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Review

Understanding the functions of kinesin-II

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Abstract

Species ranging from *Chlamydomonas* to humans possess the heterotrimeric kinesin-II holoenzyme composed of two different motor subunits and one non-motor accessory subunit. An important function of kinesin-II is that it transports the components needed for the construction and maintenance of cilia and flagella from the site of synthesis in the cell body to the site of growth at the distal tip. Recent work suggests that kinesin-II does not directly interact with these components, but rather via a large protein complex, which has been termed a raft (intraflagellar transport (IFT)). While ciliary transport is the best-established function for kinesin-II, evidence has been reported for possible roles in neuronal transport, melanosome transport, the secretory pathway and during mitosis. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Kinesin-II; Kinesin; Microtubule transport; Raft; Cilia transport

1. Introduction

Microtubule motors use energy derived from ATP hydrolysis to translocate unidirectionally along microtubules and to perform many different cellular transport functions. In most interphase cells, the microtubules are oriented with their minus ends at the center of the cell and their plus ends oriented toward the cell periphery. Kinesin and dynein motors use these microtubules to localize cellular organelles such as the Golgi apparatus, the endoplasmic reticulum (ER), mitochondria and lysosomes and to move vesicular traffic throughout the cell. During mitosis, microtubule motors also ensure that equal segregation of genetic material between two daughter cells occurs reliably (for recent reviews of mitotic motors see [1,2]). Neurons use microtubule motors to sort and transport material that is synthesized within the cell body into and along their extensive dendritic and axonal processes (for recent reviews see [3,4]). Finally, molecular motors are used for construction, maintenance and movement of flagella and cilia, which are themselves modified microtubule arrays. The KIF3 kinesin family forms the kinesin-II holoenzyme and has now been identified in species ranging from *Chlamydomonas* to humans. Considerable data implicate KIF3 family members in many cellular processes. This review will describe the data that have led to these ideas.

2. The KIF3 family

The kinesin-II holoenzyme was originally purified biochemically from sea urchin embryo extracts as a heterotrimeric holoenzyme [5]. The term kinesin-II is

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used to refer to the whole heterotrimeric holoenzyme complex, while the individual subunits are referred to by their unique protein name. Sea urchin kinesin-II is comprised of an approx. 85 kDa (spKRP85) and an approx. 95 kDa (spKRP95) motor subunit that together form a heterodimer that often is tightly associated with an approx. 115 kDa (spKAP115) non-motor accessory subunit (Fig. 1). Homologues of sea urchin heterotrimeric kinesin-II components have subsequently been identified in species ranging from *Chlamydomonas* to humans (see Table 1). Where tested, the motor subunits translocate along microtubules at a rate of approx. 0.4 μm/s [5]. The carboxyl terminal portions of the motor subunits interact with the non-motor accessory protein [6,7]. While a function has not been demonstrated for the accessory subunit, it is believed to function in either interaction with cargo or regulation of motor activity. For a more in-depth description of the structure of kinesin-II see a recent review by Scholey [8].

The nomenclature used to name the different kinesin-II subunits is different for each species and often leads to confusion. In Table 1 the names of all of the subunits that have been identified either through purification of the holoenzyme or by molecular cloning of the DNA sequence as well as the name of the corresponding mouse homologue are provided. Kinesin-II holoenzymes in which direct interaction of the two different motor subunits has been established by purification in every organism listed except for *Drosophila* (Table 1). In *Drosophila*, KLP64D and KLP68 are the sequence homologues of KIF3A and KIF3B, but evidence for direct interaction between them has not been reported.

Additional KIF3 motor subunits have been identified in mammals (KIF3C) and in *Caenorhabditis elegans* (Osm3) that are distinct from the classical kinesin-II subunits. KIF3C is a neuronally enriched KIF3 motor subunit that is slightly larger than KIF3B. Immunoprecipitation of KIF3C protein established that KIF3C is able to form a heterodimer with KIF3A, but not KIF3B [9,10]. Interestingly, KIF3C protein is distributed between two peaks in a sucrose gradient, one that is identical to the KIF3A peak and the other not. This result suggests that KIF3C can either form a homodimer or may interact with an unidentified KIF3 family member [10]. Immunoprecipitation and sucrose gradient experiments established that *C. elegans* OSM-3 protein, unlike KIF3C, does not form a complex with either of the other kinesin-II motor subunits [11]. However, like KIF3C, it is unclear whether OSM-3 forms a homodimer or a heterodimer with another KIF3 family member [11].

