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Kinesin Kar3 and Vik1 Go Head to Head

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The yeast kinesin motor protein Kar3 forms a heterodimer with a nonmotor protein Vik1. A study in this issue by Allingham et al. (2007) reveals that Vik1 unexpectedly has a structure similar to a kinesin motor domain yet lacks a nucleotide-binding site and is thus catalytically inactive. However, this does not hinder movement of the heterodimer because other features of the remarkably divergent Vik1 motor domain are retained, including the ability to bind microtubules.

Textbooks and animations usually show kinesins walking processively (that is, hand-over-hand) along microtubules, suggesting that this is the predominant mode of kinesin movement (Figure 1). The real picture, however, should not be painted in monochrome. We now know that, for example, nonprocessive kinesins do not move in this way but rather detach from the microtubule after a single power stroke. There are also motors that make use of electrostatic interactions to move continuously along microtubules. Allingham et al. (2007) now add a new color to the spectrum of kinesin movement, reporting that the yeast Kinesin-14 motor Kar3 uses a second motor head Vik1, which lacks a catalytic site, to move along microtubules (Figure 1).

Kar3 was first discovered in yeast in a screen for mutants with defects in karyogamy (the fusion of two nuclei during mating). The affected gene turned out to encode a C-terminal kinesin (the class now termed the Kinesin-14 proteins). Subsequent studies showed genetic interactions between Kar3 and a protein called Cik1, and homology searches using Cik1 uncovered Vik1, which plays a role in mitosis and meiosis. Together with biochemical approaches, these studies confirmed that Kar3 forms a heterodimer with either Cik1 or Vik1 in vivo (Barrett et al., 2000; Chu et al., 2005; Sproul et al., 2005). At the time, the primary sequences of Cik1 and Vik1 offered no clues concerning their nature and function. Now, X-ray crystallography has uncovered what no one would have guessed in their wildest dreams—that Vik1 (and presumably Cik1 as well) is a modified kinesin (Allingham et al., 2007). The C-terminal globular domain has a structural fold that is unmistakably kinesin-like, with a central eight-stranded β sheet flanked by three α helices on either side. The loops extending from the core structure are in most cases truncated when compared to other kinesins. This is remarkable because alignments of Vik1 and Cik1 with kinesins do not show any significant degree of similarity. Notably, the hallmark

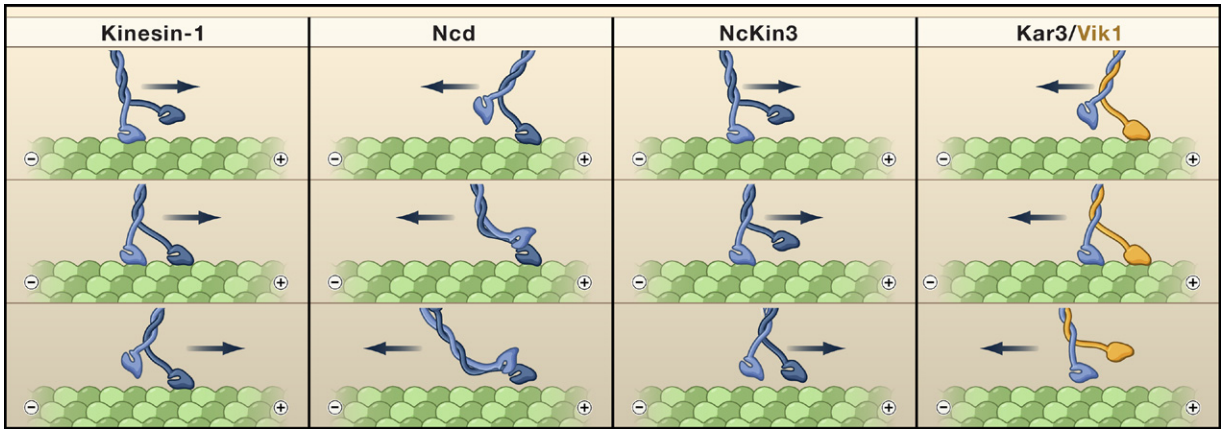

Figure 1. Different Modes of Kinesin Movement
The conventional view of kinesin motility applies to Kinesin-1 motors, which step hand-over-hand in a walking fashion (left panel). The prime example of a nonprocessive kinesin is the retrograde Ncd motor that detaches after one powerstroke toward the microtubule minus-end (second panel). A similar mechanism may apply to the fungal Kinesin-3 motor NcKin3 that moves along microtubules in the plus-end direction (third panel). Allingham et al. now provide evidence that to aid the power stroke, the yeast Kar3/Vik1 heterodimer uses a degenerate motor domain (orange) that lacks ATPase activity (right panel).

motifs of kinesins in the nucleotide-binding region are also absent.

