REVIEW

Multiple modes of cytoplasmic dynein regulation

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In performing its multiple cellular functions, the cytoplasmic dynein motor is subject to complex regulation involving allosteric mechanisms within the dynein complex, as well as numerous extramolecular interactions controlling subcellular targeting and motor activity. Recent work has distinguished high- and low-load regulatory modes for cytoplasmic dynein, which, combined with a diversity of targeting mechanisms, accounts for a very broad range of functions.

Cytoplasmic dynein is a minus-end-directed microtubule motor protein mediating a wide range of functions, including fast vesicular, macromolecular and virus transport, chromosome dynamics, mitotic spindle assembly and orientation, nucleokinesis, nuclear envelope breakdown, growth cone protrusion, axonogenesis, and cell migration[1–4]. These functions are all associated with a single major form of cytoplasmic dynein: dynein 1 (DYNC1H1; here, simply 'cytoplasmic dynein' or 'dynein'), which is ubiquitously expressed in animal cells and is the sole dynein form in some other organisms, including yeast and filamentous fungi. A second, minor form of cytoplasmic dynein, dynein 2 (DYNC2H1), is responsible for transport within cilia and flagella, whose beating behaviour is driven by the 'axonemal' class of dyneins.

Data on motor domain organization and regulation derive from studies of both axonemal and cytoplasmic dynein, and suggest a highly complex degree of allosteric communication within and between motor domains. Additional layers of complexity have been identified for cytoplasmic dynein alone. Numerous proteins participate in its recruitment to subcellular sites of action, providing insight into how it contributes to such a diversity of cellular functions. At least two of these factors — dynactin and a complex of the dynein-interacting proteins LIS1 and NudE (or its paralogue NudEL) — additionally regulate cytoplasmic dynein motor activity, indicating that its mechanochemical behaviour is also tailored to specific cellular roles. Studies of these factors and mouse dynein mutations have suggested further levels of allosteric control between motor and tail domains. In this Review, we discuss these different levels of dynein regulation and their implications for cytoplasmic dynein function.

Dynein motor structure and intramolecular regulation

Dynein is a complex with a relative molecular mass of 1,200,000 (M_r 1,200 K), with two 530 K heavy chains, light intermediate chains and a subcomplex of intermediate and light chains (Fig. 1). The latter subunits associate with the amino (N)-terminal tail portion of the heavy chain, whereas its carboxy (C)-terminal two-thirds constitute the motor domain, which is well-conserved throughout evolution and between axonemal and cytoplasmic dynein forms. The motor domain is ~380 K, far bigger than the kinesin and myosin motors (~35 and 90 K, respectively), and is related in sequence and structural organization to the AAA superfamily of ATPases, which characteristically exhibit a ring-shaped array of catalytic units (Fig. 1a). In contrast to simpler oligomeric AAA proteins, the dynein heavy chain contains six tandem ATPase units arrayed in a ring from which several projecting domains extend[5,6]. AAA1 is the main site for ATP hydrolysis[7,8], but AAA3 and AAA4 have also been implicated in motor function[9–11]. Extending N-terminally from the AAA ring is the ~500 amino-acid linker unit, considered to be the primary mechanical element of the motor. This structure arches across the N-terminal 'front' or 'linker' face of the motor ring, making contacts near AAA1 and AAA4 or AAA5 (refs 12,13), in what is probably the high-affinity microtubule-binding state of the cross-bridge cycle. Fluorescence resonance energy transfer and electron microscopy data suggest that the linker position changes in response to nucleotide occupancy in AAA1 and AAA3 (refs 6,14), and the force-producing 'power stroke' step in the dynein mechanochemical cycle is thought to involve the restorative movement of the linker. Linker domain truncations reduce ATPase rates and motor activity[6,15], suggesting that apart from acting as a lever arm, the linker may also be involved in coupling the chemical and mechanical cycles of the motor.

Also projecting from the AAA ring is the stalk, an antiparallel coiled-coil of two ~100 amino-acid α-helices with a small globular microtubule-binding domain at the distal tip[7,16] (Fig. 1). This site is separated from the ATP-binding motor core by ~15 nm, raising questions as to how microtubule binding affinity is coordinated with the state of the ATP hydrolytic cycle. Recent biochemical and biophysical experiments have demonstrated a rapidly reversible change in the register of the component α-helices, which may control microtubule binding affinity at the stalk tip[16–19]. An additional coiled-coiled 'buttress' or 'strut', which was shown to extend from AAA5 to interact laterally with the stalk coiled-coil[12,13], may further regulate stalk behaviour, although its precise role is untested.