While the cargo of kinesin-II remains elusive, work in *Chlamydomonas* demonstrates that FLA-10 transports 'rafts' composed of a 16S protein complex containing 15 different polypeptides [12–14] (Table 2). The raft complex is transported from the basal body to the tip of the flagella by FLA-10 [12–14] and then returned to the cell body by dynein [15,16]. Potential homologues of some of the raft subunits have been identified in other species suggesting that use of the raft complex is not unique to *Chlamydomonas*. For example, sequence homologues have been identified for the p52 subunit in *C. elegans* (OSM-6) and in mammals (NGD5) and for the p172 subunit in *C. elegans* (OSM-1). *C. elegans* OSM-6 and OSM-1 mutants exhibit the same ciliary defects observed in OSM-3 mutants, strongly supporting the notion that these proteins are indeed the functional homologues of their corresponding *Chlamydomonas* raft subunits.

3. Kinesin-II and ciliary transport in invertebrates

The best-established function of kinesin-II is its role in ciliary transport. Differential interference contrast (DIC) microscopy has been used to observe bidirectional movement of granule-like molecules beneath the flagellar membrane in *Chlamydomonas*. This movement has been termed intraflagellar transport or IFT and particles can be observed translocating between the cell body and tip of the flagella [17,18]. When *Chlamydomonas* cells that have a temperature sensitive mutation in FLA-10, the homologue of the kinesin-II KIF3A subunit, are shifted to the restrictive temperature, IFT ceases and the flagella shorten and eventually disappear [12,13,19]. It is now apparent that kinesin-II is responsible for transport of the raft complex and perhaps transport of the components used for cilia construction and maintenance to the tip of the flagella [12–14]. Dynein transports rafts and other proteins from the tip of

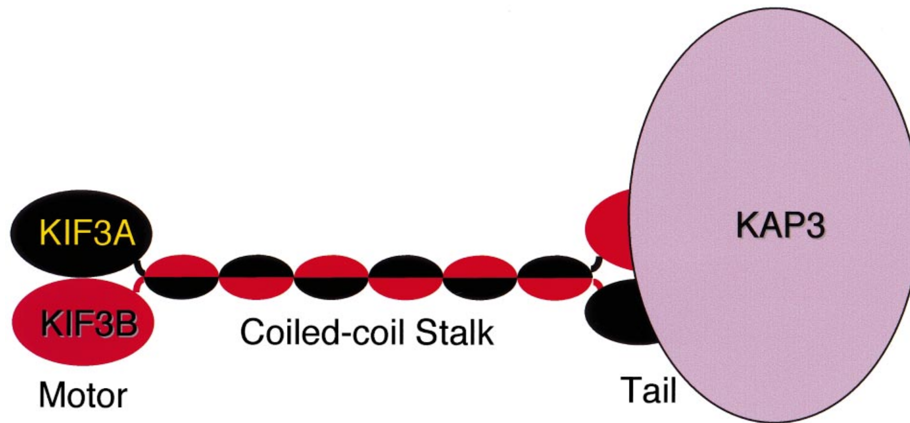

Fig. 1. Structure of kinesin-II. Kinesin-II is composed of two different motor subunits that in mouse have been named KIF3A and KIF3B. The motor domain interacts with microtubules and contains the ATPase used to translocate the holoenzyme along the microtubules. The coiled-coil stalk is where the two motor subunits interact with each other to form a stable heterodimer. The tail domains interact with the KAP3 non-motor accessory subunit. KAP3 is believed to either interact with the kinesin-II cargo, or possibly regulate motor activity.

the flagella back to the cell body [15,16]. For a more detailed discussion on ciliary and intraflagellar transport, see a recent review by Rosenbaum et al. [20].

