The UNC-104/KIF1 family of kinesins

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Most UNC-104/KIF1 kinesins are monomeric motors that transport membrane-bounded organelles toward the plus ends of microtubules. Recent evidence implies that KIF1A, a synaptic vesicle motor, moves processively. This surprising behavior for a monomeric motor depends upon a lysine-rich loop in KIF1A that binds to the negatively charged carboxyl terminus of tubulin and, in the context of motor processivity, compensates for the lack of a second motor domain on the KIF1A holoenzyme.

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Abbreviations
ALS amyotrophic lateral sclerosis
GFP green fluorescent protein

Introduction

The kinesins form a superfamily of microtubule-stimulated ATPases that share a variably conserved ~350 amino acid 'motor domain' that contains binding sites for microtubules and adenine nucleotides [1,2,3•]. The prototypic (or conventional) kinesin [4,5], as well as numerous more recently discovered kinesins, contains two catalytic subunits, but some kinesins contain just a single motor domain [1,2,3•]. Most kinesins serve as ATP-dependent motors for transport of intracellular cargo along microtubules. Each specific type of kinesin moves unidirectionally relative to microtubule polarity [6,7], and most kinesins move toward microtubule plus ends [1,2,3•]. On the basis of sequence variability within the motor domain, kinesins can be classified into at least ten families (see the Kinesin Home Page: http://www.blocks.fhcrc.org/~kinesin/). One such family, UNC-104/KIF1, is the subject of this review.

Mutations in the *Caenorhabditis elegans* gene, *unc-104*, have long been known to cause uncoordinated and abnormally slow movement in worms [8–10]. A transposon insertion strategy was used to clone *unc-104*, and in 1991, the predicted protein sequence was reported to contain an amino terminus that bore close resemblance to the motor domains of all the kinesin superfamily members known at that time [11]. Electron microscopic analysis of *unc-104* mutant worms demonstrated exceptionally high levels of synaptic vesicles in the cell bodies of neurons, coupled with an abnormal paucity of synaptic vesicles in axon termini [12]. On the basis of this molecular and ultrastructural evidence UNC-104 was proposed to be a novel kinesin for anterograde fast axonal transport of synaptic vesicles toward microtubule plus ends [12].

UNC-104 represents the first known member of a family of closely related kinesins, most of which appear to be monomeric, microtubule plus-end-directed motors for membrane transport. The next family member to be discovered was originally called KIF1, and it was one of many novel proteins found by a PCR-based screen for kinesin motor-like domains in mouse brain [13]. When a cDNA fragment of *kif1* was used to screen mouse brain libraries, evidence for two distinct forms of KIF1 protein emerged. The original KIF1 was renamed KIF1A, and on the basis of sequence and functional studies, it appears to be a neuron-enriched protein and the mouse equivalent of *C. elegans* UNC-104 [14]. The other mouse protein was named KIF1B, and was initially proposed to be a motor for moving mitochondria toward microtubule plus ends in a broad variety of cell types [15]. Additional members of the UNC-104/KIF1 family have since been detected in *C. elegans* [16], *Drosophila* [17–19], humans [20–22], rats [23,24], *Dictyostelium* [25•], striped bass [26], and a thermophilic fungus [27].

The remainder of this review will focus on findings from studies on UNC-104/KIF1 reported in the past year. Most noteworthy in that regard has been an explanation at the molecular level of the processive motor activity for a fragment of KIF1A [28••,29•]. This unexpected behavior for a monomeric motor is all the more interesting in light of a report that a fragment of UNC-104, which is also monomeric, is not processive [30••]. Additional recent findings that will be reviewed include evidence for a dimeric UNC-104/KIF1 family member in *Dictyostelium* [25•], for multiple splice variants of KIF1B [31•,32•], and for roles that UNC-104/KIF1 proteins may play in disease [33,34].