Following AAA6 is a ~32 K C-terminal domain found in most species, but lacking in yeast dynein. Vertebrate cytoplasmic dyneins, which

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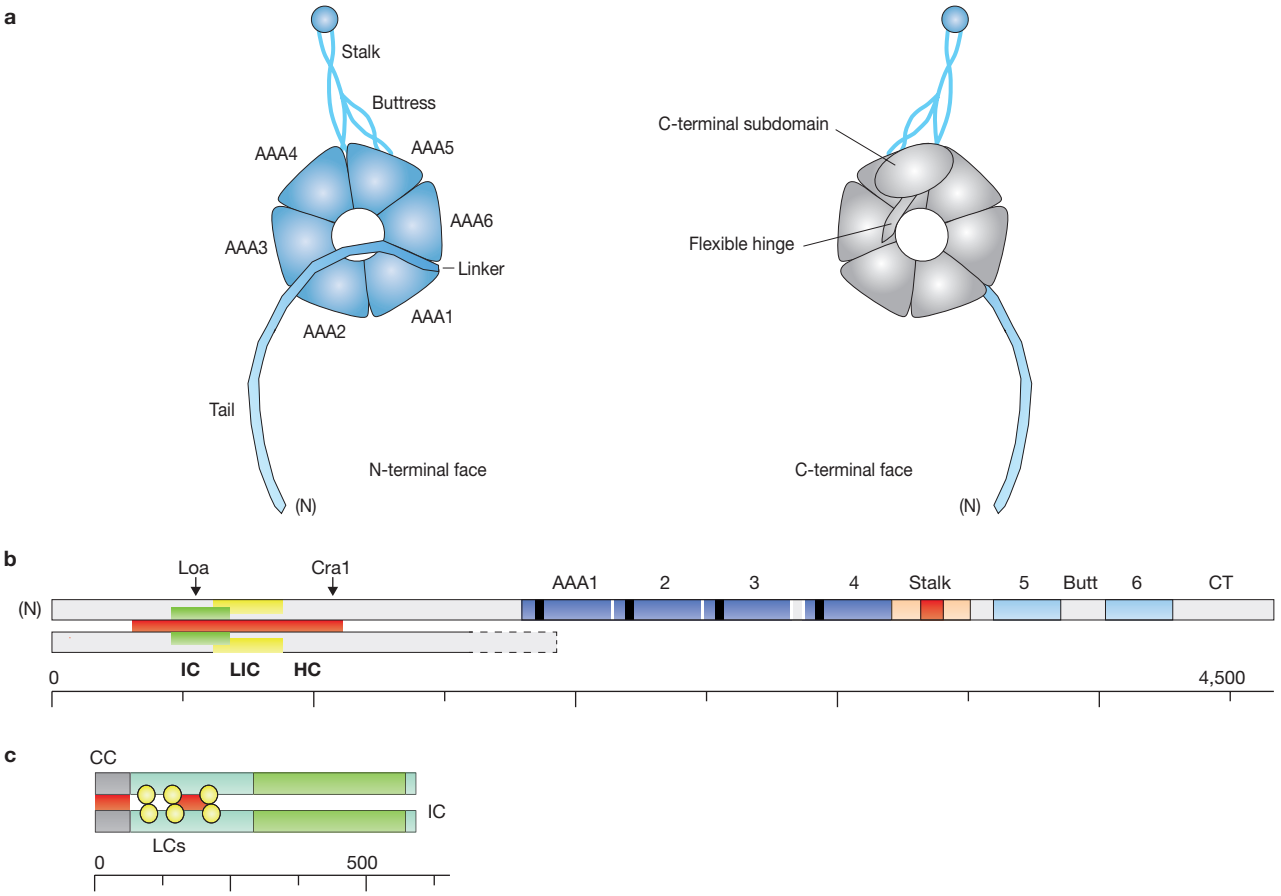