The use of kinesin-II in ciliary transport is not restricted to the motile flagella of *Chlamydomonas* cells, but has also been found in other organisms. In sea urchin embryos, when function-blocking antibodies against the spKRP85 subunit are injected into one cell stage embryos, normal cilia fail to be generated [21]. The cilia that are constructed are short and immotile, and exhibit large nodules at their tips. This result suggests that sea urchin ciliary construction is different from *Chlamydomonas* flagellar construction in that sea urchin embryos may use a kinesin-II independent mechanism to first extend a procilium. A second possibility is that the kinesin-II complex is

Table 1
Members of the KIF3 (kinesin-II) family of kinesins

Organism	Name	Mouse homologue	Dimeric partner	Ref.
Chlamydomonas	FLA-10	KIF3A	KIF3B-like	[12,19]
	KIF3B-like	KIF3B	FLA-10	
	KAP3-like	KAP3		
Sea urchin	SpKRP85	KIF3A	SpKRP95	[5,7,40]
	SpKRP95	KIF3B	SpKRP85	
	SpKAP115	KAP3		
C. elegans	CeKRP85	KIF3A	ceKRP95	[11,25,26]
	CeKRP95	KIF3B	ceKRP85	
	CeKRP115	KAP3		
	CeOSM3		ceOSM3	
Drosophila	KLP64D	KIF3A	KLP68D??	[39,55]
	KLP68D	KIF3B	KLP64D??	
Xenopus	KIF3A-like	KIF3A	Xklp3	[47,48,56]
	XKLP3	KIF3B	KIF3A-like	
	KAP3-like	KAP3		
Mouse	KIF3A		KIF3B or KIF3C	[6,9,10,41–43]
	KIF3B		KIF3A	
	KIF3C		KIF3A	
	KAP3			

Table 2
Polypeptide subunits of the raft complex in *Chlamydomonas* and the identified sequence homologues in *C. elegans* and mouse (adapted from Ref. [12])

	Chlamydomonas	*C. elegans*	Mouse
Complex A	p144		
	p140		
	p139		
	p122		
Complex B	p172	OSM-1	
	p88		
	p81		
	p80		
	p74		
	p72		
	p57/p55		
	p52	OSM-6	NGD5
	p46		
	p27		
	p20		

only partially inhibited by the antibody allowing for partial function of kinesin-II. Regardless, this result indicates that kinesin-II is essential for the construction of full length functioning cilia in the early sea urchin embryo and provides evidence that the kinesin-II ciliary transport pathway is not restricted to *Chlamydomonas*. Additionally, kinesin-II protein is present along the flagella of rat spermatids [22] and the midpiece and flagellum of sea urchin and sand dollar sperm [23], indicating that all motile cilia may utilize kinesin-II for ciliary transport.

The first evidence that kinesin-II is also used in the construction and maintenance of immotile sensory cilia was obtained by studying *C. elegans* mutants that are incapable of avoiding osmotic differences in their environment [24]. Many of these mutants were found to have defective sensory cilia in the neurons that are exposed to the external environment. Both kinesin-II and OSM-3 localize to these sensory cilia as detected by immunofluorescence suggesting that like their *Chlamydomonas* homologues, these complexes might function in transport along the cilia [11]. Indeed, mutations in the Osm3 gene result in worms that are missing their sensory cilia, thus providing genetic evidence that kinesin-II is needed to construct even immotile cilia [25,26].

In an elegant study, Orozco et al. [27] have shown that when either a GFP-OSM-6 or a GFP-KAP fusion protein is expressed in *C. elegans* sensory neurons, each protein is observed translocating along the sensory cilia. Each fusion protein translocates with a rate of 0.6 μm/s and is consistent with the known in vitro rate of kinesin-II. This is a very powerful experiment that supports two very important conclusions. First, it provides direct visualization of a raft component moving along the sensory cilium and second, it strongly supports the hypothesis that the raft complex interacts with kinesin-II.

4. Kinesin-II ciliary transport in vertebrates

While it is clear that invertebrates utilize kinesin-II in ciliary construction and maintenance, until recently it was unknown whether vertebrates also use kinesin-II in ciliary transport. This question was answered by generating mice that possess a deletion of either the *KIF3A* or *KIF3B* gene [28–30]. The first ciliated cells within the embryo are found in the embryonic node where each cell possesses a single cilium that is first detected around embryonic day 7.5 [31–33]. The embryonic node is important in establishment of left-right asymmetry [31–33], and interestingly, in humans [34] and mice [35], there has been a persistent correlation of left-right asymmetry defects with adult ciliary defects.

