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Cytoplasmic dynein

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Abstract

The organization and function of eukaryotic cells rely on the action of many different molecular motor proteins. Cytoplasmic dynein drives the movement of a wide range of cargoes towards the minus ends of microtubules, and these events are needed, not just at the single-cell level, but are vital for correct development. In the present paper, I review recent progress on understanding dynein's mechanochemistry, how it is regulated and how it binds to such a plethora of cargoes. The importance of a number of accessory factors in these processes is discussed.

Introduction

Cytoplasmic dynein-1 is a fascinating, complex molecular motor that drives the movement of an extraordinary range of cargoes towards the minus ends of microtubules. In a fibroblast, that means transport towards the cell centre, where the MTOC (microtubule-organizing centre) resides next to the nucleus. However, in other situations, such as polarized epithelial cells and neuronal dendrites, microtubules may be oriented with their plus ends towards the nucleus or have mixed polarity. Cytoplasmic dynein-1 (referred to herein as dynein) is a member of a family that includes many different axonemal (ciliary or flagellar) motors, and cytoplasmic dynein-2, whose primary role is in axoneme assembly [1–3].

The most obvious role for dynein is to transport discrete structures along microtubules. In animals, these range from individual proteins/protein complexes, through mRNPs (messenger ribonucleoproteins), to membranous organelles and chromosomes. However, dynein also drives the sliding of microtubules compared with each other, such as within the mitotic spindle, and of intermediate filaments along microtubules. Less obviously, dynein can be attached to a 'fixed' structure such as the cell cortex, where it can then pull on microtubules, and so playing a vital role in reorganizing the cell during migration or in positioning the mitotic spindle.

Dynein function is essential in animals, primarily because cells without functional dynein cannot divide properly. Interestingly, plants do not have dynein [3], and instead use multiple minus-end-directed kinesins for spindle assembly and cell division. Manipulating dynein function in organisms such as *Drosophila* and *Caenorhabditis elegans* has shown that it plays many different roles in development, particularly in the brain. For example, the branching of dendrites is dependent on dynein-driven transport of a range of cargoes [4–7], while neuronal survival depends on active retrograde transport of survival factors from the axon tip to the cell body [8]. Brain development is also crucially dependent on neuronal migration, which requires dynein to drive cell body and nuclear movement [9–11]. Even very subtle mutations in dynein subunits can lead to neurological defects [12,13]. Dynein's functions are simpler in fungi, where it pulls the nucleus into the daughter cell during budding yeast cell division, determines nuclear position within the hyphae of filamentous fungi and facilitates meiotic chromosome segregation [9]. While dynein transports membrane cargoes in filamentous fungi as it does in animal cells, yeast and plants use myosins for the same job.

Dynein composition and mechanism

Dynein is a 1.6 MDa complex containing two copies of the ATPase motor domain [heavy chain, DHC (dynein heavy chain)] and several additional subunits (Figure 1A) [1,3]. Two ICs (intermediate chains) bind directly to DHC, and then three different LCs (light chains), Tctex1, LC8 and LC7/roadblock, bind to the IC at separate sites. Two LICs (light intermediate chains) bind independently to the DHC. The ICs, LICs and LCs are each encoded by two genes in vertebrates, and the ICs and LICs may be alternatively spliced and present in different phosphoisoforms [1,3]. This variation suggests that different versions of dynein may perform distinct tasks by binding preferentially to specific cargo. While the ICs and LICs are only found within the dynein complex, the LCs have a variety of other interaction partners [1], complicating investigation of their function.

DHC is an unusual member of the hexameric AAA+ (ATPase associated with various cellular activities) family of ATPases, since its six AAA domains are encoded by a single polypeptide. Hydrolysis of ATP by AAA1 and AAA3 is most important for motility, while hydrolysis by AAA2 and AAA4 may be regulatory, and AAA5 and AAA6 do not bind ATP

Key words: Bicaudal D (BicD), cytoplasmic dynein, dynactin, lissencephaly 1 (LIS1), microtubule, Nde1.