Figure 1 Schematic representation of cytoplasmic dynein. (**a**) The present understanding of dynein heavy chain structural organization, with the linker domain represented in the 'primed' state (that is, preceding the power stroke)[6,14]. (**b**) Domain composition of the dynein heavy chain (HC) homodimer, with the heavy chain–heavy chain interaction site (red), subunit interaction sites (bold; IC, intermediate chain; LIC, light intermediate chain), and locations of the AAA1–6, stalk, buttress/strut, and C-terminal (CT) subdomains. The locations of *Loa* and *Cra1* mutations are indicated. (**c**) The intermediate chain–light chain complex, with intermediate chain–intermediate chain interaction sites (red), light chain dimers (yellow), coiled-coil (CC; dark grey) and heavy-chain-interacting WD-repeat domains (green) indicated. Only limited details of LIC structure are known[96]. Scales indicate amino-acid number (**b**,**c**).

contain this domain, move at around 10 times the speed of yeast dynein (1–3 μm s^{-1}, compared with 100 nm s^{-1} in yeast), and in most studies, exert about 20% of the force (1.4 pN, compared with 7 pN)[15,20–23]. The C-terminal domain lies on the opposite face of the motor ring from the N-terminal linker, and spans the distance between AAA6 and the stalk base[6,13] (Fig. 1a). This domain is separated from the motor ring by a flexible hinge region, as judged by limited proteolysis[24]. Removal of this domain reduced the processivity of dimeric *Dictyostelium discoideum* cytoplasmic dynein, raising the possibility that the C-terminal region may help coordinate dimeric motor function[25].

All known cytoplasmic dyneins are heavy-chain homodimers. The processive movement along microtubules exhibited by the native purified dynein complex can be mimicked by recombinant motor domain dimers, whereas individual motor domains are nonprocessive[15]. These observations suggest a form of coordination between motor domains known as 'gating', which keeps the cross-bridge cycles of the two motor domains out of phase[26]. This behaviour is probably controlled by intramolecular tension or by direct interaction of the dynein heads[26]. However, research on the mouse dynein *Loa* mutation located near the N-terminus of the heavy chain (Fig. 1) also indicates a role for the tail domain. *Loa* is one of several mutations identified in this region. It decreases the rate of retrograde axonal transport and contributes to sensory and/or motor neuron degeneration[27,28]. Strikingly, dynein purified from *Loa* mice exhibited a decrease in processive movement along microtubules, associated with an increased Michaelis constant for microtubules (K_{mMT}; ref. 29). Further analysis attributed these effects to miscoordination of the two motor domains, implicating the dynein tail in regulating motor activity[29]. Head–tail crosstalk has been independently suggested by evidence that yeast dynein motor and tail domains are individually targeted to microtubule plus-ends and the cell cortex respectively; this is proposed to reflect sequential activation of the domains to 'offload' dynein at the cell cortex[30].

Extramolecular regulation through dynactin and NudE–LIS1

Dynactin. Dynactin is a large, multi-subunit protein complex involved in most aspects of cytoplasmic dynein function (Fig. 2a). It consists of a ~40 nm filament of actin-related protein 1 (Arp1), decorated by capping proteins at the barbed (+) end, and a subcomplex of Arp11 and accessory subunits at the pointed (-) end. The working portion of dynactin is its 150 K subunit, an orthologue of the *Drosophila melanogaster Glued* gene product[31]. $p150^{Glued}$ contains a small microtubule-binding CAP-Gly (cytoskeleton-associated protein-glycine-rich) domain near