Deletion of either the *KIF3A* or *KIF3B* gene results in embryos that are missing the cilium that is normally present on every nodal cell [28–30]. In addition, embryos subsequently exhibit bilateral or no expression of the molecular markers of the left-right determination pathway (i.e. Pitx2, lefty-2), and randomization of cardiac looping before the embryos die at embryonic day 10.5, thus making a connection between embryonic nodal cilia and left-right asymmetry. Wild type nodal cilia are chiral and may be normally motile. The chiral movement of the cilia and the architecture of the node together have been proposed to produce a net flow of fluid toward the left side of the node [29,30]. This flow may enrich an unknown morphogen to one side of the embryo by their concerted movement where it can then interact with an unknown receptor thus establishing the first asymmetry within the embryo. In KIF3 null animals, the cilia are absent and 'nodal flow' is lost, therefore the initial left-right asymmetry is never established

[28–30]. While this is a very attractive model, further experimentation is needed to assess its validity. Additionally, mutant embryos exhibit anterior-posterior defects, neurological defects and severe growth retardation first noticeable at day 8.5–9.0, which may be independent of or secondary to the ciliary defects [28–30].

5. Kinesin-II and photoreceptor transport

While it is clear that *C. elegans* use the kinesin-II transport pathway for their immotile sensory cilia, it is unclear whether mammalian immotile sensory cilia (e.g. photoreceptor cell) also use this pathway. KIF3 family members have been shown biochemically and by immunofluorescence to be present in the connecting cilia of photoreceptors from many different species [36,37]. However, there is no evidence that kinesin-II actually functions in ciliary transport in these cells. In fact, KIF3A protein is also present in the ribbon synapses of photoreceptors at a much higher concentration than along the connecting cilium, suggesting it may have a role in axonal transport or synaptic transmission [38].

6. Neuronal functions for KIF3 family members

There is quite a bit of evidence that suggests that kinesin-II may be an anterograde motor used to transport vesicular cargoes from neuronal cell bodies to axonal terminals. During *Drosophila melanogaster* embryogenesis, KLP64D and KLP68D mRNA is most abundant in neurons of the central nervous system and a subset of peripheral nervous system neurons, suggesting a function in axonal transport [39]. In fact, KLP68D protein is restricted primarily to cholinergic neurons. KLP64D mutants fail to transport choline acetyltransferase out of their cell bodies, suggesting that kinesin-II in neurons may transport soluble proteins along axons [54].

In *C. elegans*, two different kinesin-II complexes have been identified and the expression of both is restricted primarily to neurons. Germline transformation of worms with Osm3:lacZ and Osm3:GFP fusion proteins result in detectable signal exclusively within 26 chemosensory neurons [11,26]. When the same experiment was performed with the kinesin-II subunits ceKRP95:GFP and ceKAP:GFP, signal was detected throughout the nervous system including the chemosensory neurons [11]. Staining of worms with antibodies to ceKRP95 and OSM-3 identified strong signal within the ciliated region of the chemosensory neurons and punctate staining throughout the nervous system [11]. This punctate staining is very similar to the membranous vesicle staining that has been observed in sea urchin embryos [40] and mouse neurons [9,10,38,41–43] and supports a role for kinesin-II in transport of membranous cargoes in axons and during mitosis.

In mouse, all three kinesin motor subunits, KIF3A, KIF3B and KIF3C, are expressed in most neuronal cell types throughout the nervous system, suggesting that kinesin-II might have a role in axonal transport [9,10,38,41–43]. Biochemical and immunofluorescent experiments indicate that while a portion of the motor pool interacts with membranous vesicles, a large portion of the protein appears to be soluble [9,10,38,41,42]. All three KIF3 motor subunits accumulate on the proximal side of a sciatic nerve ligation, which is consistent with each motor subunit participating in anterograde axonal transport [9,41,42]. However, the identity of the cargo(es) is not known at this time, except that the potential cargo is not the same synaptic vesicle precursors that are transported by KIF1A [41]. Interestingly, KIF3A was found to be highly enriched in the synaptic ribbon of photoreceptor cells, suggesting that kinesin-II might be responsible for delivery of synaptic components to these synapses [38]. Further experiments (i.e. gene knockout or cargo identification) will need to be conducted to establish the functions kinesin-II is performing in axonal transport.