Abbreviations used: AAA+, ATPase associated with various cellular activities; Arp1, actin-related protein 1; BicD, Bicaudal D; CAP-Gly, cytoskeleton-associated protein glycine-rich; CENP-F, centromere protein F; CLIP170, CAP-Gly domain-containing linker protein 170; DHC, dynein heavy chain; ER, endoplasmic reticulum; GFP, green fluorescent protein; IC, intermediate chain; JIP, c-Jun N-terminal kinase-interacting proteins; LC, light chain; LIC, light intermediate chain; LIS1, lissencephaly 1; mRNP, messenger ribonucleoprotein; MTOC, microtubule-organizing centre; NudE, nuclear distribution protein E; RZZ, ROD/ZW10/Zwilch; SAC, spindle assembly checkpoint; +TIP, microtubule plus-end-interacting protein; ZW10, Zest White 10.

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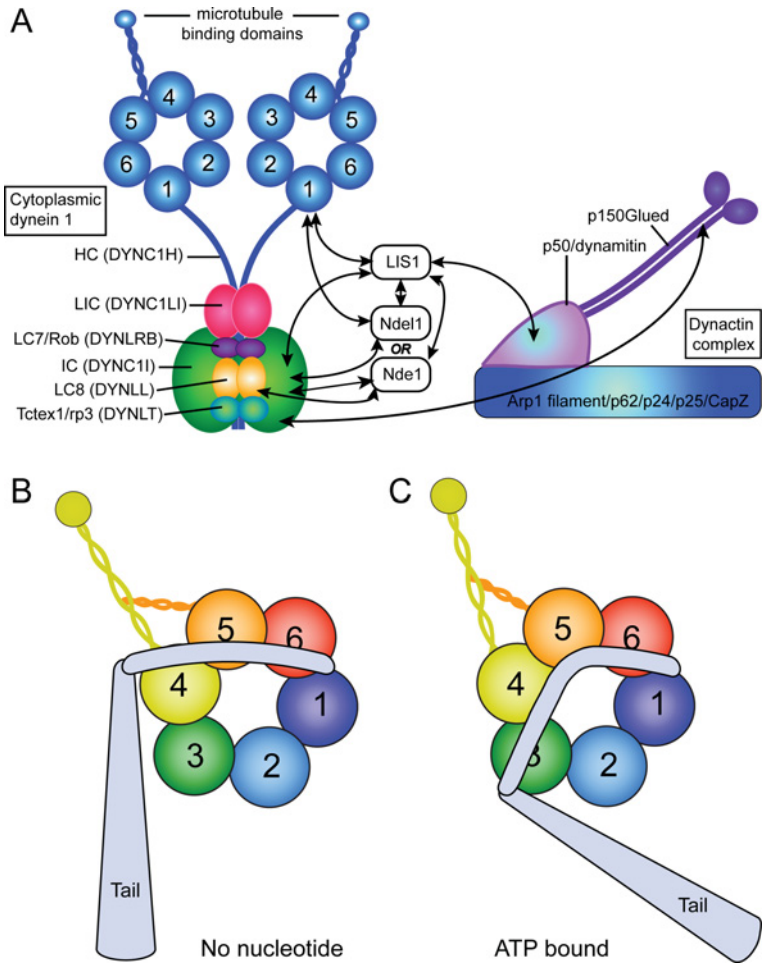
Figure 1 | Dynein subunit composition, accessory proteins and proposed structure

(**A**) Cartoon view of dynein and its subunits. The individual AAA domains are numbered. Interactions between accessory proteins and dynein subunits are indicated. (**B** and **C**) Proposed organization of a single DHC in the absence (**B**) and presence (**C**) of ATP. This model is based on X-ray crystallographic and EM data [16–18]. The microtubule-binding domain and stalk extend from between AAA4 and AAA5, whereas the 'strut' (orange coil) extends from AAA5. The position of the linker (grey bar) is known [16–18], whereas the position of the tail (grey wedge) is hypothetical. Other dynein subunits are not shown.



