Enzymes for Microtubule-dependent Motility*

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Many of the motions by and within cells are dependent on mechanochemical enzymes that interact with cytoskeletal filaments to generate force. For example, myosin interacts with actin filaments to generate the forces for muscle contraction, cytokinesis in animal cells, and some cases of vesicle motion in plant cells (1). Cilia and flagella are constructed from microtubules (MTs)1 and accessory proteins assembled to form the "axoneme," and ATPases called dynein or kinesin derived from MTs and small particles with high contrast optics that associate with MTs and contribute to their motility. Like myosin, they use the chemical energy derived from ATP binding and hydrolysis to force a sliding of adjacent filaments. ATP binding and hydrolysis is rate-limiting in the absence of MTs but is rapidly dissociated following ATP binding to its heavy chain; ATP hydrolysis then proceeds more slowly on the dissociated enzyme. The release of reaction products is rate-limiting in the absence of MTs, but the addition of MTs stimulates product release, resulting in an activation of ATPase activity (16).

Dynein heavy chains can be cleaved at specific sites by nuclease and are present in the absence of vanadate (3, 17). A different UV-stimulated cleavage pattern is observed without vanadate at higher concentrations of vanadate (3). These properties have been used, together with nucleotide and antibody binding, to construct one-dimensional maps of the dynein heavy chains (Fig. 2A) (3, 18). The refinement of these maps and an understanding of their relationships to both the electron microscope images and the binding sites for the other dynein polypeptides are active areas of current work.

Dynein was originally defined as a high molecular weight ATPase that associates with MTs and contributes to their motility (2). The majority of work on dynein has thus far concentrated on axonemal enzymes because of their availability and ease of isolation. The best studied dyneins derive from two sets of "arms" that attach to the "A subfiber" of outer doublet MTs (the subfiber that looks like a complete MT in cross-sections). Each dynein arm appears in the electron microscope to comprise two or three globular domains, depending on the species of origin; these are connected by stalks to a common base (Fig. 1a) (reviewed in Ref. 10). Axonemal dyneins come in several types. The outer and inner arms are made from different polypeptides and have distinct ATPase activities (11).

Axonemal dyneins contain two or three "heavy chains" with apparent molecular masses of 400–500 kDa and also several chains of intermediate (40–120 kDa) and low (15–25 kDa) molecular masses. The specific functions of the smaller chains are unknown, but the identity of one has been determined: a 45-kDa polypeptide of inner arm dynein from the axonemes of *Chlamydomonas* is actin (12). Dynein can be dissociated into multiprotein subunits with several mild treatments. Each globular domain so far studied binds ATP and shows ATP-sensitive MT binding (10). This MT binding in *vitro* is thought to represent the transient association that occurs in *vivo* between the dynein arms and the B subfiber of the outer doublet MTs. Axonemal dynein's opposite end is probably involved in an ATP-insensitive binding to the A subfibers (10), but the exact arrangement of the enzyme in axonemes is still in dispute (3).

Knowledge about axonemal proteins in general and about dynein in particular has profited from a genetic dissection of flagellar motility in *Chlamydomonas* (11). This approach has corroborated the biochemical complexity of dynein. Some mutations that inactivate only a single polypeptide result in the absence of an entire dynein arm; electrophoresis shows that 12 polypeptides are then missing from the axoneme (13). The importance of dynein in regulation of the flagellar wave form is also being analyzed by genetics (3).

Axonemal dynein's nucleotide binding is specific for Mg-ATP (14). Its ATPase activity is strongly inhibited by vanadate (VO43-) (15) but is stimulated by MTs at high concentrations (16). The mechanism of ATP hydrolysis has been examined for outer arm dynein from the cilia of *Tetrahymena* (10). This enzyme binds tightly to MTs in the absence of ATP but is rapidly dissociated following ATP binding to its heavy chain; ATP hydrolysis then proceeds more slowly on the dissociated enzyme. The release of reaction products is rate-limiting in the absence of MTs, but the addition of MTs stimulates product release, resulting in an activation of ATPase activity (16).

Dynein heavy chains can be cleaved at specific sites by nuclease and are present in the presence of ADP and VO4. A different UV-stimulated cleavage pattern is observed without nuclease at higher concentrations of vanadate (3). These properties have been used, together with nuclease and antibody binding, to construct one-dimensional maps of the dynein heavy chains (Fig. 2A) (3, 18). The refinement of these maps and an understanding of their relationships to both the electron microscope images and the binding sites for the other dynein polypeptides are active areas of current work.

