ribbon, translocate along the ribbon towards the active zone, but the nature of this transport, whether active or passive, is not known (Morgans, 2000). Since in these synaptic terminals microtubules penetrate into the space between the plasma membrane and the ribbon to reach the active zone (Usukura & Yamada, 1987), it is possible that the two kinesins are involved in vesicle translocation to, and recycling from the active zone.

The traditional model of fast axonal transport envisions various kinesin motors carrying a number of individual cargoes, each containing some of the components needed at the nerve terminal (e.g., synaptic vesicle precursors, proteins of the presynaptic plasma membrane, dense core synaptic vesicles, cytoplasmic components used in synaptic vesicle recycling). This model is supported by studies showing that membrane compartments of different biochemical composition are transported as separate entities and at different velocities within axons (Hirokawa, 1996, Kaether *et al.*, 2000). However, recent studies have suggested that many of these components may be transported to the synaptic terminal as preassembled packets (Ahmari *et al.*, 2000, Friedman *et al.*, 2000). Although kinesins have not yet been identified in association with these packets, their transport is fast and saltatory, typical for kinesin-driven motility. Future studies will determine the extent of this sort of transport.

There has been speculation over the years on the role of kinesin motors in the transport of localized mRNAs and of signaling complexes, but clear evidence for such roles was only recently published. Thus, kinesin I was shown to be required for the transport of the *oskar* mRNA, a morphogenetic factor, to the posterior pole of the *Drosophila* oocyte during development (Brendza *et al.*, 2000). Interestingly, localization of Staufen, a protein that binds to *oskar* mRNA and is required for its posterior accumulation, was also shown to be dependent on kinesin I activity. A recent report indicated that kinesin I also transports and localizes preassembled components of the JNK kinase signaling pathway in neurons, suggesting that kinesins may play a more general role in the spatial regulation of signal transduction pathways (Verhey *et al.*, 2001). Taken together, these studies suggest that many transport processes in cells—not only in axons—involve preassembled functional units, whether they are pre- or postsynaptic zones, signal-

ing complexes assembled on a scaffold, or RNA-protein complexes containing the entire translation machinery.

### The principles of axonal transport by kinesins

In recent years, a lot has been learned about the organization of axonal transport by kinesins. As detailed above, evidence that a particular kinesin motor is responsible for the transport of one or a few classes of intracellular vesicles in axons is growing. However, it is still unresolved how kinesins are recruited to their axonal cargoes and how they are activated and deactivated. While these and other questions still remain to be answered, our current knowledge allows us to draw the basic principles that appear to guide axonal transport.

#### Principle 1

*One type of kinesin motor may be involved in different transport processes.* The number of different cargoes in an axon certainly exceeds the number of axonal kinesins. Therefore, one type of kinesin may carry several different axonal cargoes. More than that, it is likely that kinesins that participate in axonal transport also perform transport functions in other parts of the cell, such as the dendrites. As described above, kinesin I and kinesin II have been proposed to transport a number of different cargoes. In retinal photoreceptors, for example, KIF3A plays a role in the transport of opsin towards the outer segment (Marszalek *et al.*, 2000), and of some vesicles and components of the synaptic ribbon to the photoreceptor synapse (Muresan *et al.*, 1999). Also, kinesin I functions at least in the transport of mitochondria and lysosomes in the same cell (Tanaka *et al.*, 1998). In axons, kinesin I transports at least two types of vesicular cargoes (i.e., containing APP and JNK signaling complexes), and is a likely candidate motor for slow axonal transport as well (see above).

#### Principle 2.

*Similar types of cargo may bind different kinesin motors in different cellular contexts.* I will illustrate this principle with two examples. First, a number of kinesin motors have been localized to the Golgi, and appear to function in transport processes from the Golgi to the endoplasmic reticulum (Le Bot *et al.*, 1998, Dorner *et al.*, 1998, Echard *et al.*, 1998, Lippincott-Schwartz *et al.*, 1995). Second, at least three kinesins (i.e., kinesin I, KIF1B, and KLP67A) have been proposed to reside on mitochondria and to promote their motility on microtubules (Nangaku *et al.*, 1994, Pereira *et al.*, 1997, Tanaka *et al.*, 1998). More than that, mitochondrial motility may be promoted by kinesin I motors containing any of the three KHCs expressed in mammals (Tanaka *et al.*, 1998). It is likely that many important transport pathways rely on more than one kinesin motor.