[14]. DHC binds to microtubules via a small globular domain at the end of a 10 nm anti-parallel coiled coil, the stalk, that extends from between AAA4 and AAA5 [15–17], with the base of the stalk being supported by a 'buttress' or 'strut' extending out of AAA5 [17,18]. There must be long-range communication across the head, since microtubule binding stimulates AAA1's ATPase activity, and microtubule binding is in turn affected by the nucleotide state of AAA1 [18] on the opposite side of the motor domain (Figures 1B and 1C). Force is thought to be generated by a large shift in position of a linker domain that joins the tail and AAA1 (Figures 1B and 1C) [16–19]. In contrast, the angle of the stalk compared with the head remains fairly constant during the ATPase cycle [16–19]. Surprisingly, a mutation in the tail domain reduces dynein's processivity and alters several other mechanochemical properties, suggesting that the tail plays an important role in movement, perhaps by co-ordinating the action of the two heads [20].

Studies on dynein's movement using purified protein have shown that it mainly takes steps of 8 nm (the distance between tubulin dimers), but occasionally steps of 16, 24 or 36 nm along the microtubule lattice [21–23]. This intriguing behaviour is different from that of kinesins and myosins, which have one step size, and has also been seen in living cells [21]. Interestingly, increasing the load on the motor led to smaller steps, suggesting that dynein can 'change gears' depending on the force it has to generate [23]. As yet, the significance of this behaviour for the cell is unknown. Is the ability to alter step size fundamental to dynein's function, and is it a focus for regulation *in vivo*?

A conundrum is why dynein moves up to 10 times faster in living cells than *in vitro* (e.g. [24,25]). One possibility is simply that native cargoes might engage multiple active dyneins, with their speed of movement increasing by ~1 μm/s per motor recruited [25]. However, other studies have shown that a few (perhaps only one) dyneins are

sufficient to drive rapid movement [26–28], and that multiple motors may actually slow down translocation *in vivo* [29,30]. Nevertheless, the presence of more than one dynein on a cargo will certainly provide additional force to drive motility through the crowded cytoplasm. Additionally, it should also help cargoes side-step obstructions by switching to another microtubule [31]. The ability of dynein to take backward steps [22,23,32,33] is also likely to help in this regard.

Dynein accessory factors: effect on dynein activity

It is clear from many studies that dynein needs other molecules to work optimally. So far, however, none of the known dynein accessory proteins have been found to increase dynein's rate of translocation, but they have a range of effects on dynein's mechanochemistry, as well as being implicated in cargo binding (see below).

The dynactin complex (Figure 1A) [34] is needed for virtually all dynein functions, and enhances dynein's processivity (the number of steps a motor takes along the microtubule before falling off) [24,35,36], without affecting its rate of movement or its ability to step backwards [24,35,36]. This was thought to be due to the ability of the p150 subunit of dynactin to bind to microtubules either via its CAP-Gly (cytoskeleton-associated protein glycine-rich) domain or a neighbouring basic domain [35,37,38], thus serving to anchor dynein to the microtubule if both motor domains became unattached. Surprisingly, however, replacing p150 with a truncated version that could not bind microtubules had no effect on the processive movement of peroxisomes or mRNPs *in vivo*, nor on Golgi apparatus morphology [39,40]. Similar short p150 isoforms exist naturally [39], and yeast dynactin complexes containing truncated p150 still enhance dynein's processivity [41], suggesting that it is the p150–IC interaction that is important for stimulating dynein activity. Indeed, while an antibody to p150 that inhibits microtubule binding but not the IC–p150 interaction reduced the number of vesicles that associated with microtubules *in vitro*, it actually increased processive movement [27]. p150's microtubule binding activity may be necessary, however, when large forces are required, such as during nuclear migration [41], and for organizing microtubules within the cell [40].

