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Minireview

Universal and Unique Features of Kinesin Motors: Insights from a Comparison of Fungal and Animal Conventional Kinesins

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Kinesins are microtubule motors that use the energy derived from the hydrolysis of ATP to move unidirectionally along microtubules. The founding member of this still growing superfamily is conventional kinesin, a dimeric motor that moves processively towards the plus end of microtubules. Within the family of conventional kinesins, two groups can be distinguished to date, one derived from animal species, and one originating from filamentous fungi. So far no conventional kinesin has been reported from plant cells. Fungal and animal conventional kinesins differ in several respects, both in terms of their primary sequence and their physiological properties. Thus all fungal conventional kinesins move at velocities that are 4 – 5 times higher than those of animal conventional kinesins, and all of them appear to lack associated light chains. Both groups of motors are characterized by a number of group-specific sequence features which are considered here with respect to their functional importance. Animal and fungal conventional kinesins also share a number of sequence characteristics which point to common principles of motor function. The overall domain organization is remarkably similar. A C-terminal sequence motif common to all kinesins, which constitutes the only region of high homology outside the motor domain, suggests common principles of cargo association in both groups of motors. Consideration of the differences of, and similarities between, fungal and animal kinesins offers novel possibilities for experimentation (e. g., by constructing chimeras) that can be expected to contribute to our understanding of motor function.

Key words: Cargo association / Kinesin / Molecular motors / Sequence organization.

Conventional Kinesins: A Brief Summary

In 1985, a novel type of motor protein was isolated from squid neural tissue (Vale *et al.*, 1985), bovine brain (Brady, 1985) and sea urchin eggs (Scholey *et al.*, 1985) that could move microtubules *in vitro* in the presence of ATP, and was named kinesin. Since then, kinesins have been found to constitute a superfamily of proteins with now more than 100 members. The defining common denominator of kinesins is the catalytic motor domain, which enables kinesin to hydrolyze ATP in the presence of microtubules. Within members of the superfamily the position of this domain varies: it can be found at either the N- or C-terminal, or in a central part of the molecule. Within these three subgroups further distinctions can be made, depending on the oligomerization states and homology in the neck regions adjacent to the core motor domains (see Vale and Fletterick, 1997). Using these criteria the kinesin superfamily has been divided into 10 subfamilies.

This structural heterogeneity is thought to reflect functional specifications: kinesins have been found to fulfill various roles in the cell, e. g., as transporters of a wide variety of membranous organelles, chromosomes, and protein complexes (for reviews see Hirokawa, 1998; Lane and Allan, 1998; Steinberg, 1998), and as modulators of the *gestalt* (structure) of the microtubule cytoskeleton (Sharp *et al.*, 1999) and of microtubule stability (Desai *et al.*, 1999). The best studied kinesin subfamily comprises the conventional kinesins. 14 conventional kinesins from 10 different organisms have been sequenced completely, six animal and four fungal species, covering a wide evolutionary spectrum in both kingdoms (Figure 1A, for a review see Hirokawa, 1998). In mouse and man, three different kinesin genes have been found (Nagakawa *et al.*, 1997; Xia *et al.*, 1998). Two of their gene products (KIF5a and KIF5c) are specific for neural tissues, while the third (KIF5b) is expressed ubiquitously. Fungal and animal kinesins form two distinct subgroups within the conventional kinesins. The overall sequence homology is about 30%, while within each subgroup the homology is 45% (animals) and 60% (fungi). Conventional kinesins from animals are heterotetramers consisting of two identical motor molecules, the heavy chains (100 – 130 kDa), and two light chains (60 – 70 kDa). Rotary shadow EM images reveal two globular heads, followed by a rod or stalk that is sometimes kinked in the middle, and a fan-shaped tail where the light chains bind in animal kinesins (Hirokawa *et al.*, 1989;