#### Principle 3.

*Kinesin motors bind to proteins with defined cellular functions. These proteins serve as receptors for kinesins during transport.* For a long time it was thought that the

different kinesin motors would bind to specialized vesicle proteins, whose only function was to bind the motor. The protein, kinectin, was proposed to be such a receptor for anchoring kinesin I to the endoplasmic reticulum (Kumar *et al.*, 1995). However, recent studies have suggested that the proteins, which link kinesins to the cargo, are *bona fide* components of the cargo, and have specific functions—other than binding a kinesin—at their destination. Examples of proteins that, in addition to their specific function, may also serve as receptors for a particular kinesin during transport include: fodrin (Takeda *et al.*, 2000); the adaptor complex, AP-1 (Nakagawa *et al.*, 2000); the scaffolding proteins for the JNK/MAPK signaling complex, JIP1, JIP2 (Verhey *et al.*, 2001), and JIP3 (Bowman *et al.*, 2000); the transmembrane protein, APP (Kamal *et al.*, 2000); vesicle-associated myosin V (Huang *et al.*, 1999, Prekeris & Terrian, 1997); hDlg (Hanada *et al.*, 2000); the 14-3-3 protein (Dorner *et al.*, 1999); and the small GTPase, Rab6 (Echard *et al.*, 1998) (Fig. 4).

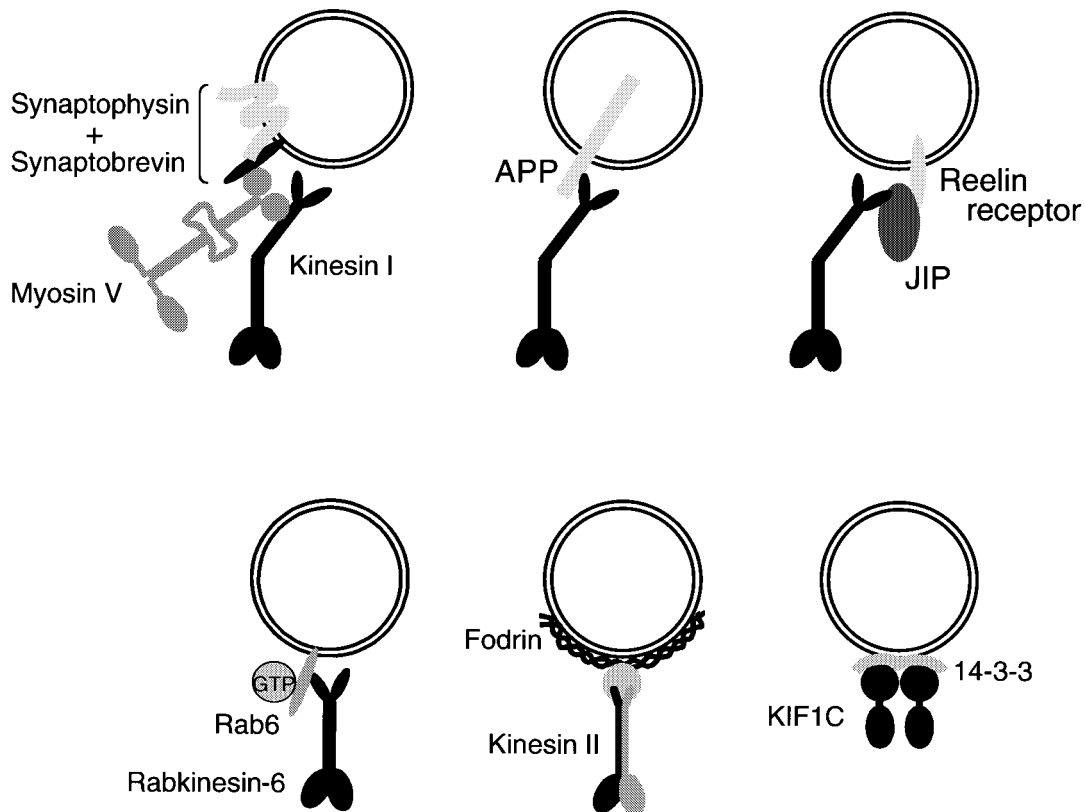
Principle 4.