An important development has been the identification of several proteins, such as NudF (nuclear distribution protein F)/LIS1 (lissencephaly 1), NudE (nuclear distribution protein E)/Nde1, NudE-like/Ndel1, BicD (Bicaudal D) and ZW10 (Zeste White 10), that are required for many dynein functions (reviewed in [14]). BicD and ZW10 are involved primarily in recruiting dynein to cargoes, and are discussed in the next section. LIS1 is mutated in lissencephaly, or smooth brain, where defective neuronal migration leads to disorganized brain architecture [11]. LIS1, Nde1 and Ndel1 engage in a complex network of interactions with each other, and with dynein/dynactin (Figure 1A), but are lost from purified dynein (e.g. [42,43]). LIS1 and the C-terminal domain of Ndel1 bind to the catalytic AAA1 domain of DHC [44,45], whereas Nde1 does not [43]; instead, Nde1 binds to IC and LC8 [14,46]. Interestingly, both Nde1 and Ndel1 can also bind to dynein via their N-terminal coiled-coil domains [47], which contain independent binding sites for IC [48] and LIS1 [47]. This has led to a model where the coiled-coil region of the Ndel1 dimer spans the dynein molecule from the IC in the cargo-binding domain to the head, where it interacts with LIS1 that is bound to the AAA1 domain of DHC [47]. This scaffolding role is proposed to be regulated by phosphorylation of the C-terminal of Ndel1 [47].

As one might expect from the location of these interactions, LIS1 and Nde1/Ndel1 have a profound influence on dynein's motor activity [42,43,49]. Rather surprisingly, however, LIS1 and Ndel1 individually decreased dynein's motor activity, which was restored when both LIS1 and Ndel1 were added together [42]. Subsequently, LIS1 has been shown to bind to dynein in its pre-power stroke conformation, enhancing its binding to microtubules and the force generated, but reducing the rate of movement due to increased pausing [43]. The presence of Nde1 promoted tight binding of LIS1 to dynein in any nucleotide state, and led to increased force generation [43]. However, Nde1 on its own reduced dynein's ability to bind to microtubules and to generate force [43]. Another study dissected the roles of different regions of Ndel1, and found that the C-terminus of Ndel1 was sufficient to cause dynein's release from microtubules, suggesting that it is a negative regulator [49]. Importantly, the binding of LIS1 by Ndel1 amino acids 44–183 was enough to reactivate dynein motility [49], and this truncation lacks the ability to bind to IC [48,49].

Altogether, these results highlight the crucial importance of dynein's accessory factors in regulating dynein mechanochemistry. An interesting question for the future is whether these interactors are a focus for regulating dynein function in the cell. For example, there is evidence that both the IC–p150 and Ndel1–DHC/LIS1 interactions are regulated by phosphorylation [47,50]. The function of dynein accessory proteins is not limited to influencing dynein activity; however, they also play roles in dynein–cargo interactions.

Targeting dynein to different cargoes

How dynein binds to its wide range of cargoes is a poorly understood topic. Given that there is considerable subunit heterogeneity, one appealing idea is that cargo-specific dyneins are defined by their composition of particular subunit splice variants or phosphoisoforms. Indeed, a wide range of IC splice forms are found in neuronal tissues [51], and the IC1B isoform specifically associates with TrkB (tropomyosin receptor kinase B)-positive endosomes in neurons [52]. However, only one splice form, IC2C, is found in non-neuronal mouse tissues [51].

Further evidence, both for and against the hypothesis that specific subunits define functional dynein subsets, has

Table 1 | Selected dynein–cargo interactions

A range of recent and key earlier examples of dynein–cargo interactions are listed, along with the small GTPase involved, where appropriate. ASFV, African swine fever virus; ERGIC, endoplasmic recticulum–Golgi intermediate compartment; GKAP, guanylate kinase-associated protein; KIBRA, kidney- and brain-expressed protein.

Dynein subunit	Cargo	GTPase	Other adaptor molecules	Reference(s)
Not specified	Secretory vesicles, ERGIC, Golgi	Rab6	BicD1/2	[77,79]
Not specified	Rab6-positive vesicles	Rab6	BicD-related protein 1	[103]
IC	Lysosomes/autophagosomes in neurons		Snapin	[112]
IC	Adenovirus particles		Hexon subunit	[113]
IC	Kinetochores		ZW10	[61]
LIC1	Endosomes	Rab4		[114]
LIC1 and LIC2	Endosomes	Rab11a	FIP3	[57,58]
LIC1	Centrosomes		Pericentrin	[53]
LIC2	Cell cortex		Par3	[54]
LIC	Nuclei		Zyg12	[83]
LIC	APP (amyloid precursor protein)-containing vesicles in neurons		Unc-16/JIP3	[105]
LIC	Adenovirus particles		Hexon subunit	[113]
LC8	Cell cortex	Cdc42 (cell division cycle 42; indirect)	hDlg1/SAP97 via GKAP	[115]
LC8	RNPs (ribonucleoproteins)		Egalitarian (that binds BicD)	[116]
LC8	Piccolo–Bassoon transport vesicles (neurons)		Bassoon	[117]
LC8	Early endosomes		KIBRA, which binds sorting nexin 4	[118]
LC8	ASFV		ASFV p54	[119]
LC7/rbl	Rab6 vesicles	Rab6		[120]