Computer processing of light microscopic images (5, 6) has made it possible to assess the movement of small objects in cell extracts (5, 10), spawning an assay for MT motility (7) that has been used to analyze the mechanical action of MT-dependent motors in *vitro*. Axonemal dynein will adsorb to glass and move MTs over that surface in an ATP-dependent manner (20, 21). The polarity of motion observed in *vitro* is the same as that shown for dynein in *situ* (21, 22); axonemal dynein walks along a MT toward its "minus" end, i.e. the end that is slow to add tubulin and that lies proximal to the basal body of the axoneme. The motion is Mg-ATP-specific, vanadate-sensitive, and proceeds at a velocity comparable to that observed in *situ*. Sea urchin outer arm dynein is dissociable by dialysis against low ionic strength into a soluble complex of one heavy chain plus one intermediate chain (IC-1/IC-1) and an insoluble residue. The soluble moiety will move MTs over glass, so a single heavy chain complex (i.e. one head) is sufficient for dynein-driven MT motility (23).

The frequent observation of MT-dependent motility outside an axoneme has led to speculations about the existence of non-axonemal or "cytoplasmic" dyneins. Early work on such enzymes focused on

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1. The abbreviations used are: MT, microtubule; AMP-PNP, adenylyl-5'-yl imidodiphosphate; CTPase, cytidine triphosphatase.

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FIG. 1. Dyneins and kinesins prepared for electron microscopy by J. Heuser (Washington University, St. Louis, MO) using fast freezing and etching (× 250,000). A, protozoan axonemal dynein prepared by U. Goodenough (Washington Univ.). The heads corresponding to the dynein heavy chains are evident. The stems and bases probably correspond to the intermediate and light chains that associate to form the active complex. B, chicken brain kinesin prepared by E. Steuer (Washington Univ.). C, chicken brain kinesin prepared by T. Schroer and M. Sheetz (Washington Univ.).
enzymes are all very similar to dynein from C. elegans, and recent work has greatly expanded our knowledge of their characteristics. The brain enzymes have been visualized in the electron microscope, where they appear as two globular heads connected by stalks to a common base (Fig. 1B) (27, 31). Cleavage of their heavy chains by ADP-Vo-UV results in polypeptides that differ slightly in size from those obtained from axonal dynein (Fig. 2B) (8, 9, 24). Most cytoplasmic dyneins appear to include several chains of lower molecular weight (9, 31). Some have been shown to form ATP-sensitive bundles of MTs (27), and some hydrolize CTP faster than ATP, though this nucleotide will not support motility (32). It seems likely, therefore, that the high molecular weight CTPases mentioned above (30) are cytoplasmic dyneins. Data comparing the ATPase and motility of axonal and cytoplasmic dyneins are summarized in Table 1.

The localizations and functions of cytoplasmic dynein are receiving much current attention. The presence of the enzyme in neurons, where many vesicles move from the axon terminus toward the cell body, is consistent with its serving as a motor for organelle movement toward the minus ends of MTs, e.g. "retrograde" axonal transport (33, 34). Dynein from chick embryo fibroblasts can promote such motion of cell-derived vesicles in vitro (35).

**Kinesin**

During 1985 a factor was identified in the cytoplasm of squid giant axons that could bind MTs to glass and move them along their axes in the presence of ATP (7, 24). This motile activity was frozen by the ATP analog, AMP-PNP (36), and AMP-PNP-stimulated binding to MTs was soon used to purify the motility factor from brain (7, 37) and sea urchin eggs (38). This protein, called kinesin, will bind to MTs of all types, including MTs that have been deacetylated and rendered insensitive to microtubule destabilizing chemicals shown. The N terminus is acetylated. Fragment A is a proteolytic cleavage product that retains ATPase activity, while fragment B has none (redrawn from Ref. 18). C, cytoplasmic dynein heavy chain from brain (9), though the diagram is approximately applicable to all cytoplasmic dyneins known. C, kinesin heavy chain from Drosophila (arrows as in A).

Kinesin comprises at least two polypeptides with relative molecular masses of about 120 and 65 kDa; it migrates on gel filtration columns with a solution molecular mass of about 360 kDa, suggesting that the native molecule contains two copies of each polypeptide (39, 40). Affinity labeling of native kinesin with azido-ATP (24, 40) and affinity labeling of native MTs to kinesin synthesized in vitro (41) show that both the nucleotide and the MT-binding sites reside on the heavier chain. Electron microscopy reveals that kinesin has two small heads at one end connected by a rodlike segment to a feathery tail (Fig. 1C) (24, 42, 43). Some monoclonal antibodies to the larger kinesin polypeptide will block its motility but stimulate its MT-activated ATPase activity. These antibodies recognize a 45-kDa chymotryptic fragment that retains ATP-sensitive MT binding (44). They bind to native kinesin at or near its heads, suggesting that this region of the molecule, like subfragment 1 of heavy meromyosin, contains both the nucleotide and the fiber binding sites (45). Kinesin's feathery tail is the location of at least one epitope on its lower molecular weight component(s) (24).