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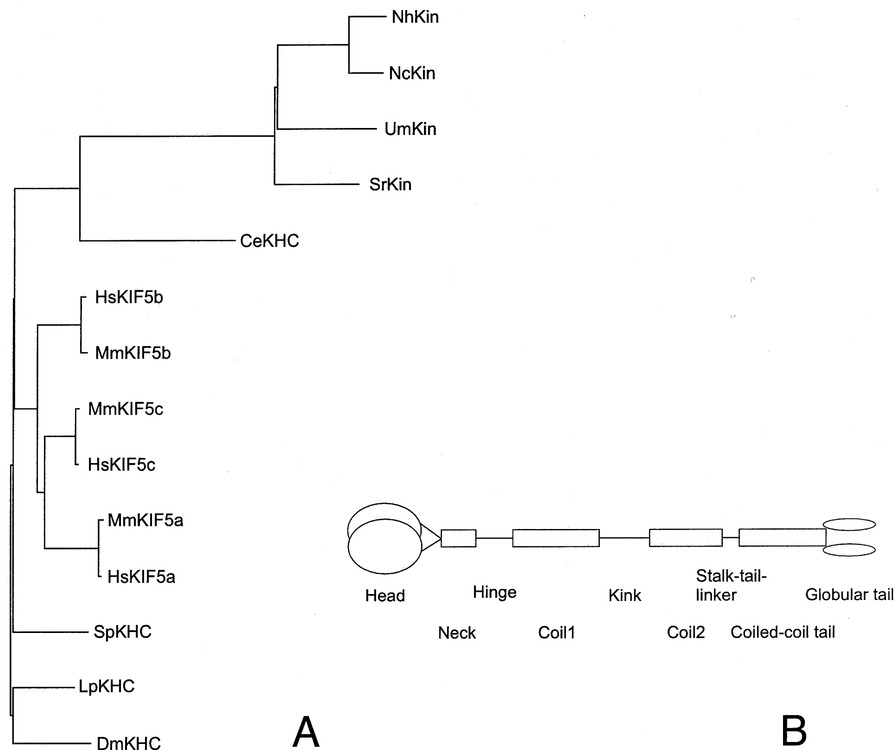

Domain homologies of fungal and animal kinesins

Species	Head	Neck	Hinge	Coil1	Kink	Coil2	Stalk-tail-linker	Coiled-coil tail	Globular tail	whole molecule
All	55%	35%	0%	20%	10%	5%	0%	60%	5%	30%
Fungi	75%	75%	15%	60%	35%	40%	30%	80%	20%	60%
Animals	70%	65%	5%	45%	30%	15%	30%	85%	10%	45%
Animals*	75%	70%	15%	60%	70%	75%	70%	90%	10%	65%

* Animals without *C. elegans*

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Fig. 1 A Phylogenetic Tree of Conventional Kinesins.
(A) The tree was constructed by the clustal w program of the GCG package. The GenBank accession numbers for the included sequences are: U86521 (NhKin), L47106 (NcKin), U92845 (UmKin), AJ225894 (SrKin), L19120 (CeKHC), X65873 (HsKIF5b), U86090 (MmKIF5b), AF067180 (MmKIF5c), ABO11103 (HsKIF5c), AF067179 (MmKIF5a), U06698 (HsKIF5a), X56844 (SpKHC), J05258 (LpKHC) and M24441 (DmKHC). (B) A schematic drawing showing the subdomains of conventional kinesins. Non-coiled-coil domains are in the first, coiled-coil domains in the second row. (C) Table showing the homologies of the subdomains of conventional kinesin within the two kingdoms.

Bloom and Endow, 1995). The ability of the kinesin heavy chain (KHC) to form dimers is based on the existence of several stretches that form a coiled-coil according to a prediction based on the Lupas algorithm (Lupas *et al.*, 1991). According to this prediction, the KHC dimer can be divided into 9 subdomains (Figure 1B). These domains are: the catalytic motor domain or head (domain 1), neck (domain 2), hinge (domain 3), coil 1 (domain 4), kink (domain 5), coil 2 (domain 6), stalk-tail-linker (domain 7), coiled-coil tail (domain 8) and globular tail (domain 9).

Both the ATP binding site (Kull *et al.*, 1996; Sablin *et al.*, 1996; Gulick *et al.*, 1998; Yang *et al.*, 1990) and the microtubule-binding interface (Woehlke *et al.*, 1997; Alonso *et al.*, 1998) have been mapped to the catalytic motor domain. The neck and its link to the head are important for the determination of the directionality of movement (Henningsen and Schliwa, 1997; Case *et al.*, 1997; Endow and Waligora, 1998). The neck of animal kinesins has been found to form a coiled-coil (Kozielski *et al.*, 1997; Morii *et al.*, 1997; Tripet *et al.*, 1997) and to be involved in kinesin's processivity (Romberg *et al.*, 1998), while both the neck and hinge have been shown to play a role in mechanochemical coupling (Grummt *et al.*, 1998).