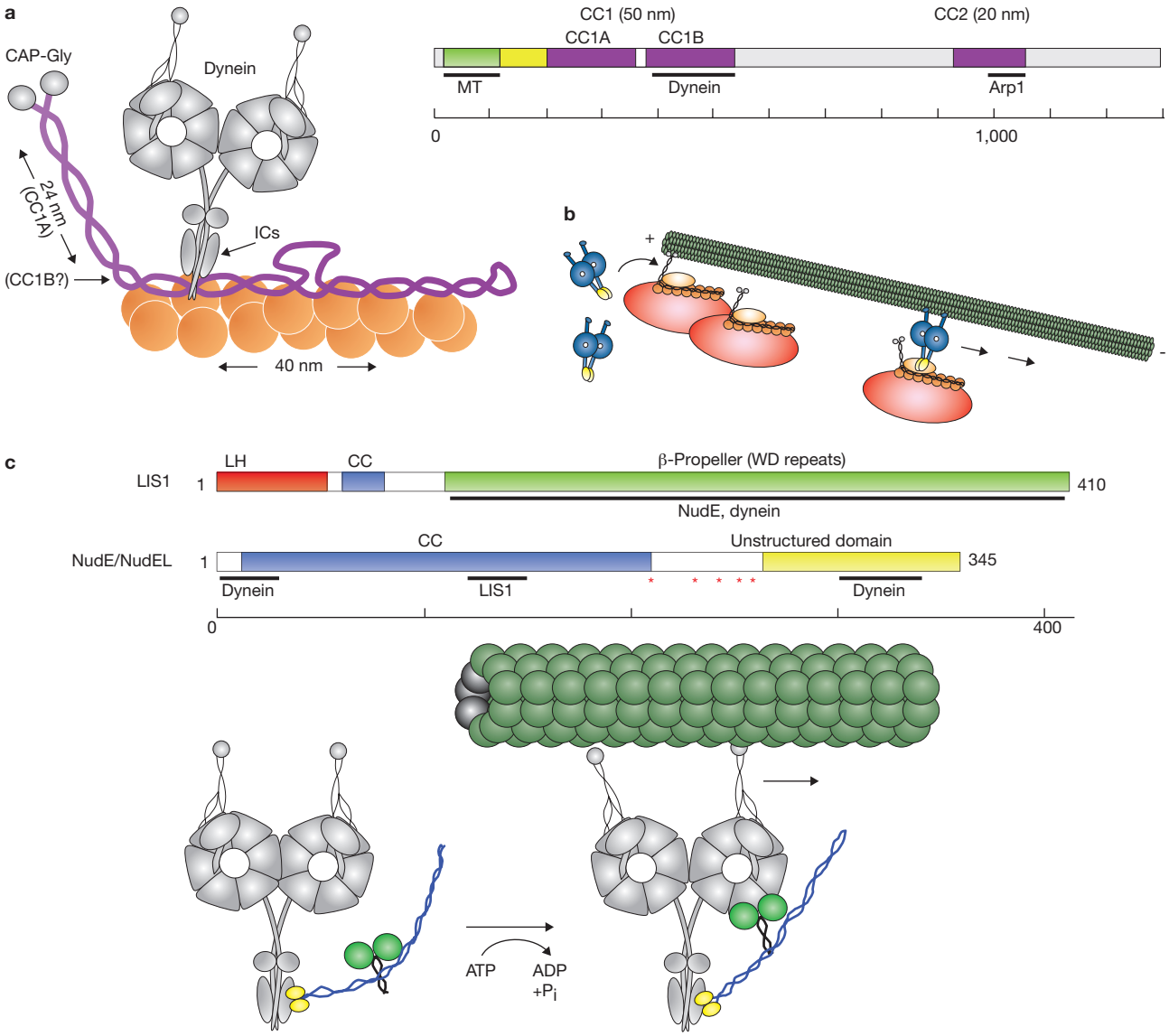

Figure 2 Dynactin, NudE and LIS1 structure and function. (**a**) The major functional dynactin subunit, p150^{Glued}, is shown as a bar diagram (top), with coiled-coil (CC, purple), serine/proline-rich (yellow) and associated-protein-binding subdomains (MT, microtubule; dynein; Arp1). It is also shown schematically (bottom) with a hypothetical interrupted coiled-coil structure (purple) associated with a filament composed of Arp1 subunits (orange). Dynein (grey) is shown associated through its intermediate chains (ICs) with the CC1B domain of p150^{Glued}. Arp1 plus- and minus-end associated proteins, and the dynamitin-containing shoulder complex[97–99], have been omitted for clarity. (**b**) Dynactin-associated vesicles (red ovals) decorating growing microtubule (dark green) plus ends, an arrangement which may help capture membranous organelles for microtubule minus-end-directed dynein (red) transport[50]. (**c**) Bar diagrams of LIS1 and NudE (similar to NudEL) are shown. LIS1 is a dimer of subunits containing LH (LIS-homology), coiled-coil and WD-repeat domains for NudE/NudEL and dynein binding. The dynein-binding site in NudE and NudEL was initially identified near their C-termini, and an additional site was discovered more recently near the N-terminus. Phosphorylation sites in NudE are labelled with asterisks. The schematic (bottom) depicts proposed modes of interaction of the triple complex of LIS1 (green and black), NudE (yellow and blue) and dynein (grey)[21]. LIS1 is shown positioned near the dynein motor domains by NudE or NudEL. LIS1 interacts with the dynein motor domain when the latter is occupied by ADP and phosphate (P_i). LIS1 binding enhances the affinity of dynein for microtubules (dark green), resulting in prolonged interactions with microtubules when dynein is under load. Scales indicate amino acid number (**a**,**c**).

its N-terminus, followed by two predicted α-helical coiled-coil regions (the first of which binds dynein through its intermediate chains[32]) and a C-terminal Arp1-binding site[33] (Fig. 2a).