come from studies on the LIC. There are two LIC genes in vertebrates, but only one type of LIC is found in each dynein molecule, generating distinct dynein subtypes [53]. There are two clear instances of isoform-specific interactions: LIC1 with pericentrin [53] and LIC2 with the polarity molecule Par3 [54]. Melanosomes also possess only one of three possible LIC forms [55]. RNAi (RNA interference) knockdown of LICs individually has generated conflicting data over their roles in the secretory and endocytic pathways [2,56]. My group's work has shown that knockdown of both LICs always gives a more profound phenotype than single deletions, and that either LIC can rescue defects in organelle positioning in both the secretory and endocytic pathways (C. Villemant, A. Mironov, N. Flores-Rodriguez, P.G. Woodman and V.J. Allan, unpublished work). Similarly, both LICs influence the position of recycling endosomes and interact with the recycling endosome protein FIP3 (Rab11 family-interacting protein 3) (Table 1; [57,58]). In mitosis, single depletion of LIC1, but not LIC2, delayed mitotic progression [59], but we have again found that depleting both LICs causes more severe inhibition than LIC1 depletion alone (C. Villemant, A. Mironov, N. Flores-Rodriguez, P.G. Woodman and V.J. Allan, unpublished work).

The identification of LIC-interacting partners demonstrates that dynein can bind directly to cargo-specific components. Other direct interactions may involve the ICs or LCs (Table 1). Confusingly, some cargoes have several potential dynein 'receptors', while others have none as yet. Since the LCs also function outside the dynein complex, it is particularly important that LC interactors are shown to recruit the dynein whole complex, not just the LC, but this has not always been done.

Long before any of these cargo-specific dynein-binding partners were identified, dynactin was proposed to recruit dynein to structures ranging from kinetochores [60] to membranes [34]. In mitosis, dynein is needed at the kinetochore both to drive the movement of chromosomes along microtubules during chromosome alignment, and to remove components of the SAC (spindle assembly checkpoint) machinery from the kinetochore as they become properly attached to microtubules [14]. A recently identified protein, spindly, is needed for kinetochore recruitment of dynactin in some organisms, but not others (reviewed in [14]). ZW10 is part of a kinetochore-associated complex, RZZ (ROD/ZW10/Zwilch), which also recruits dynactin to the kinetochore and may work in combination with spindly [14,46]. However, ZW10 also interacts directly with a phosphorylated form of IC that is found only on unattached kinetochores, and this association is needed for dynein recruitment [61]. It has been proposed that, as

Table 2 | Selected dynactin–cargo interactions

A range of key dynactin–cargo interactions is listed, along with the small GTPase involved, where appropriate. BPAG1n4, bullous pemphigoid antigen 1n4; ERGIC, endoplasmic reticulum–Golgi intermediate compartment; ORP1L, OSBP (oxysterol-binding protein)-related protein 1L; RILP, Rab-interacting lysosomal protein.

Dynactin subunit	Cargo	GTPase	Other adaptor molecules	Reference(s)
p150 C-terminal	COPII (coatamer protein II)-coated vesicles		Sec23p	[121]
p150 C-terminal	Neuronal endosomes		BPAG1n4, via retrolinkin	[122,123]
p150 C-terminal	Lysosomes	Rab7	RILP, ORP1L, spectrin	[66,124]
p150 C-terminal	Early endosomes		Sorting nexins 5 and 6	[125,126]
p50	Kinetochores		ZW10 (RZZ)	[14,46]
p50	Secretory vesicles, ERGIC, Golgi	Rab6	BicD1/2	[77–79]
Arp1	Golgi		βIII spectrin	[67]

kinetochores attach to the spindle and come under tension, IC is dephosphorylated, making it able to interact with p150 and triggering dynein-mediated removal of SAC components from the kinetochore [61].