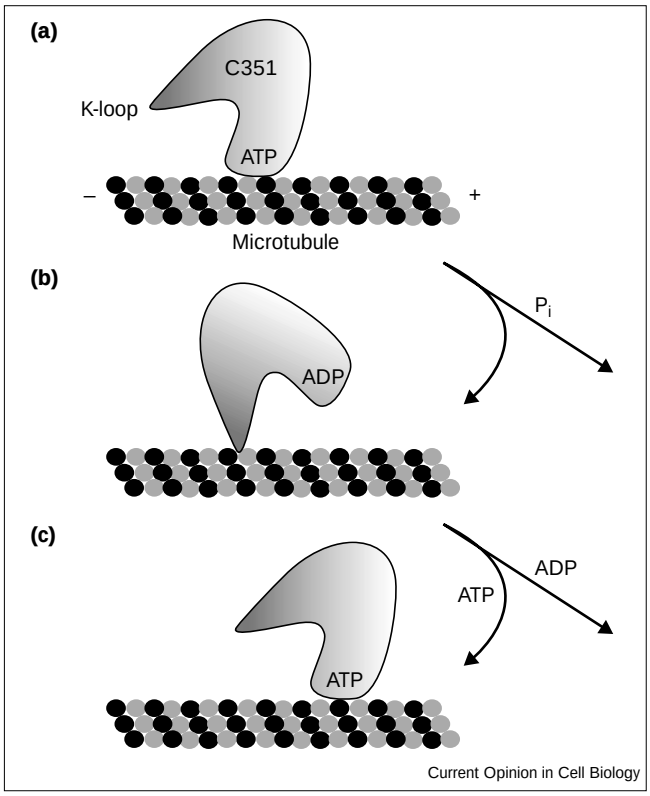
Processivity of KIF1A

The processivity of a motor protein refers to how far, on average, it can move along a cytoskeletal track before it loses its grip and then diffuses away from the track. Conventional kinesin is well known for its high processivity [35,36]. A recent study incorporating biophysical, enzymatic and ultrastructural data led to an elegant model that may explain conventional kinesin's processivity in detailed molecular terms [37••]. Distilled to its basic essence, the model states that when ATP exchanges for ADP on a kinesin motor domain bound to a microtubule, the neck-linker region of that motor domain stiffens and enables its companion motor domain to swivel past it and bind closer to the plus end of the same microtubule. Stated more simply, conventional kinesin is highly processive because it walks along a microtubule in a manner that rarely results in both of its feet (motor domains) detaching from the microtubule at the same time. A vivid animation of this model can be found at the web site, http://motorhead.ucsf.edu/valelab/.

A reasonable prediction from this model is that monomeric motors should not be processive, at least when studied at the level of individual molecules. Mother Nature never skimps on surprises however, and to aficionados of molecular motors, an early 1999 report from the Hirokawa laboratory [38••] that a recombinant fragment of the monomeric kinesin KIF1A can move processively is one of her more amusing recent revelations. The most convincing evidence for this unexpected behavior came from studies of C351, a fusion protein containing the first 356 amino acids of KIF1A coupled to residues 330–351 of conventional kinesin heavy chain. The entire core catalytic region of KIF1A was present in C351, which was covalently coupled to a red fluorescent Alexa dye. By comparison, Alexa-red-labeled K351, which corresponds to the first 351 residues of the conventional kinesin catalytic subunit and is known to be monomeric, was not observed to move along microtubules in motility assays for single motor molecules. A sequence comparison of C351 and K351 suggested that a 'K-loop' (a cluster of six lysines uniquely present in the catalytic core of C351) might be important for its processivity. Bolstering this suspicion were the findings that hexameric polylysine inhibited the microtubule-stimulated ATPase activity of C351 and that a modified C351 lacking the K-loop did not bind to microtubules in single motor assays [38••].

In January 2000, the Hirokawa laboratory published two additional papers that shed light on how C351 can move processively. For one of the papers, cryo-electron microscopy was used to demonstrate attachment of the K-loop, which is strongly positively charged, to the 'E-hook', or glutamate-rich, negatively charged carboxyl termini of α-tubulin and β-tubulin [29•]. The second paper provided evidence that the K-loop associates with the E-hook only during the weak binding state of C351 for tubulin, which follows hydrolysis of ATP. During this weak binding state, the K-loop is thought to anchor C351 on the microtubule until the motor domain can move closer to the microtubule plus end, by either a power stroke or ratcheted Brownian motion. The motor domain then exchanges its ADP for ATP, an event that triggers strong binding by the motor domain and dissociation of the K-loop. The cycle is completed when the ATP is hydrolyzed, the affinity of the motor domain for the microtubule is weakened substantially, and binding of the K-loop to the microtubule is favored once again [28••]. A summary of this model for KIF1A processivity is shown in Figure 1.