7. Kinesin-II involvement in melanophore transport

A role for kinesin-II in the transport of pigment granules (melanosomes) has recently been identified in *Xenopus* melanophores. Melanosomes aggregate and disperse along microtubules in response to the concentration of intracellular cAMP, which can be altered by melatonin (aggregation) and melanocyte stimulating hormone (MSH) (dispersion) [44,45]. These observations suggest that microtubule motors

are most likely responsible for the movement of the melanosomes within the cell. Indeed, when melanosomes are biochemically purified from melanophores, they are capable of bidirectional movement along microtubules [46]. Interestingly, in vitro and in vivo movement of melanosomes is not exclusively unidirectional during periods of aggregation or dispersion. While melanosomes will tend toward one direction, they will occasionally reverse their direction for a short period of time, indicating that counteracting plus and minus end directed motors are both present. Rogers et al. [46] found that kinesin-II and dynein both co-purify with *Xenopus* melanosomes suggesting that they might be the motors responsible for the transport of melanosomes to the plus ends (kinesin-II) and minus ends (dynein) of microtubules.

Experiments by Tuma et al. provide functional data that kinesin-II is responsible for transporting melanosomes to the plus end of microtubules [47]. They expressed a dominant negative form of Xklp3 consisting of the stalk and tail domain, but lacking the motor domain in melanophores to determine whether pigment dispersion would be affected. The transfected cells were treated with melatonin to aggregate melanosomes and subsequently with MSH to disperse the melanosomes. Cells expressing mutant Xklp3 do not exhibit melanosome dispersion, supporting the conclusion that kinesin-II is the motor responsible for melanosome dispersion.

It will be interesting to see whether kinesin-II is responsible for pigment granule movement in other pigmented cells, or whether this is a specialized function for *Xenopus* melanophores. The most exciting consequence of these results is that in vitro melanosome movement can be used in conjunction with biochemical, cell biological and genetic techniques to identify kinesin-II interacting proteins as well as the signaling cascade used to regulate kinesin-II activity.

8. Kinesin-II involvement in the secretory transport pathway

Evidence from a series of provocative experiments suggests that kinesin-II may be involved in transporting proteins from the ER to the Golgi apparatus [48]. Le Bot et al. [48] provide biochemical and immunofluorescent evidence that wild type Xklp3 (a KIF3B homologue) co-localizes primarily with vesicles of the so-called intermediate compartment, which exists between the ER and Golgi in cultured frog XL177 epithelial cells. Upon treatment with brefeldin A (BFA), Xklp3 staining was found to partially co-localize with vesicular structures that also stained for the KDEL receptor, but not with any Golgi markers, further suggesting that Xklp3 is not a Golgi associated motor.

Le Bot et al. also performed a series of experiments in which they expressed the same dominant negative Xklp3 that was used by Tuma et al. [47] in an A6 frog epithelial cell line. Surprisingly, in cells expressing the mutant Xklp3, both wild type and mutant kinesin-II interaction with vesicular structures is lost. In these transfected cells, the structure of the Golgi apparatus is unaltered, but staining of O-linked glycosylated proteins by a lectin from *Helix pomatia* is no longer detected. This lack of staining by the *H. pomatia* lectin is also observed when protein synthesis is inhibited in wild type cells. From these experiments, the authors suggest that kinesin-II is not required to maintain the structure or localization of the Golgi apparatus within the cell, but rather is required for delivery of components of the glycosylation machinery and/or substrates to the *cis*-Golgi from the ER.

This result is surprising since cytoplasmic dyneins are believed to be responsible for the movement of vesicles from the ER to Golgi in most cells [49]. In most cells, the Golgi apparatus co-localizes with the microtubule-organizing center (MTOC), where the minus ends of microtubules are situated. In these cells, minus end directed motors transport vesicles from the ER to the Golgi apparatus. However, in polarized epithelial cells the minus ends of microtubules are located near the apical surface. Golgi stacks are often located near the nucleus, away from the minus ends, thus making possible the use of a plus end directed motor for ER to Golgi trafficking. While the microtubule polarity and organization have not been established in A6 or XL177 cells, they may retain microtubule organization that is observed in normal polarized epithelial cells.