LIS1, Nde1 and Ndel1 are also required for dynein function at the kinetochore. So far, it is not completely clear as to whether they act by recruiting dynein to kinetochores or by regulating dynein activity during microtubule attachment and SAC inactivation, or a combination of both. Again, the exact details vary between systems (reviewed in [14]). CENP-F (centromere protein F) targets Nde1 and Ndel1 to the kinetochore [62,63], independently of dynactin [62]. Nde1 and Ndel1 appear to have distinct functions at the kinetochore and during mitosis [63,64], with only Nde1 being needed for dynein recruitment [63]. Whether LIS1 is needed for Nde1/Ndel1 kinetochore association or vice versa, and how the microtubule plus end-binding protein CLIP170 (CAP-Gly domain-containing linker protein 170) is involved, is again system-dependent [14]. While RZZ is clearly needed for dynactin localization to kinetochores, disrupting its function has little or no effect on kinetochore Nde1 or Ndel1 levels or vice versa [62,65]. Dynein recruitment and function at the kinetochore is demonstrably complex, and further work is needed to determine the full network of interactions in each cell type or species.

Dynein association with membranous cargoes is similarly complicated. As outlined above and in Table 1, a range of membrane proteins have been identified that bind to dynein subunits. In addition, dynactin has also been thought to play a crucial role in dynein recruitment [34]. Attachment of dynactin to membranes has been proposed to be via the Arp1 (actin-related protein 1) filament binding to βIII spectrin (Table 2) [66,67]. In addition, several interactions between membrane proteins and the C-terminus of p150 have been discovered (Table 2). Interestingly, this same region of p150 is proposed to control the ability of dynactin to bind to membranes [68]. Furthermore, dynactin p50 binds to ZW10, which in interphase is part of a protein complex involved in trafficking between the ER (endoplasmic reticulum) and Golgi apparatus [14]. These results hint at a direct mechanistic link between dynactin, dynein and protein sorting in the secretory and endocytic pathways. Surprisingly, however, dynactin may actually play only a minor role in recruiting dynein, since dynein is still membrane-bound in *Drosophila* mutants lacking Arp1 [69]. Nevertheless, membrane movement in both directions is profoundly inhibited in Arp1 mutants [69], reinforcing the importance of dynactin for dynein function, and also underlining a close tie between dynein and kinesin activity (see below).

As is the case for kinetochores, LIS1, Nde1 and Ndel1 also play important roles in supporting dynein-driven positioning and movement of membranes [64,70–74]. While this could be by regulating dynein's ATPase and force-generating properties, there is a simpler explanation: depletion of Nde1 and Ndel1 leads to a profound loss of dynein from membranes [64]. In contrast with the situation at the kinetochore, Nde1 and Ndel1 act redundantly in organelle positioning [64]. No membrane receptors for Nde1 and Ndel1 have been identified as yet, but they could conceivably associate directly with the lipid bilayer, since they are palmitoylated [75]. Knockdown of LIS1 also removed dynein, but to a lesser extent [64]. Interestingly, LIS1 is a subunit of the phospholipase PAFAH (platelet-activating factor acetylhydrolase) Ib, which is Golgi-localized and controls the formation of membrane tubules [71]. Loss of LIS1 could therefore affect Golgi apparatus morphology and position in two ways: via inhibition of dynein activity and its loss from the membrane, and by reduction in phospholipase activity. This could explain why LIS1 depletion leads to greater Golgi apparatus fragmentation than loss of Nde1 and Ndel1 [64]. Nde1 and Ndel1 appear to act upstream of LIS1, however, as LIS1 depletion had no effect on levels of Nde1 and Ndel1 on membranes [64].

The final dynein cargo adaptor I will describe is BicD. It was identified in *Drosophila*, and has since been shown to play a role in dynein-driven transport of mRNA, Rab6-positive membranes, lipid droplets and the nuclear envelope in higher eukaryotes [14]. It binds to dynein and dynactin p50, and to cargo-specific components such as Rab6, Egalitarian and the nuclear pore protein Ran-BP2 (Tables 1 and 2) [14,76]. In turn, Rab6 interacts with dynactin p150, dynein LC7 and membranes [14,77,78] while Egalitarian associates with mRNA and dynein LC8 [14]. However, the dynein-binding region of BicD when targeted artificially to mitochondria

was sufficient to recruit dynein [79]. Interestingly, BicD2 also binds the kinesin-1 motor subunit [76,80] (see below).