Figure 1



A model for the processivity of KIF1A. C351, a truncated version of the monomeric synaptic vesicle motor KIF1A, has been shown to move processively along microtubules [38••]. This is thought to be accomplished by weak binding of a positively charged, polylysine-rich domain (K-loop) on C351 to the negatively charged, glutamate-rich carboxyl terminus (E-hooks) of α-tubulin and β-tubulin. Binding to the microtubule of the K-loop of C351 and dissociation of its motor domain from the microtubule are believed to be triggered by hydrolysis of ATP by the motor domain [28••,29•]. With the K-loop maintaining an attachment to the microtubule, the motor domain is able to move toward the microtubule plus end by either ratcheted Brownian motion or a power stroke and then reattach to the microtubule upon exchange of ADP for ATP. Repetition of this cycle is thought to move the C351 motor processively toward the plus end of the microtubule [28••].

UNC-104 is not processive

Like KIF1A, UNC-104 contains a K-loop, and thus might also be expected to move processively along microtubules. Evidence from the Vale laboratory does not agree with this prediction. In this case, a fusion protein (UNC-104_{635}–GFP) containing the first 653 residues of UNC-104 coupled to green fluorescent protein (GFP) [39,40] was used in single motor assays. The fusion protein was never observed to move even 40 nm along a microtubule, the shortest distance that could be detected [30••]. By comparison, C351 was reported by the Hirokawa and colleagues [38••] to move an average distance of ~840 nm.

What could account for the processivity of C351 but not UNC-104_{635}–GFP? Several explanations are possible, but two come foremost to mind. First, the K-loop of KIF1A (KNKKKKK) comprises six lysines, including five in succession, within a span of seven total amino acids. By comparison, the K-loop of UNC-104 comprises only five lysines (KKKKSNK) and a two residue gap between the fourth and fifth lysines. Thus, the density of negative charge in the K-loop is higher for KIF1A than for UNC-104 and may be insufficient in UNC-104 to support processive motility. Arguing against that viewpoint, Okada and Hirokawa [28••] report that a modified C351, containing a K-loop of just four

continuous lysines, was able to move processively, albeit not quite as well as its unmodified counterpart.

A second possible explanation for the processivity of C351 but not UNC-104_{635}–GFP is their different ATPase activities. Each C351 molecule reportedly hydrolyzes 110 ATP molecules per second in the presence of microtubules [38••], whereas the turnover rate for UNC-104_{635}–GFP under comparable conditions was reported to be just 5.5 ATP molecules per second [30••]. Such a slow rate of ATP hydrolysis may signal that the duty ratio for UNC-104_{635}–GFP (the proportion of its ATPase cycle during which the motor is bound to the microtubule) is so low that it precludes the possibility of an individual molecule moving processively.

It is important to emphasize that processivity has not been convincingly demonstrated for full length versions of either KIF1A or UNC-104. Perhaps the processive motility exhibited by C351 is non-physiological and reflects the absence of the carboxyl terminus of KIF1A or the 22 amino acid stretch of conventional kinesin sequence at the carboxyl terminus of C351. Likewise, maybe modifying UNC-104 by replacing some of its carboxyl terminus with GFP converted it from a processive to a non-processive motor. Clearly, further investigation will be required to establish whether full length KIF1A and UNC-104 are processive. In the meantime, however, the example of the KIF1A-derived protein C351 provides fascinating insight into mechanisms by which molecular motors, even single-headed varieties, can move processively.

A dimeric UNC-104/KIF1 family member

At least one member of the UNC-104/KIF1 family was recently reported to be naturally dimeric. The protein in question, DdUnc104, was purified from extracts of *Dictyostelium discoideum* using a video-enhanced light microscopic assay for organelle transport *in vitro* to monitor purification [25•]. Five peptide sequences obtained from DdUnc104 enabled corresponding cDNAs to be cloned, and a full length predicted amino acid sequence to be obtained. The subunit molecular weight was thus predicted to be ~248,000, but the measured sedimentation coefficient and Stoke's radius of the purified protein indicated a native molecular weight of ~480,000. The logical conclusion is that DdUnc104, in contrast to other UNC-104/KIF1 proteins (but see below), is dimeric [25•].