Polyclonal antibodies have been used to identify the single gene that encodes kinesin's heavy chain in Drosophila (41, 45). This gene has been cloned from Caenorhabditis elegans (29) and Dictyostelium discoideum (30). It is a single gene and is transcribed in all tissues, but the gene is thought to be expressed most highly in growing tissues. This gene encodes a single polypeptide that is most likely to be the heavy chain of cytoplasmic dynein, and the nucleotide triphosphate is hydrolyzed rapidly. The steady state reaction rate is limited by the release of products from the enzyme's active site (47, 48), but unlike myosin, kinesin releases P and holds tightly to MTs. The addition of MgATP to kinesin results in ATP release and thereby activates the ATPase (47).

Kinesins from different sources appear to be rather similar (24). Their enzymatic and motility properties are summarized in Table I. More divergence is seen, however, in the plus-directed MT motors from Acarhydrochaeta testis (25) and Dicyostelium discoideum (9). These kinesins may not show enhanced binding to MTs in the presence of AMP-PNP, but functional criteria suggest that they too are probably kinesins.

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**Fig. 2. One-dimensional maps of the structure of heavy chain polypeptides from microtubule-dependent motor enzymes.**

| A. Sea urchin flagellar dynein heavy chain (475 kd) | B. Bovine brain cytoplasmic dynein (410 kd) | C. Drosophila kinesin (115 kd) |
|---|---|---|
| ATP-MT | --- | ATP-MT |
| Fragment A (head) | Fragment B (tail) | ATP-MT |
| Fig. 2 | --- | ATP-MT |

| Numbers under the line represent kilodaltons. | | No. Terminus is acetylated. Fragment A is a proteolytic cleavage product that retains ATPase activity, while fragment B has none (redrawn from Ref. 18). | | Kinesin heavy chain from brain (9), though the diagram is approximately applicable to all cytoplasmic dyneins known. C, kinesin heavy chain from Drosophila (arrows as in A). | | **Kinesin** | | **Enzymes for Microtubule-dependent Motility** | **Fig. 2.** |
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A comparison of microtubule motility enzymes

Table I

| Property | Axonal dynein | Cytoplasmic dynein | Kinesin |
|----------|---------------|--------------------|---------|
| 1. ATPase activities | | | |
| Substrate preference | ATP >> GTP >> CTP | CTP >> GTP >> ATP | ATP >> GTP |
| ATP turnover/head (±MTs) | 2-6-8 s⁻¹ (16) | 0.3 s⁻¹ (32) | 0.009 s⁻¹ (47) |
| ATP turnover/head (+MTs) | 6-33 s⁻¹ (16) | 2-2.5 s⁻¹ (32) | 9 s⁻¹ (47) |
| Apparent 2nd order rate constant/head for MT binding (m⁻² s⁻¹) | | | |
| 0.7-0.1 | 1.2-6 x 10⁻⁶ (16) | 4.7 x 10⁻⁶ (32) | 9 x 10⁻⁶ (48) |
| 5. 50% inhibition of ATPase by vanadate (µM) | | | |
| 0.01-0.06 (3) | 5-10 (8, 32) | 420 µM (24) |
| 2. Motility in vitro (MT gliding) | | | |
| 1. NTP for MT motility | ATP (21) | ATP (8, 34) | ATP = GTP+ATP (24) |
| Kₐ ATP for motility | ~100 µM (21) | ND* | 20-120 µM (24, 45) |
| Vmax for motility (µm s⁻¹) | 4-8 (20, 21, 23) | 1-2 (8, 34) | 0.5-9.0 (7, 24, 45) |
| Inhibition of motility | | | |
| By vanadate | <1 µM (21) | 1-10 µM (8, 34) | 0.1 x [ATP] (24) |
| By N-ethylmaleimide | <1 mM (21) | <1 mM (8, 34) | >2 mM (7, 24) |
| By AMP-PNP | ND | 2 mM (34) | s[ATP] (24) |

*These rate constants were calculated by measuring the initial slopes of the data describing MT activation of the enzyme's ATPase activity (Fig. 6 in Ref. 48 and Fig. 1 in Ref. 32) and assuming the presence of two active sites/molecule, based on Refs. 31, 39, and 40.

ND, not determined.

Fig. 3. Diagram of kinesin, incorporating the information from Goldstein's, Scholey's, Heuser's, Bloom's, Brady's, and Hirokawa's laboratories (see text for references).