Initial evidence of a role for dynactin in dynein cargo recruitment came from overexpression of its 50 K 'dynamitin' subunit, which dissociates p150^{Glued} from the Arp1 filament and causes severe mitotic and subcellular transport defects[34–36]. Cytoplasmic dynein was displaced from mitotic kinetochores and the Golgi apparatus, consistent with a role for dynactin in dynein cargo interactions. However, cytoplasmic dynein remains associated with lysosomes and late endosomes[37], total *Drosophila* larval membranes[38], and adenovirus particles[39] under conditions of dynactin inhibition, indicating alternative dynein recruitment mechanisms. Cargo distribution and motility are, nonetheless, severely affected in these cases, supporting an independent role for dynactin in dynein motor regulation.

The compositional and structural complexity of dynactin would seem to argue against a simple role in dynein regulation. Dynactin has been found to increase dynein processivity by approximately two-fold in *in vitro* latex bead and single-molecule fluorescence assays[40–42]. Dynactin alone exhibits bidirectional diffusive behaviour along microtubules, and may also increase the frequency of bidirectional dynein movements[41,43]. Although these effects were originally thought to involve the p150^{Glued} microtubule-binding CAP-Gly domain, its deletion had no effect on peroxisome transport in *Drosophila* S2 cells[44], or on yeast dynein processivity in single-molecule analysis[42]. Nonetheless, mutations in the CAP-Gly domain are linked to neurodegenerative disease[45]. Mutations in this region also disrupt mitotic spindle organization in *Drosophila* S2 cells[44] and nuclear entry into the *Saccharomyces cerevisiae* bud[46]. This domain, possibly in association with the end-binding 1 (EB1) protein[47,48], is required for dynactin decoration of growing microtubule plus-ends in mammalian cells[49], which has been proposed to contribute to loading dynein-containing cargos to initiate minus-end transport[50] (Fig. 2b).

The contribution of dynactin to dynein processivity was abolished by N-terminal truncation of p150^{Glued} through coiled-coil domain 1 (CC1; ref. 42; Fig. 2a). This domain has also been implicated in dynein binding[32], and whether it contributes to processivity directly or indirectly remains to be explored. However, as dynactin interacts with the dynein intermediate chains, these results again raise the possibility of long-range allosteric control of dynein processivity by a mechanism acting through its tail. The dynein–dynactin interaction is reported to be inhibited by intermediate chain phosphorylation *in vitro*[50]; however, the consequence for dynein motor regulation remains untested.

Dynactin has also been implicated in microtubule plus-end-directed motor protein transport. p150^{Glued} interacts with some kinesins[51], including kinesin II, which it recruits to *Xenopus laevis* melanosomes through a site overlapping with or adjacent to the dynein binding site within p150^{Glued} (ref. 52). Both plus- and minus-end-directed transport along microtubules were inhibited by mutations in the *Drosophila Glued* gene[53] and by RNA interference (RNAi) of *Xenopus* p150^{Glued}, cytoplasmic dynein heavy chain and kinesin 1 (ref. 44). However, recent high temporal resolution analysis of vesicular transport in mammalian cells acutely inhibited for dynein and dynactin revealed the immediate effects to be specifically on microtubule minus-end-directed transport[54].

NudE/NudEL–LIS1. Classic (type I) lissencephaly in humans is caused by sporadic mutations in one of the two *LIS1* alleles, and the decrease in functional LIS1 severely affects brain development[55]. Nonetheless, LIS1 is a general and ubiquitous regulator of cytoplasmic dynein. LIS1 and cytoplasmic dynein each interact with NudE and its isoform NudEL, which are also involved in brain development and in general LIS1–dynein function.