Although the results described above paint a rather confusing picture of dynein–cargo interactions, the most straightforward interpretation is that dynein uses more than one mechanism to bind to most cargoes. These may include direct coupling between dynein and cargo molecules, and indirect associations brought about via adaptors such as dynactin or BicD, and the accessory factors Nde1 and Ndel1. A final example that underscores this complexity is dynein's binding to the nuclear envelope. This is required to maintain association between the nucleus and the MTOC, to establish correct nuclear position within the cell, especially during neuronal migration, and to facilitate nuclear envelope breakdown at the end of prophase (reviewed in [9,10]). SUN family members in the inner nuclear envelope provide a structural link from the nuclear lamina or chromosomes through to outer nuclear envelope proteins of the KASH family [9,10]. KASH proteins in turn can link directly to dynein, or indirectly via BicD or Nde1 (Table 1; [81–83]). In an interesting parallel with kinetochores, CENP-F provides an alternative means of recruiting Nde1/Ndel1 (and hence dynein and LIS1) to the nuclear envelope via its interaction with the nuclear pore protein Nup133 [84]. The recruitment of dynein, LIS1 and Ndel1 to the nuclear envelope also depends on functional dynactin [85,86]. A third route for securing dynein to the nucleus is provided by BicD2, which is recruited to the nuclear envelope by binding to the nuclear pore component Ran-BP2 [76]. A final twist is that KASH proteins, Ran-BP2 and BicD all bind to kinesin-1, which is needed to enable bidirectional movement of the nucleus and the MTOC [9,10,76,82,87]. As discussed in the following section, bidirectional transport is common within the cell, generating important questions about how dynein function is controlled.

Regulation of dynein function in the cell

Since motor proteins in the cell fulfil such a wide range of functions in so many different contexts, they must clearly be regulated in some way. For example, any given cargo may be moving or not, and this control could be exerted over time (such as through the cell cycle) or in concert with other cellular functions, such as a particular membrane trafficking step. Indeed, as mentioned above, there are links between dynein, dynactin and important trafficking components (Tables 1 and 2). It is likely, too, that dynein will be regulated independently on different cargoes.

Two obvious possibilities exist for modulating dynein-dependent movement, and there is evidence for both. One is that active dynein is recruited when it is needed, then removed again when movement is complete. The second is that dynein is bound at all times, but can be switched between active and inactive states.

Since dynein generally transports cargo towards the cell centre, and is also active at the cell cortex, it would be useful to have a means of enriching dynein in the cell periphery ready for action. The accumulation of dynein and dynactin on the plus ends of growing microtubules achieves this in many organisms [14]. In yeast, delivery of dynein to the bud cortex via attachment to growing microtubules is important for subsequent transport of the nucleus into the bud during mitosis [14]. In filamentous fungi, dynein is transported to microtubule plus ends by kinesin-1 [88,89] where interactions with dynactin help it accumulate [90]. Early endosomes that move towards plus ends using kinesin-3 were shown to lack dynein [28], and it was initially proposed that they picked up dynein from the plus end pool, ready for the return journey [89]. However, more recent work has shown that plus-end-directed endosomes often switched direction before reaching the tip by recruiting dynein molecules that were moving towards them along the same microtubule [28].

In vertebrates, dynein is rarely seen at microtubule plus ends, while dynactin clearly behaves as a +TIP (microtubule plus-end-interacting protein) [14,91]. It has been suggested that contact between a growing microtubule and a stationary membrane cargo delivers dynactin, thus initiating dynein-driven movement [91]. However, other work has shown that loss of p150 from plus ends has no effect on membrane movement in vertebrates [92,93]. Instead, the +TIP CLIP170 was seen to activate motility of *Xenopus* melanosomes [92], but not of secretory and endocytic organelles [93].