The *Drosophila* conventional kinesin is observed in two conformations resulting in a 9S and 6S sedimentation constant when placed on sucrose gradients of high and

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low ionic strength, respectively (Hackney *et al.*, 1992). This is now believed to be the consequence of folding at the kink that brings the tail in contact with the head domain, thereby regulating its ATPase activity. C-terminal deletion constructs of KHC coexpressed with different KLC constructs (Verhey *et al.*, 1998) in cultured cells localize to the cell periphery, supporting the model of inactivation by folding of the C-terminus if no cargo is present (Verhey *et al.*, 1998).

From the very beginning, conventional kinesin has been believed to play a role in organelle transport (Vale *et al.*, 1985; Brady, 1985; Schroer *et al.*, 1988). In support of this contention, kinesin has been found to colocalize with a variety of organelles (for a review, see Hirokawa, 1998; Lane and Allan, 1998) including certain types of axonal vesicles (Schnapp *et al.*, 1992), endoplasmic reticulum, Golgi apparatus, mitochondria and lysosomes. Although a potential interaction site of *Neurospora crassa* kinesin with its cargo has now been located within the coiled-coil tail (Kirchner *et al.*, manuscript submitted), the search for a kinesin receptor has so far proved elusive. The only molecule proposed to be involved in kinesin organelle binding is kinectin (Kumar *et al.*, 1995; Yu et al., 1995), a 160 kDa coiled-coil protein with an N-terminal transmembrane region. It seems to interact with kinesin as well as dynein (Blocker *et al.*, 1997), but its exact role in motor-cargo interaction is still under debate (for reviews see Burkhardt, 1996; Sheetz, 1996). Finally, a kinesin heavy chain knockout mouse (Tanaka *et al.*, 1998) as well as a *Drosophila* KHC null mutant (Gho *et al.*, 1992) have been generated. While both of these were lethal, some less severe mutations in the *Drosophila* KHC gene were viable (Hurd and Saxton, 1996). In contrast, conventional kinesin is nonessential in fungi (Seiler *et al.*, 1997; Wu *et al.*, 1998; Lehmler *et al.*, 1997), and its deletion yields informative phenotypes.

Fungal vs. Animal Conventional Kinesins

What are the differences and similarities between fungal and animal kinesins, and what can be learned about their function from an analysis of sequence features? Besides the similarities just discussed, there are two functional differences between the groups that stand out. Firstly, fungal kinesins display a much faster *in vitro* gliding velocity (2.0–2.5 μm per second) than do their animal counterparts (0.6–0.8 μm per second). Secondly, until now, no kinesin light chains have been found to copurify with the heavy chains in fungi. Are these differences (and similarities) reflected in the amino acid sequence? With about 55% sequence homology, the head is the second-most highly conserved domain of the conventional kinesins (Figure 1C). The head sequences of fungal conventional kinesins comprise groups of amino acids that are highly specific for fungal kinesins and differ significantly