Since kinesin-II does not appear to have a role in Golgi localization, its function may be to counteract the activity of dynein to transport vesicles from the

ER, through the so-called intermediate compartment to the *cis*-Golgi in polarized cells. While Le Bot et al. [48] did not show that kinesin-II and dynein function antagonistically to each other, this antagonism appears to occur in other kinesin-II pathways. It will be interesting to know whether kinesin-II performs a similar ER to Golgi trafficking function in other cell types and organisms or whether this function is unique to the frog polarized epithelial cells types used in this study.

Additional circumstantial evidence for kinesin-II involvement in Golgi trafficking comes from the localization of neuronally enriched KIF3C. KIF3C was found to co-localize with the Golgi marker giantin in neurons [9], but no functional studies have been reported showing that KIF3C or kinesin-II is an active participant in ER to Golgi trafficking in these or any other cells in any organisms besides *Xenopus*.

9. Evidence for KIF3 family involvement in mitosis

There is limited evidence that raises the possibility that kinesin-II has some function during cell division. In *Chlamydomonas*, FLA-10 protein is most abundant near the centrioles and the mitotic spindle in cells that are undergoing mitosis [50], which could signal a function in mitotic spindle formation and/or possibly involvement in spindle dynamics during mitosis. This hypothesis is supported by the identification of several temperature sensitive FLA-10 alleles, in combination with mutant alleles at the *APM1* locus, that display synthetic cell division defects [51]. However, none of these FLA-10 or AMP1 mutants exhibit cell division defects on their own.

Similar evidence for kinesin-II involvement in mitosis was obtained in early stage sea urchin embryos. SpKRP85 protein is present on the mitotic apparatus of dividing sea urchin embryos, where it co-localizes with detergent extractable vesicles [40]. However, the association of kinesin-II with the mitotic apparatus is transient, not continuing beyond the early cell divisions. In these early sea urchin embryos, kinesin-II could be responsible for delivering vesicular material and membranes to the prospective cleavage furrow.

Further evidence for kinesin-II involvement in mitosis was obtained from a yeast two-hybrid screen in which the human spKAP115 homologue, SMAP (Smg GDS-associated protein), was found to interact with HCAP (human chromosome-associated polypeptide). Shimizu et al. suggest that SMAP may interact with mitotic chromosomes through HCAP and has a role in tethering chromosomes to the spindle or chromosome movement [52,53]. However, there are no functional data that support this conclusion.

While it is possible that kinesin-II performs some specialized or minor role in mitosis, three sets of experiments suggest that kinesin-II is not an essential mitotic kinesin. First, injection of a kinesin-II antibody that inhibits motor activity into sea urchin embryos does not have any deleterious effects on mitosis in these cells [21]. Second, mouse embryos lacking either motor subunit of kinesin-II develop normally until embryonic day 8, indicating that normal cell division occurs without functioning kinesin-II [28–30]. Third, *Drosophila* larvae that lack either kinesin-II motor subunit do not exhibit mitotic defects [54]. While an essential role for kinesin-II during mitosis is doubtful, more in-depth analysis will be needed to determine whether there are any subtle mitotic defects in cells that are missing or have defective kinesin-II subunits.

10. Unresolved issues about kinesin-II function

Since the initial identification of kinesin-II in sea urchin, kinesin-II homologues have been identified in almost every species examined. Studying these homologues has aided in the identification of many different potential functions for the kinesin-II motor complex in numerous contexts. In the future, these potential functions will need to be more closely dissected to determine whether a function identified in one cell type and organism applies to other cell types or organisms. While there is convincing evidence that kinesin-II has a role in ciliary construction and maintenance in numerous cell types and organisms, its role in membrane vesicle transport in axons and during mitosis and its role in ER to Golgi transport are less well understood. The latter may represent highly specialized functions of the kinesin-II complex and may not be applicable to all cell types or organisms.

Important future questions include: How is the motor activity of kinesin-II regulated? What are

the cargoes of kinesin-II and how is their interaction regulated? Does kinesin-II interact with 'raft' complexes in non-ciliated cells like neurons? Are defects in components of the kinesin-II ciliary transport pathway responsible for human ciliary defects? Since kinesin-II homologues exist in almost every eukaryotic organism examined, exploitation of the strengths of each experimental system should make answering many of these questions easier.

