

and posterior terminal regions are specified differentially. This basic mechanism appears to be instrumental even if the two terminal regions are specified differentially in the same egg and no matter which is the final development of those terminal regions in different species. Thus, it appears that the Torso pathway has been co-opted to match distinct developmental scenarios. Now, it remains to be shown whether Torso signalling is also involved in the development of other short germ animals.

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Dynein Motility: Four Heads Are Better Than Two

Cytoplasmic dynein is a microtubule-based motor protein that transports membranes in cells. The movement driven by a single dynein molecule *in vitro* is not as robust as dynein-driven movements in cells. A new study suggests that transport by multiple dyneins is more similar to cellular motions.

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Of the three major types of cytoskeletal motors — dyneins, kinesins and myosins — only kinesins are strongly processive. Analysis of single molecule runs along microtubules show that kinesins move steadily toward the plus end of microtubules for several microns before detaching. Kinesin processivity arises because the two motors of the dimeric molecule coordinate their chemical and mechanical cycles to move ‘hand-over-hand’ and keep one motor bound to the microtubule throughout motion. By contrast, the motor domains of most dimeric myosins operate independently (a likely exception is the processive transport specialist myosin V). Myosin

heads spend most of their cycle unbound from an actin filament and so many myosin molecules are required to sustain filament movement in reconstitution assays. Cytoplasmic dynein — a minus-end-directed microtubule motor — appears to fall between these extremes. Reconstitution studies reveal that short (< 1 μm) minus-end runs are frequently interrupted by pauses and plus-end motion. So, while dynein molecules can remain attached to microtubules for long periods, they appear to be processive only part of the time.

Meanwhile, in living cells, the minus-end-directed motions of organelles along microtubules often span several microns [1,2]. A sufficient explanation for the difference in processivity between

dynein-mediated movements *in vivo* and *in vitro* is provided by the adaptor molecule dynactin, a very large molecular complex that links dynein to its membrane-based cargos in cells [3]. Work by King and Schroer [4] demonstrated that dynactin enhances the processivity of single dynein molecules to values measured in cells. Dynactin also has a microtubule-binding arm that is essential for enhancing dynein’s processivity [4]. So, by providing an additional interaction with the microtubule rail, dynactin apparently stabilizes the finicky attachment of dynein to a microtubule.

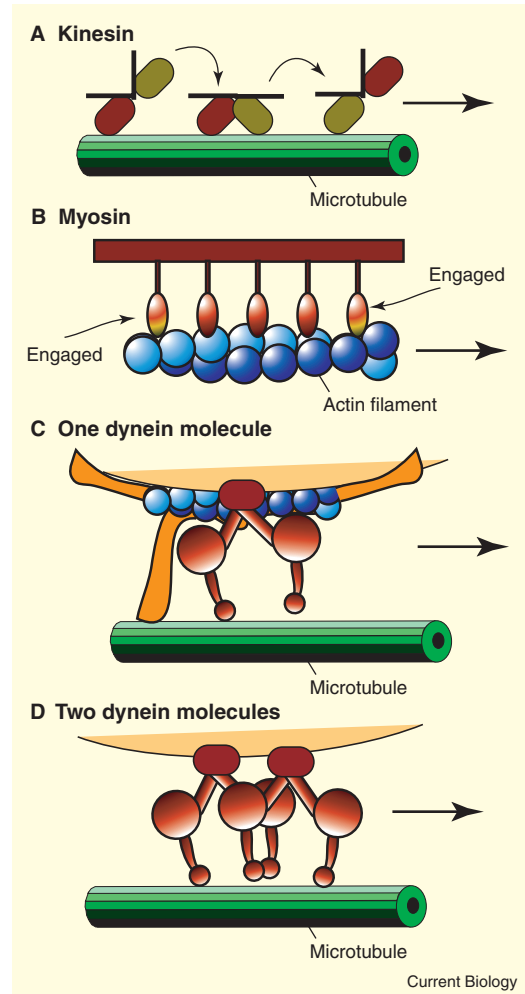
There is, however, a second aspect to the *in vitro/in vivo* paradox of dynein motility that is not easily explained by dynactin. Not only do the dynein-mediated movements of organelles proceed over longer distances in cells, but these movements also appear to be more forceful. Single molecules of dynein *in vitro* stall in optical traps at forces of around 1 pN, while the forces required to stall dynein-mediated movements in cells can exceed 5 pN [5,6]. Because dynactin is not a motor, the most reasonable explanation