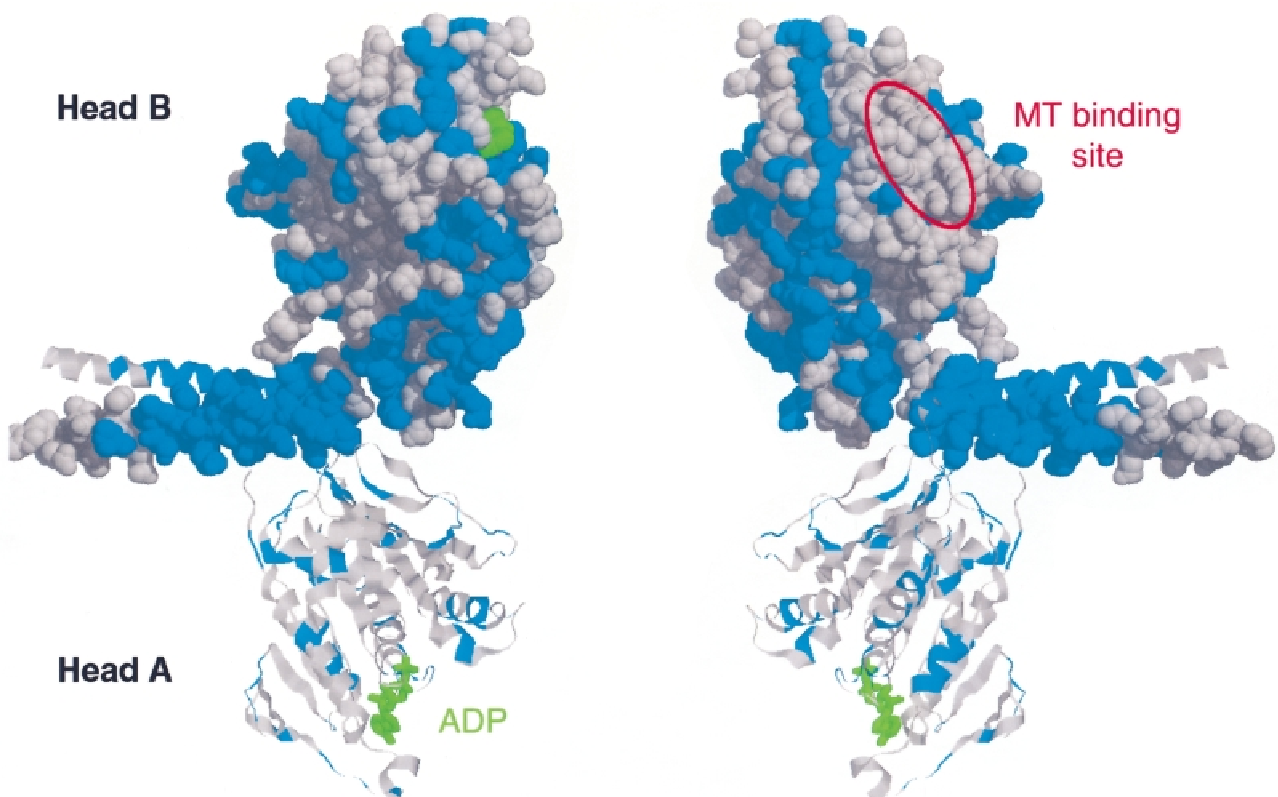

Fig. 2 Crystallographic Model of the Rat Kinesin Motor Domain (Kozielski *et al.*, 1997).
Head A is depicted as a ribbon, head B as a space-filling structure. Positions where fungal kinesins display group-specific sequence features are displayed in blue. The sites of ADP- and microtubule-binding are indicated.

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from their animal relatives. If these specific patches are mapped in the 3D-crystal structure it becomes apparent that all of them are located on the molecule's surface (Figure 2). Whereas catalytically important structures such as P-loop, switch I and II (Vale, 1996) and the L12-α5 microtubule binding site are well conserved (as they are for the entire superfamily) the remainder of the molecule displays a patchwork of common and more or less specific residues. Among fungi, parts of helix 1 (amino acid 62–69 in NcKin), helix 2 (amino acid 121–126) and helix 3 (amino acid 185–190) are conserved as well as small groups of residues of the β-sheets 4 and 5 (133–176) and loop 10 (217–227). The sequence alignments suggest a 7 amino acid insertion before β-sheet 1c. For none of these regions any functional role has been reported so far. The proximity of helix 3, in particular, to the bound nucleotide may indicate some influence of the fungi-specific exchanges on the enzymatic properties of fungal kinesins, but a simple phylogenetic diversion without functional implications of some of the specific residues cannot be excluded either. Interestingly, the loop 11 which is disordered in all available structures (Kull *et al.*, 1996; Sablin *et al.*, 1996; Sack *et al.*, 1997; Kozielski *et al.*, 1997; Gulick *et al.*, 1998) comprises a subgroup-specific pattern (GKTGASGQT in fungi). That the N-terminal part of this sequence matches the P-loop sequence motif seems to be a coincidence. It has been suggested that this structure participates in microtubule binding (Sosa *et al.*, 1997) but crucial involvement in communication between the nucleotide and microtubule binding sites is also possible (Vale, 1996; Gulick *et al.*, 1998). Either scenario may imply a functional importance of this motif for the high velocities of fungal kinesins.

One of the most obvious regions of dissimilarity between fungal and animal kinesins is the N-terminal part of the neck. It shows the highest degree of kingdom-specific exchanges within the first two domains (Figure 2). Because it has also been shown to be important for the velocity of movement (Grummt *et al.*, 1998), it is conceivable that the differences observed in this domain are directly linked to this parameter. Additionally, the fungal-specific loop 10 (located between β-sheets 6 and 7; amino acid 217–227 in NcKin) is found close to the neck region in the crystal structure, suggesting that it is important for head/neck communication and coordination during movement. However, fast gliding velocities may be an additive effect requiring tuning of several structural domains.