Why reduced *LIS1* expression specifically affects brain development has been unclear until only recently, as have the cellular and molecular roles of LIS1 in dynein behaviour. RNAi studies in embryonic rat brain indicated roles for LIS1, NudE/NudEL and cytoplasmic dynein in neuronal migration, mitotic divisions of neural progenitor cells and growth cone advance (reviewed in ref. 3). Live imaging of centrosomes, nuclei and microtubules in brain slices revealed specific roles for LIS1 and dynein in minus-end-directed nuclear transport and anterograde translocation of the centrosome and its associated microtubule cytoskeleton[56]. Related roles for LIS1, dynein and NudE/NudEL have also been reported in non-neuronal cells, where these proteins co-localize at kinetochores, centrosomes, cell cortical regions

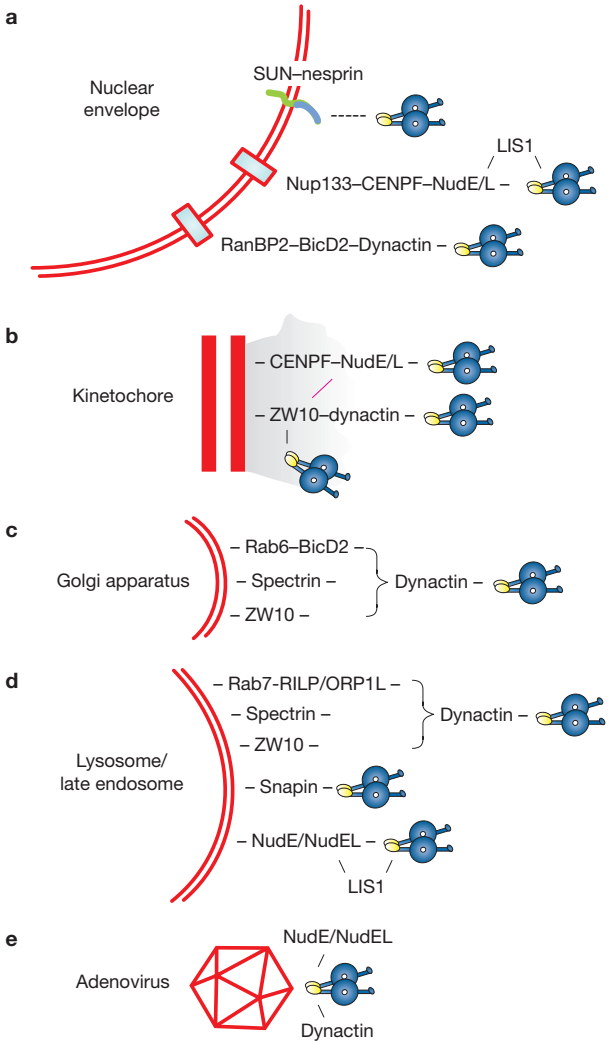

Figure 3 Cytoplasmic dynein cargo recruitment mechanisms. The diagram depicts the composition and organization of proteins currently known to be involved in recruitment or regulation of dynein (grey schematic) at selected better-studied forms of subcellular cargo (see main text for details). (**a**) Cytoplasmic dynein accumulates at the G2-prophase nuclear envelope through interactions with nuclear-pore-tethered factors and contributes to centrosome–nucleus attachment and nuclear envelope breakdown[62,75,76]. SUN–nesprin-mediated dynein recruitment contributes to nuclear migration in *Caenorhabditis elegans* embryos[81] and participates in mammalian brain development[82]. (**b**) Kinetochores recruit dynein, their sole microtubule minus-end-directed motor protein, using multiple recruitment mechanisms involving the factors CENPF, NudE/NudEL, ZW10 and dynactin[93–95], as well as spindly[100] (the role of which is less well understood). Whether these factors act in parallel or sequentially is unknown. (**c**) The Golgi apparatus owes its pericentrosomal localization to cytoplasmic dynein. Rab6, dynactin, ZW10, BicD1 and BicD2 have each been implicated in dynein recruitment to this organelle[36,84,88,89], as has spectrin[101]. (**d**) Lysosome/late endosome behaviour is also affected by multiple dynein regulatory factors, but which of these contribute to dynein recruitment in particular is uncertain. Rab7 recruits RILP and, in turn, dynactin[34,83,84]. Although dynactin is required for lysosome and late endosome transport, dynein can be recruited to these organelles independently through its light intermediate chain subunits[37]. NudE and NudEL might also prove to participate in dynein recruitment as evidenced by their more general role in lysosome and late endosome transport (compared with the more limited contribution of LIS1)[54]. (**e**) Adenovirus is the best-studied pathogenic form of dynein cargo. Dynactin, NudE/NudEL, and dynein each co-localize with adenovirus particles in infected cells. However, dynein is recruited directly through its light intermediate chain and intermediate chain subunits to the hexon capsid protein[39], suggesting that dynactin and NudE/NudEL may contribute only to dynein motor regulation.