Kinesin's role in cells is a subject of active current investigation. Its prevalence in neurons and its capacity to bind small spheres or vesicles to MTs and move them suggest that it plays a role in particle movement in vivo (7). Kinesin is probably a motor for the motion of cytoplasmic vesicles toward the plus ends of MTs, e.g. "orthograde" axonal transport (24, 33), and it may link MTs with the membranes of endoplasmic reticulum, stretching them to the edge of the cytoskeleton (51). The localization of kinesin in vivo could help to identify kinesin's role in cells, but this issue is still unresolved. Most kinesin is soluble in cell extracts (7), but some is fixed by treatment of cells with aldehydes or cold methanol. Kinesin is concentrated in the spindle poles of several cultured cell types (24). Other studies with different antibodies and cell types have found fixed kinesin on tiny cytoplasmic spheres (52) or diffusely distributed with some concentration along MTs (27). All these patterns can be attributed to membrane or MT binding, consistent with the enzyme's playing a role in membrane-cytoskeleton interactions, but the diversity of localizations precludes strong inferences about kinesin's function. Probes that perturb specific aspects of kinesin's action will therefore be needed to define kinesin's roles in cells. Since motility-blocking antibodies are now available (44) and mutants with modified kinesins are being sought (27), we can expect information about this motor's role in cell behavior rather soon.

Functional Comparison of Dynein and Kinesin

Polarity of Motor Action—For most cases so far studied, dynein moves toward the minus end of a MT (21, 34), while kinesin moves toward the plus (24, 33). One apparent exception was the assignment of plus-directed motility to nematode dynein (8), but this direction has subsequently been corrected (24). The missassignment was a result of dynein's differential effect on tubulin disassembly from the plus and minus ends of MTs (27). There is, however, an organism in which dynein-like molecules appear to be involved in both plus- and minus-directed movements. MT-dependent vesicle transport in Reticulomyxa is bidirectional, and both directions of movement are revived in detergent-extracted cell models by the addition of dynein prepared from this organism (29). Both directions of movement are inhibited by treatments with vanadate or with vanadate-ADP-UV (27), suggesting that dynein-like molecules in this organism contribute to motility in both directions. It remains to be seen whether there are dynein isoforms with opposite directions of action, whether dynein can interact with a "gear box" to reverse its polarity of motion, or whether dynein associates with a kinesin-like molecule to make a bidirectional complex whose function is sensitive to inactivation of only one of the component motors. A monoclonal antibody to kinesin has been found to block both directions of granule motion in extracts of squid axoplasm (53), consistent with the latter idea.

An Analogy with Actin-dependent Motors—The existence of two MT-dependent motors with opposite polarities of motion raises the intriguing question of whether there is an actin-dependent motor that works in the direction opposite to myosin's. The flexibility of individual microfilaments may be too great to support transport toward a free filament end, so it may be only MTs that can sustain a bidirectional motor system. However, many plant cells show bidirectional streaming in their transvacuolar strands, and this appears to be an actin-based motility (1).

Patterns of Movement—Dynein and kinesin differ in the details of their motile behavior. Image processing of light micrographs showing kinesin-coated microspheres moving on MTs reveals a 4-nm step (54). At high ATP concentrations, the bead motion is smooth, and at all ATP concentrations the motion is largely parallel to the MT axis. Microspheres coated with cytoplasmic dynein show a more circuitous motion with a significant component of motion perpendicular to the MT axis and occasional large steps (27). At low ATP or in [ADP] = [ATP], dynein-driven motion of MTs over glass is jittery with steps back and forth as large as a micrometer.

Motor Enzymology and the Value of Inhibitors—Cytoplasmic dynein hydrolyzes high concentrations of CTP faster than ATP, but this hydrolysis appears to be analogous to the increased ATPase activity shown by some axonemal dyneins after treatment with Triton X-100 or by kinesin after binding to some monoclonal antibodies; the enzymes hydrolyze NTP more rapidly but become mechanochemically inactive. Cytoplasmic dynein does not waste the cell's CTP because of the high Kₐ for this reaction (27).

Both axonal and cytoplasmic dyneins show MT activation of their ATPase activities (9, 16, 35). The effect appears more dramatic for the cytoplasmic isozyme because of both a lower basal activity and a 10-fold higher rate constant for MT binding (62) (Table I). The same factors give kinesin an even stronger MT activation than cytoplasmic dynein (47, 48). It is not surprising that the activities of cytoplasmic motors are strongly coupled to MT binding, since ATP hydrolysis without polymer binding cannot promote motility. The motors from axonemes are not as tightly constrained, because the...
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centration of MTs in cilia or flagella is about 60-fold higher than in cytoplasm, and structural considerations make the effective tubulin concentration for axonemal dynein even higher. The dyneins are particularly sensitive to inhibition by vanadate and N-ethylmaleimide, while kinesin is more strongly inhibited by ATP and 

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2 Space constraints have demanded an abbreviated reference list. More complete citations will accompany a reprint.