The hinge regions show no visible conservation among conventional kinesins, except between very closely related species (e. g., mouse/man homologs), and also vary in length. Within the fungi this region is rich in prolines and glycines, suggesting a high degree of flexibility. Its conformation but not its primary structure seems to be important as the hinge of *Drosophila melanogaster* can be substituted into SrKin without loss in gliding velocity, whereas a proline-rich region from an unrelated protein cannot (Grummt *et al.*, 1998).

Coil 1 seems to be of relatively uniform length (ca. 130 aa) in all conventional kinesins. Although homology between all kinesins is only about 20%, the homology within the two kingdoms is still quite prominent (60% in fungi, 60% in animals without *Caenorhabditis elegans*; Figure 1C).

In animal conventional kinesins the kink is still well-conserved (70% homology for animals without *C. elegans*) while the kinks of fungal kinesins are about 20 amino acids shorter and only half as conserved (35% homology). Nevertheless, the same back-folding mechanism that is discussed for kinesin from *D. melanogaster* (Hackney *et al.*, 1992) could also exist in *Neurospora crassa*, since deletions of the kink results in severely compromised *in vivo* activity (Kirchner *et al.*, manuscript submitted).

Coil 2 is the most variable region concerning its size. It varies between about 90 residues in *C. elegans*, *N. crassa* and *Nectria haematococca*, and about 200 residues in animal kinesins. Sequence conservation exists only between close relatives. In animal kinesins, however, the last 30 amino acids are well conserved. This region is strongly suspected to bind the light chains (Diefenbach *et al.*, 1998).

Because of the widely accepted importance of the tail for the association of kinesin with its cargo(es) and the potential regulatory functions localized in this domain, the 3 C-terminal domains have been analyzed in more detail (Figure 3). The break in the coiled-coil prediction that marks the transition between the stalk and the tail (stalk-tail-linker) is still partially conserved in animals, but not in fungi, either in length or in primary structure. An exception are the close relatives *N. crassa* and *N. haematococca*. It should be noted that in animals the stalk-tail-linker is located 30–40 amino acids downstream from its fungal counterpart. The region in animal kinesins that aligns with the fungal kinesin stalk-tail-linker contains the light-chain binding site as identified by Diefenbach *et al.* (1998; highlighted in green in Figure 3). The region in fungal kinesins that aligns with the animal kinesin stalk-tail-linker is highly conserved among fungi and might represent a site of protein protein interaction (highlighted in blue in Figure 3). Whether it represents a site for interaction with light chain equivalents is questionable since no light chains have been found to copurify with KHC in fungi. Also, this region is already part of the tail coiled-coil of fungal kinesins, only separated from the following conserved region by a discontinuity in the heptad repeat pattern (marked with three blue dashes in Figure 3). The differences in the positioning of this conserved stretch of ca. 30 amino acids in fungi and animals (blue box and green box in Figure 3, respectively) suggests different molecular geometries of the conventional kinesin stalk and tail in fungi and in animals.

One segment of about 50 amino acids in length (red box in Figure 3) clearly stands out in the coiled-coil tail. It is highly conserved between all conventional kinesins and the only large segment outside the catalytic motor domain that exhibits a high degree of homology. Based on an *in vivo* analysis of mutant kinesins (Kirchner *et al.*, manuscript submitted), this region may participate in cargo binding. If confirmed, this would suggest that the basic mech-