Another UNC-104/KIF1 family member, the human protein KIF1C, which is localized to the Golgi complex [21], can also exist as a dimer [41], at least under some circumstances. A yeast two-hybrid screen, in which the carboxy-terminal 350 residues of KIF1C was used as bait, yielded 14-3-3 proteins and a carboxy-terminal fragment of KIF1C itself as binding partners [41]. In addition, evidence for KIF1C dimers was obtained by chemical crosslinking and immunoprecipitation studies of cultured human embryonic kidney 293 cells [41]. It must be noted, however, that apparent dimerization was dramatically enhanced in 293 cells that transiently overexpressed KIF1C by transfection. It is therefore possible that KIF1C dimerizes only when it is present at concentrations far higher than those normally encountered *in vivo*.

Splice variants of KIF1B

Mouse KIF1B was heralded for years as a microtubule motor specifically targeted to mitochondria [15]. In biology, things rarely turn out to be as simple as they initially appear, and KIF1B is no exception. The first published clue that it would be more complicated was reported in June 1999 by Conforti *et al.* [32•]. While searching for the slow Wallerian degeneration mutation on mouse chromosome 4, they stumbled upon a *kif1b* exon that bore high homology to a comparable region in *kif1a*. RT-PCR and screening of a cDNA library confirmed that the novel *kif1b* exon is expressed in mouse brain and encodes a protein with a predicted molecular weight of ~204,000.

Just four months later, Gong and colleagues [31•] provided evidence for far greater complexity of *kif1b* gene products. The net result of their analysis is that *kif1b* may encode as many as eight different splice variants that fall into two general classes of molecular weights, ~130,000 (KIF1Bp130) and ~204,000 (KIF1Bp204). The former class corresponds to the originally described KIF1B [15], and the latter is identical to the KIF1B isoform described by Conforti *et al.* [32•]. Except for a six amino acid insert unique to KIF1Bp204, KIF1Bp130 and KIF1Bp204 are predicted to be identical for their first 706 amino acids. Beyond that point, KIF1Bp130 and KIF1Bp204 have an additional 491 and 1,110 amino acids, respectively. Two additional exons were found within the nearly identical 706 amino acid sections of KIF1Bp130 and KIF1Bp204 but outside of the motor domain. These exons can be expressed individually, together, or not at all for both KIF1Bp130 and KIF1Bp204. Therefore, there may be four different splice variants of each of the two classes of KIF1B or eight KIF1B splice variants altogether [31•]. In light of the idea that the originally described KIF1B (KIF1Bp130) binds to mitochondria via its unique carboxy-terminal region, a question that naturally arises is whether the cargo for KIF1Bp204 is something other than mitochondria.

UNC-104/KIF1 proteins in disease

Two recent papers [33,34] raise the possiblity that underexpression or overexpression of UNC-104/KIF1 proteins may lead to disease. Kageyama and colleagues [34] reported that the *kif1b* gene, among many others, was found within a distal region of chromosome 1p, where loss of heterozygosity is commonly observed in human neuroblastomas. They also observed that low levels of mRNA expression for KIF1B are correlated with subsets of particularly aggressive neuroblastomas grown in primary culture [34]. In a study of a transgenic mouse model for amyotrophic lateral sclerosis (ALS), Dupuis and colleagues [33] reported upregulation of mRNA expression for KIF1A. These data identify KIF1A and KIF1B as proteins that may contribute to neuroblastoma

or ALS when expressed at improper levels, but much more compelling evidence is required before either protein can be elevated beyond candidate status.

Conclusions

The evidence that C351, a truncated version of the monomeric synaptic vesicle motor from mouse KIF1A, moves processively along microtubules represents a fascinating and unexpected discovery [28••,29•,38••]. What makes this discovery all the more intriguing is the finding that UNC-104_{635}–GFP, a truncated version of the equivalent *C. elegans* protein UNC-104, is not a processive motor [30••]. This contrasting set of results might indicate that requirements for synaptic vesicle transport motors vary according to species or body size. Before any such conclusions can be made, though, it will be necessary to determine whether the full length versions of KIF1A and UNC-104 behave the same as their truncated fusion protein derivatives.

The issue of KIF1B heterogeneity also represents an important area for future investigation. The finding that the *kif1b* gene encodes two classes of KIF1B protein, each with a distinct carboxy-terminal tail [31•,32•], suggests functional heterogeneity for KIF1B. Mitochondria were originally proposed to be the cargo for KIF1B [15], but there may be additional types of KIF1B cargo, and if so, their identities remain to be discovered.

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