Analysis of cargoes that move bidirectionally has provided support for the second model, where activity is regulated rather than cargo association. For example, GFP (green fluorescent protein)-tagged dynein localizes to particles that move in both directions along microtubules in living cells (e.g. [42,52,94,95]). Furthermore, prion-protein-containing vesicles possess similar levels of dynein and kinesin-1 *in vivo*, irrespective of which direction they are moving, or indeed whether they are moving at all [96], while vesicles labelled with GFP–p50/dynamitin move bidirectionally *in vitro* [27].

How bidirectional cargoes switch their direction of movement has fascinated many researchers (reviewed in [97]). One proposal is that both motors are always active and participate in a tug-of-war [26,27,97]. In vertebrates and *Dictyostelium*, several relatively weak dyneins compete against single stronger kinesins [26,27], whereas in *Ustilago maydis*, one dynein competes against four to five kinesin-3 molecules [28]. However, a tug-of-war seems rather a wasteful mechanism, and a refinement of this model is that the competition only lasts until one motor wins, and, after that, the loser is inactivated [97,98]. Alternatively, opposing forces could be harnessed to deform membranes such as endosomes in a way that facilitates sorting events [26]. The number of each motor per cargo will clearly be important in determining the bias in direction of movement, and BicD and Egalitarian levels have been shown to be influence the amount of dynein loaded on to mRNPs in *Drosophila* [99].

In the simplest tug-of-war model, if one motor is turned off, the other motor will always win. However, in many instances this is not the case; inhibition of one direction of movement leads to inactivation of the other direction

as well [40,69,97,98]. The clearest demonstration of this is peroxisome movement, where loss of kinesin-1 activity inhibits dynein-driven translocations as well [40,98]. However, replacement of kinesin-1 with any functional plus-end motor that is artificially targeted to the peroxisome will reactivate dynein, even if the artificial motor moves far more slowly than kinesin-1 [98]. This suggests that the generation of force in the plus-end direction is all that is needed to activate dynein, perhaps by a tension-sensing mechanism [98,100].

How might this tension-based coupling be achieved? One possibility is that the presence of two opposing motors within a small structure is sufficient, as force generated by one will necessarily exert tension on the other. This idea is supported by the apparently contradictory finding that kinesin-1 and dynein act independently of each other in the ER [101]; the ER is such a large, dynamic and deformable membrane structure that dynein and kinesin may simply end up in distinct regions of the organelle, acting independently.

An alternative means of communicating tension between motors is for them to be physically associated. This may well be the case, at least in some circumstances, since IC has been shown to bind to kinesin LC [102]. Indirect associations are also likely via scaffolding complexes. For example, dynactin also interacts with kinesin-2 and kinesin-5 [14], but whether it plays a role in co-ordinating motor switching is not clear. Furthermore, both Ran-BP2 and BicD interact with kinesin-1 heavy chain [76,80] while BicD-related protein 1 binds Kif1C [103], and BicD levels have been shown to affect both directions of lipid droplet movement [104]. In addition, there is considerable evidence that JIPs (c-Jun N-terminal kinase-interacting proteins), originally identified as kinesin-1 binding proteins, are involved in regulating dynein-driven movement in neurons (Table 1; [105–107]) and non-neuronal cells [108].

While a tug-of-war may control the direction of movement over short time-scales, there is clearly scope for longer-term changes that involve motor recruitment/loss or activation/inactivation [27,98]. How dynactin, LIS1, Nde1, Ndel1 and BicD contribute to this regulation remains to be determined in detail. Additional regulatory molecules such as huntingtin [109], and a variety of GTPases (Tables 1 and 2; [14,110,111]) are also likely to influence dynein activity. Phosphorylation is another obvious means of controlling dynein function, but again, detailed mechanisms are lacking.

Conclusion

Recent years have seen great progress in understanding dynein's structure and mechanism, and the contribution made by accessory proteins to its function. We now know much more about how dynein is targeted to cargoes, but this has added further complexity, given that there are often several parallel sets of molecules that contribute. Our knowledge of how dynein is regulated *in vivo* is still fairly limited, however, and it seems likely that systematic studies which look at the whole range of potential regulators together will be needed to unravel the details of control mechanisms.

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