References

[1] L.S.B. Goldstein, Z. Yang, Annu. Rev. Neurosci. (1999).
[2] C.E. Walczak, T.J. Mitchison, Cell 85 (1996) 943–946.
[3] N. Hirokawa, Curr. Opin. Neurobiol. 7 (1997) 605–614.
[4] L.S.B. Goldstein, A.V. Philp, Annu. Rev. Cell Dev. Biol. 15 (1999) 141–183.
[5] D.G. Cole, S.W. Chinn, K.P. Wedaman, K. Hall, T. Vuong, J.M. Scholey, Nature 366 (1993) 268–270.
[6] H. Yamazaki, T. Nakata, Y. Okada, N. Hirokawa, Proc. Natl. Acad. Sci. USA 93 (1996) 8443–8448.
[7] K.P. Wedaman, D.W. Meyer, D.J. Rashid, D.G. Cole, J.M. Scholey, J. Cell Biol. 132 (1996) 371–380.
[8] J.M. Scholey, J. Cell Biol. 133 (1996) 1–4.
[9] Z. Yang, L.S. Goldstein, Mol. Biol. Cell 9 (1998) 249–261.
[10] V. Muresan, T. Abramson, A. Lyass, D. Winter, E. Porro, F. Hong, N.L. Chamberlin, B.J. Schnapp, Mol. Biol. Cell 9 (1998) 637–652.
[11] D. Signor, K.P. Wedaman, L.S. Rose, J.M. Scholey, Mol. Biol. Cell 10 (1999) 345–360.
[12] D.G. Cole, D.R. Diener, A.L. Himelblau, P.L. Beech, J.C. Fuster, J.L. Rosenbaum, J. Cell Biol. 141 (1998) 993–1008.
[13] K.G. Kozminski, P.L. Beech, J.L. Rosenbaum, J. Cell Biol. 131 (1995) 1517–1527.
[14] G. Piperno, K. Mead, Proc. Natl. Acad. Sci. USA 94 (1997) 4457–4462.
[15] G.J. Pazour, B.L. Dickert, G.B. Witman, J. Cell Biol. 144 (1999) 473–481.
[16] G.J. Pazour, C.G. Wilkerson, G.B. Witman, J. Cell Biol. 141 (1998) 979–992.
[17] K.G. Kozminski, Methods Cell Biol. 47 (1995) 263–271.
[18] K.G. Kozminski, K.A. Johnson, P. Forscher, J.L. Rosenbaum, Proc. Natl. Acad. Sci. USA 90 (1993) 5519–5523.
[19] Z. Walther, M. Vashishtha, J.L. Hall, J. Cell Biol. 126 (1994) 175–188.
[20] J.L. Rosenbaum, D.G. Cole, D.R. Diener, J. Cell Biol. 144 (1999) 385–388.
[21] R.L. Morris, J.M. Scholey, J. Cell Biol. 138 (1997) 1009–1022.
[22] M.G. Miller, D.J. Mulholland, A.W. Vogl, Biol. Reprod. 60 (1999) 1047–1056.
[23] J.H. Henson, D.G. Cole, C.D. Roesener, S. Capuano, R.J. Mendola, J.M. Scholey, Cell Motil. Cytoskeleton 38 (1997) 29–37.
[24] L.A. Perkins, E.M. Hedgecock, J.N. Thomson, J.G. Culotti, Dev. Biol. 117 (1986) 456–487.
[25] M.A. Shakir, T. Fukushige, H. Yasuda, J. Miwa, S.S. Siddiqui, Neuroreport 4 (1993) 891–894.
[26] M. Tabish, Z.K. Siddiqui, K. Nishikawa, S.S. Siddiqui, J. Mol. Biol. 247 (1995) 377–389.
[27] J.T. Orozco, K.P. Wedaman, D. Signor, H. Brown, L. Rose, J.M. Scholey, Nature 398 (1999) 674.
[28] J.R. Marszalek, P. Ruiz-Lozano, E. Roberts, K.R. Chien, L.S. Goldstein, Proc. Natl. Acad. Sci. USA 96 (1999) 5043–5048.
[29] S. Nonaka, Y. Tanaka, Y. Okada, S. Takeda, A. Harada, Y. Kanai, M. Kido, N. Hirokawa, Cell 95 (1998) 829–837.