is that multiple dynein molecules are bound to cellular cargo. This idea led Mallik *et al.* [7] to examine the motion of artificial cargo bound to more than one dynein molecule. The group found that the motion of cargo moved by multiple dyneins exhibited the persistence and strength of movements within cells. In fact, movement by just two dynein molecules virtually eliminates backward motions and allows cargo to run four times the distance seen with a single dynein motor. With multiple dyneins and dynactin present on cellular cargos, retrograde transport in cells is understandably robust.

Most impressive is the clarity with which Mallik *et al.* [7] reveal the reason that multiple dynein molecules enhance movement. It has been known for some time that single dynein molecules can passively diffuse along the length of microtubules [8,9]. Such movements indicate that dynein is capable of binding through a weak, non-specific attachment when its motor is inactive. Through a sophisticated separation of the multiple contributions to cargo trajectories, Mallik *et al.* [7] show that the diffusive state is a frequent contributor to single dynein movements. In fact, the plus-end movements that frequently interrupt minus-end runs are likely just episodes of diffusion. The group also shows that adding resistance to the cargo motion with an optical trap causes the cargo to slip and to diffuse back to the center of trap. This indicates that the microtubule attachments made by processive dyneins are not very robust. The low-affinity interaction that permits diffusion might be a continuous or regular part of the cycle that allows the motor to disengage regularly without falling off its tracks. It is unclear what causes the motor to become inactive or to restart later, but a second dynein molecule makes the molecule much more persistent because it is likely to be actively engaged when the first molecule disengages. Surprisingly, a cargo moved under load by two (or three) dynein

Figure 1. Cytoskeletal motors have multiple mechanisms for taking long walks along filaments.

(A) Kinesin is a highly processive molecule that walks hand-over-hand remaining in contact with the microtubule throughout motion. (B) Myosin molecules are disengaged throughout most of their working cycle, and therefore many myosin molecules are needed to maintain contact during long movements. (C) Single dynein molecules are not very processive, but they become more processive when bound to the accessory molecule dynactin, which provides an additional attachment to the microtubule. (D) The addition of a second dynein molecule to a cargo, even in the absence of dynactin, allows transport along microtubules for several microns.



molecules still advances in 8 nm step sizes just as when moved by a single dynein molecule. This suggests that two dynein molecules coordinate their movements even while both are engaged with a filament.

Compared with myosin and kinesin, the operation of the dynein motor is not well understood, but the new measurements on multi-dynein movement provide some constraints. The motors of both myosin and kinesin appear to work as ratchets in which the rotation of a cargo-connected lever arm is transduced to a step advancement of the filament-binding domain [10]. By contrast, dynein molecules have two processes emerging from a massive central body [11]. One process is a cargo-binding tail and the second is a microtubule-binding stalk. Structural studies show that both processes rotate

in response to changes in nucleotide states [12]. This, and the fact that the step size of the motor increases at low load, suggests that the central body of dynein may function as a motorized gear box that transduces the rotation of the cargo-connected tail to the microtubule-connected stalk [13]. One challenge to the idea of the stalk as a lever is its apparent flexibility [12]. However, the data from Mallik *et al.* [7] suggest that randomly positioned dyneins on a cargo can step together and that structural flexibility might be needed for such intermolecular coordination. Whatever the explanation for how multiple dyneins move cargo, it is clear that transport is enhanced because of their action. It also appears that dynein motility has provided another mechanism for taking long walks along cytoskeletal filaments (Figure 1).

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