Given these significant differences, does Vik1 have any kinesin-like function? The answer is yes. Vik1, like kinesin, binds to microtubules and shows structural similarities to kinesin in regions implicated in microtubule binding. Vik1 binds even tighter to microtubules than Kar3. Of course, this observation poses an interesting problem: If you walk with one functional leg (that is, Kar3) and a crutch that gets stuck in the ground (Vik1), you have to pull hard to get it unstuck. Binding assays by Allingham et al. show that the Kar3/Vik1 dimer binds most tightly to microtubules when ADP is present. The binding of the heterodimer is as tight as that of Vik1 alone, suggesting that the dimer binds via Vik1 under these conditions, and that the catalytically active Kar3 head uses the energy of ATP hydrolysis to remove its partner's head from the microtubule.

How does motility occur during this process? The authors suggest two alternative power stroke models, both based on motility of the Ncd protein in *Drosophila*, the best-studied Kinesin-14 motor. Ncd forms homodimers by virtue of a long coiled-coil region N-terminal to the motor core. A body of experimental evidence has led to a model in which Ncd first attaches to microtubules with one motor head then uses the energy of ATP hydrolysis to tilt the coiled-coil dimerization domain by ~70° before detaching from the filament (Endres et al., 2006; Yun et al., 2003). Allingham et al. have a similar picture in mind to explain motility of Kar3/Vik1 (Figure 1). However, the similarity stops here because the current model of Ncd motility does not predict binding of the second head to microtubules. Do the heads of Kar3/Vik1 bind to consecutive tubulin dimers, or do they bind to tubulin in neighboring protofilaments? This study is eye opening because it raises these new questions concerning the movement of nonprocessive motors.

The comparison of Kar3/Vik1 and Ncd is interesting with regard to general aspects of kinesin motility. In these microtubule minus-end-directed motors, motility is apparently achieved by a power stroke with either two identical motor heads or one catalytically active head in combination with an inactive one. What about plus-end-directed motors? Adio et al. (2006) recently discovered a nonprocessive Kinesin-3 motor that most likely also uses a power stroke mechanism but moves toward microtubule plus-ends (Figure 1). This motor also has two identical motor heads but uses only one of them. There is no evidence that the second motor head interacts with microtubules, and thus the motor resembles Ncd. It cannot be said with certainty whether this or any other kinesin motor forms heterodimers with a partner head lacking catalytic activity in vivo because genomic searches may fail to detect partners due to a low degree of sequence conservation, as in the case of Cik1 and Vik1. A whole class of kinesins is known that form dimers of two related but nonidentical motor heads (Scholey, 1996). However, they are difficult to express and have not been studied extensively. Once their working principles are known better, these motors may have surprises in store for us. Are all Kinesin-2 motors processive, as reported for mouse KIF3A/B (Zhang and Hancock, 2004)? How do the motor heads of these kinesins influence each other, and how do they co-operate? The functional variability among these motors may be larger than initially expected and more kinesins may be able to form alternative oligomers.

The impact of the Allingham et al. study on the kinesin motor field is one aspect of the Vik1 story, but there is another side to it. It is a prime example of how the analysis of protein structure can have a decisive role in determining biological function. Previous examples in the cytoskeleton field include the discovery that kinesins and myosin motor domains have nearly identical core structures that are themselves similar to G proteins (Vale, 1996) and the identification of FtsZ as a bacterial tubulin homolog (Lowe and Amos, 1998). In each of these cases, their secrets were disclosed only after seeing the structures. Homology searches failed because the primary sequences were only distantly related.

Although Vik1/Cik1 appear to be found only in a small group of fungi, the Saccharomycotina, these new findings suggest that there are likely to be other kinesin-like proteins in other organisms that are so distantly related that they are unrecognizable as such. Vik1 vividly reminds us how far evolution may drive apart paralogous structures. In this case, certain core characteristics (i.e., the fold and the microtubule-binding site) were preserved, but there may be other examples where different selection pressures have retained other features.

We should be prepared for further twists and turns that evolution may have taken along other branches of the phylogenetic tree. Why should evolution have stopped playing its tricks in a small group of yeasts? What about ferns and worms, arthropods and tetrapods? Even well-studied model organisms may hide stealth kinesins and myosins. This is an exciting prospect, and one that may have medical relevance because these distant cousins may be very specific drug targets. With these lessons in mind, we may expect unexpected findings that add yet more color to the kinesin spectrum.

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