[30] S. Takeda, Y. Yonekawa, Y. Tanaka, Y. Okada, S. Nonaka, N. Hirokawa, J. Cell Biol. 145 (1999) 825–836.
[31] K. Sulik, D.B. Dehart, T. Iangaki, J.L. Carson, T. Vrablic, K. Gesteland, G.C. Schoenwolf, Dev. Dyn. 201 (1994) 260–278.
[32] D. Bellomo, A. Lander, I. Harragan, N.A. Brown, Dev. Dyn. 205 (1996) 471–485.
[33] R.P. Harvey, Cell 94 (1998) 273–276.
[34] B.A. Afzelius, CRC Crit. Rev. Biochem. 19 (1985) 63–87.
[35] J. Chen, H.J. Knowles, J.L. Hebert, B.P. Hackett, J. Clin. Invest. 102 (1998) 1077–1082.
[36] V. Muresan, E. Bendala-Tufanisco, B.A. Hollander, J.C. Besharse, Exp. Eye Res. 64 (1997) 895–903.
[37] P.L. Beech, K. Pagh-Roehl, Y. Noda, N. Hirokawa, B. Burnside, J.L. Rosenbaum, J. Cell Sci. 109 (1996) 889–897.
[38] V. Muresan, A. Lyass, B.J. Schnapp, J. Neurosci. 19 (1999) 1027–1037.
[39] P.A. Pesavento, R.J. Stewart, L.S. Goldstein, J. Cell Biol. 127 (1994) 1041–1048.
[40] J.H. Henson, D.G. Cole, M. Terasaki, D. Rashid, J.M. Scholey, Dev. Biol. 171 (1995) 182–194.
[41] H. Yamazaki, T. Nakata, Y. Okada, N. Hirokawa, J. Cell Biol. 130 (1995) 1387–1399.
[42] S. Kondo, R. Sato-Yoshitake, Y. Noda, H. Aizawa, T. Nakata, Y. Matsuura, N. Hirokawa, J. Cell Biol. 125 (1994) 1095–1107.
[43] H. Aizawa, Y. Sekine, R. Takemura, Z. Zhang, M. Nangaku, N. Hirokawa, J. Cell Biol. 119 (1992) 1287–1296.
[44] P.J. Sammak, S.R. Adams, A.T. Harootunian, M. Schliwa, R.Y. Tsien, J. Cell Biol. 117 (1992) 57–72.
[45] M.M. Rozdzial, L.T. Haimo, Cell 47 (1986) 1061–1070.
[46] S.L. Rogers, I.S. Tint, P.C. Fanapour, V.I. Gelfand, Proc. Natl. Acad. Sci. USA 94 (1997) 3720–3725.
[47] M.C. Tuma, A. Zill, N. Le Bot, I. Vernos, V. Gelfand, J. Cell Biol. 143 (1998) 1547–1558.
[48] N. Le Bot, C. Antony, J. White, E. Karsenti, I. Vernos, J. Cell Biol. 143 (1998) 1559–1573.
[49] J.K. Burkhardt, Biochim. Biophys. Acta 1404 (1998) 113–126.
[50] M. Vashishtha, Z. Walther, J.L. Hall, J. Cell Sci. 109 (1996) 541–549.

[51] F.G.D. Lux, S.K. Dutcher, Genetics 128 (1991) 549–561.

[52] K. Shimizu, H. Kawabe, S. Minami, T. Honda, K. Takaishi, H. Shirataki, Y. Takai, J. Biol. Chem. 271 (1996) 27013–27017.

[53] K. Shimizu, H. Shirataki, T. Honda, S. Minami, Y. Takai, J. Biol. Chem. 273 (1998) 6591–6594.

[54] K. Ray, S.E. Perez, Z. Yang, J. Yu, B.W. Ritchings, H. Steller, L.S. Goldstein, J. Cell Biol. 147 (1999) 507–518.

[55] R.J. Stewart, P.A. Pesavento, D.N. Woerpel, L.S. Goldstein, Proc. Natl. Acad. Sci. USA 88 (1991) 8470–8474.

[56] I. Vernos, J. Haesman, C. Wylie, Dev. Biol. 157 (1993) 232–239.