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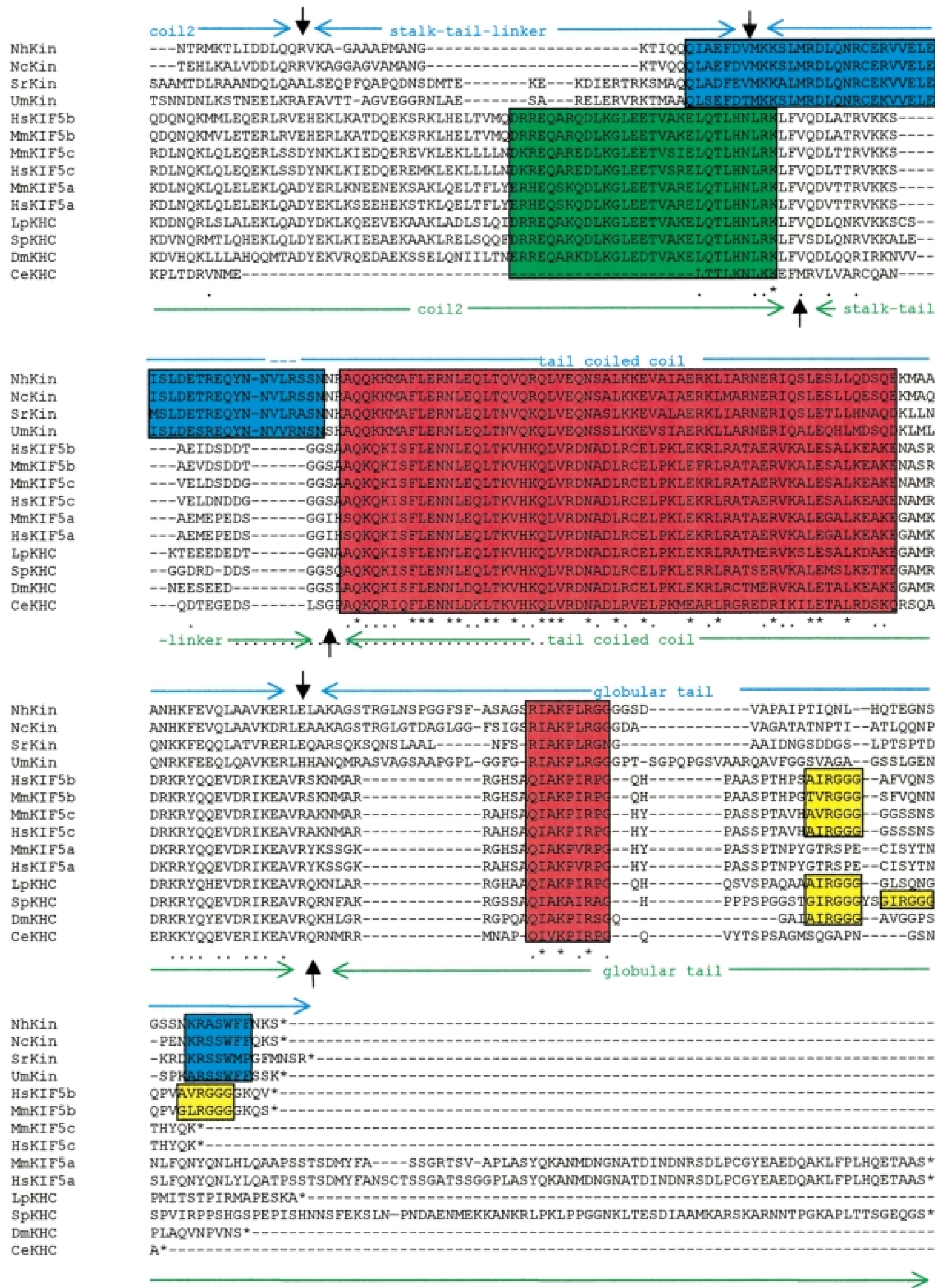

Fig. 3 A Sequence Alignment of the Tail of Conventional Kinesins.
Motifs conserved between all conventional kinesins are highlighted in red. Fungal-specific sequences are highlighted in blue, the animal-specific region thought to represent the light chain binding site is highlighted in green. Domains are marked by blue and green horizontal arrows, respectively, with black vertical arrows indicating the boundaries. An irregularity in the fungal tail coiled-coil is marked with three blue dashes. A motif occuring only in some animal kinesins is shown in yellow.

anisms of cargo association are conserved in both animal and fungal kinesins.

The globular tail domain is of variable length. Almost nonexistent in *C. elegans*, it extends over ca. 120 amino acids in KIF 5a and sea urchin kinesin, and about 70 amino acids in fungal kinesins (see Figure 3). It contains a short motif conserved in all conventional kinesins (IAKP-(L/I/V)RxG, highlighted in red in Figure 3) as well as a protein kinase A consensus site KRSSW) conserved only in fungal kinesins (boxed in blue in Figure 3). Another interesting feature is the motif (A/T/G)(V/I/L)RGGG, which occurs even twice in KIF5b and SpKHC (highlighted in yellow in Figure 3). Both the common and class-specific conserved motifs of conventional kinesins might be associated with different aspects of kinesin regulation. The (A/T/G)(I/V/L)RGGG motif is reminiscent of the RGG repeat that constitutes an RNA binding motif (Burd and Dreyfuss 1994). However, the RGG repeat usually occurs 5 times in RNA-binding proteins, so the question of an RNA-binding site in conventional kinesins remains open.