*Kinesins are activated upon attachment to the cargo.* Early and more recent work on activation of kinesin I has in-

dicated that most of this motor is present in an inactive form *in vivo* (Hackney *et al.*, 1992, Verhey *et al.*, 1998). Interestingly, the microtubule-stimulated ATPase activity of soluble kinesin I *in vitro* is substantially increased upon attachment to beads or glass surfaces, and this ATPase activity is consistent with the speed and processivity of substrate-attached kinesin I motility (Coy *et al.*, 1999a). These and other results led to the proposal that, similar to its binding to artificial substrates, binding of kinesin I to its natural cargo may lead to its activation. If so, soluble, cytosolic kinesin I—and, possibly, other kinesin motors as well—are kept in an inactive state until they are needed for transport.

Principle 5.

*Kinesin motors used for the transport of different cargoes are independently regulated.* Compared to having a single type of kinesin, which could bind to a receptor molecule present in all cargoes, the existence of multiple kinesin motors, each targeted to a specific cargo, would allow for independent regulation of the trafficking pathways (Schnapp, 1997). Since motors differ in their speed and processivity, delivery of the various cargoes would occur at the required rates. In addition, as shown above,



**Fig. 4.** Hypothetical model for attachment of kinesin motors to a vesicular cargo. Kinesin I interacts with myosin V (Huang *et al.*, 1999), which itself may bind to a complex of integral membrane proteins (Prekeris & Terrian, 1997); or binds to the transmembrane protein, amyloid precursor protein (APP) (Kamal *et al.*, 2000); or interacts with a JIP scaffolding protein (Verhey *et al.*, 2001), which may associate to a transmembrane protein (e.g., the Reelin receptor). Rabkinesin-6 may bind to a vesicle *via* the small GTPase, Rab6 (Echard *et al.*, 1998). Kinesin II binds to a vesicle-associated fodrin meshwork *via* an interaction between the KAP3 subunit and  $\alpha$  fodrin (Takeda *et al.*, 2000). Two KIF1C polypeptides interact with a 14-3-3 polypeptide dimer (Dorner *et al.*, 1999), which itself may bind to the vesicle membrane (Roth *et al.*, 1994).

the activation and deactivation of specific kinesins, as well as their association with their cargoes, is subject to differential regulation by a large variety of factors (e.g., phosphorylation, small GTPases, ions).

### Conclusion: The logic of axonal transport by kinesins

As detailed above, most kinesin motors are expressed—and are present at high levels—in neurons, and many are likely to be present in a single axon. This large number of kinesins is used to transport an even larger number of axonal cargoes of different biochemical compositions. It is proposed that kinesins may select for the correct cargo by binding to *bona fide* cargo proteins, which have specific functions at their destination. These proteins become “ad hoc” kinesin receptors and act as kinesin anchors only for the time of the transport. Once destination is reached, motors are discarded, and the proteins, which served as kinesin anchors, engage in other cellular functions. In this way, no special kinesin receptors are required. The recent identification of a number of proteins, which act as binding sites for specific kinesins, is consistent with this hypothesis. Interestingly, some of these are scaffolds (e.g., hDlg, PSD95, 14-3-3, fodrin, mLin10) for assembling multiprotein complexes, such as signal transduction complexes or ion channel complexes destined to function at the pre- or postsynaptic terminal. It is likely that several different proteins, present on different cargoes, may be capable of binding a particular kinesin motor. The challenge for future studies is to identify the entire spectrum of binding partners for any type of kinesin, and to characterize their regulated interaction.

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