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Comparison of Kinesin Mutants from Animals and Fungi

While all animal kinesin knock-outs that have been performed so far (*C. elegans*, *D. melanogaster*, mouse) were lethal because of damage to neural tissues (Gho *et al.*, 1992; Saxton *et al.*, 1991; Patel *et al.*, 1993; Tanaka *et al.*, 1998) all three fungal kinesin null mutants from *N. crassa* (Seiler *et al.*, 1997), *N. haematococca* (Wu *et al.*, 1998) and *Ustilago maydis* (Lehmler *et al.*, 1997) are viable and display informative phenotypes. In *N. crassa* the most prominent feature of the kinesin null mutant is its reduced hyphal growth speed (1.4 vs. 6.8 cm/day, Seiler *et al.*, 1997). Also, the hyphae become thicker and less regular in shape, and the *Spitzenkörper*, an accumulation of vesicles at the growing tip, is much reduced. However, the transport of microscopically visible organelles in hyphae appears normal (Seiler *et al.*, 1997). In the *N. haematococca* kinesin null mutant the growth rate is reduced to 50% and the shape of hyphae also becomes more irregular, but hyphae appear thinner and the distribution of mitochondria near the growing tip seems to be disturbed (Wu *et al.*, 1998). The *Spitzenkörper* is smaller and loses its central positioning in the growing tip. In *U. maydis*, the dikaryon of the null mutant exhibits delayed growth after mating, and plant pathogenicity is almost completely abolished (Lehmler *et al.*, 1997). Also, the organization of the subapical part of the growing tip is altered.

In animal kinesin null mutants two interesting cellular defects have been observed. In *D. melanogaster*, the kinesin null mutant shows axonal swellings packed with supposedly stalled organelles (Hurd and Saxton, 1996), while in mouse KIF5b null mutants cells cultured from the visceral yolk sack displayed a perinuclear clustering of mitochondria (Tanaka *et al.*, 1998).

The common denominator of all these null mutants is defective coordination of a process presumably involving the transport of membranous organelles. Interestingly, in two cases conventional kinesin has been found to play a role in mitochondrial distribution (Wu *et al.*, 1998; Tanaka *et al.*, 1998), while in another study the transport of organelles visible in the light microscope was unaffected (Seiler *et al.*, 1997). Thus, so far no unifying picture has emerged, and the participation of kinesin in a variety of cellular processes may be fine-tuned in a class-specific and possibly even species-specific fashion.

Conclusions

The comparison of animal and fungal conventional kinesins allows to differentiate between basic features of kinesin function (conserved between all conventional kinesins) and more specialized aspects that have evolved in a subset of conventional kinesins to meet specialized needs. The catalytic and microtubule-binding activities, the subdomain pattern (Figure 1B), the folding mechanism to inhibit the ATPase, and the prospective cargo binding site all seem to be expressed in a similar fashion in animal and fungal kinesins.

On the other hand, fungal kinesins apparently lack light chains, which could reflect the fact that, as primitive multicellular organisms in which basically a single cell type is reiterated, they can do with a less complex regulatory machinery for kinesin. The higher speed of fungal kinesins could be necessary to maintain the extremely fast longitudinal growth of *N. crassa* (ca. 1 μm/s under optimal conditions).

Finally, one important question stands out. Conventional kinesins have been found to be associated with, or affect the distribution of, a variety of organelles in different organisms with no unifying pattern emerging. While conventional kinesin knock-outs affect similar organelles in highly divergent species (e. g., mitochondria in the mouse and *N. haematococca*), even in closely related species the effects may vary (e. g., *N. haematococca* and *N. crassa*). So far the available evidence neither suggests a clear difference between animals and fungi, nor a striking similarity between closely related species. On the other hand, the region in the tail domain conserved between all conventional kinesins seems to be important for cargo binding and can be expected to associate with a similarly conserved partner on the cargo. To resolve this apparent contradiction will be an exciting task in the future.

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