and the nuclear envelope[57–62]. NudE and NudEL recruit LIS1 and dynein to these sites through direct interactions with LIS1 and with the cytoplasmic dynein intermediate chains and 8 K light chain subunit (LC8; refs 57,63; Fig. 2b). The ability of NudE, LIS1 and dynein to form a triple complex and the location of interaction sites within the components suggest that NudE/NudEL recruits LIS1 to the dynein complex, and may help position it close to the motor domain[21] (Fig. 2b).

LIS1 alone can bind to the dynein motor domain, but only during the pre-power-stroke stage of the cross-bridge cycle (mimicked by the presence of ADP-Vi; ref. 21; Fig. 2c). LIS1 strengthened the dynein–microtubule interaction, which is normally weak at this stage. Single-molecule laser bead trap analysis revealed that LIS1 substantially prolonged dynein stalls under load, leading to a marked increase in the ability of multiple dynein molecules to transport high loads[21] and identifying a previously unrecognized form of cytoplasmic dynein regulation. Curiously, NudE alone inhibited dynein motor activity in the same assays, although the complete LIS1–NudE–dynein complex showed a pronounced increase in the duration of the dynein–microtubule interaction under load[21].

The site of LIS1 binding within the dynein motor domain remains uncertain. Yeast two-hybrid[64] and mammalian cell co-expression experiments[65] demonstrated that LIS1 interacts with AAA1. Conventional steady-state solution assays revealed a relatively small inhibitory effect of LIS1 on dynein ATPase activity[21,66], although one study reported 40% stimulation[67]. It remains to be tested whether ATP hydrolysis is affected by LIS1 preferentially under high load conditions. An additional important issue is how the dimeric LIS1 molecule interacts with the two motor domains of the dynein complex. Laser trap escape experiments[21] imply that dynein movement along microtubules can persist in the presence of LIS1 under high load conditions. This conclusion argues against synchronization of cross-bridge cycles by LIS1, and suggests that it acts reciprocally on the two motor domains as they progress through the cross-bridge cycle out of phase.

LIS1 and NudE/NudEL are phosphorylated, the latter by CDK1, CDK5, Aurora B and ERK1 kinases. Specific effects of these modifications on the interactions of the components have been reported[59,61,68–70], although the functional consequences remain to be fully explored.

Tail-mediated motor regulation. The underlying mechanism for NudE and NudEL inhibition of dynein is unknown. NudEL was reported to interact with dynein motor domain fragments in a yeast two-hybrid assay[64]. No interaction was observed with the complete recombinant motor domain, however, although robust interactions with recombinant dynein intermediate and light chains were observed[57,63]. Reports that dynein bound NudE and NudEL through their intrinsically unstructured C-terminal domains[64,71] suggested that their N-terminal coiled-coils may extend from the base of the dynein molecule, potentially reaching the motor domains to sterically inhibit mechanochemical function[21] (Fig. 2c). A second dynein binding site has been identified near the NudEL N-terminus[70,72], although the relationship between the two sites remains uncertain.

As suggested earlier for dynactin, NudE might also modify dynein motor activity allosterically through the intermediate–light chain complex at the base of the dynein molecule. NudE and dynactin could thus influence a common process, conceivably the same one affected by the *Loa* mutation in the dynein tail. Further work is required to test this possibility, and to explore alternative models involving steric hindrance of dynein motor activity by the NudE and NudEL coiled-coil tail (Fig. 2b).

Relative contributions of dynein regulators to transport of specific cargoes

Numerous other dynein interactors have been identified in addition to dynactin, NudE/NudEL and LIS1 (reviewed in ref. 73; Fig. 3). Much of this complexity probably reflects diverse dynein cargo recruitment mechanisms, although contributions of the additional interactors to motor regulation directly or through dynactin and/or NudE/NudEL–LIS1 are also possible. Another important issue is whether individual cargoes use either one or both motor regulatory mechanisms for their transport.

Despite the number of dynein recruitment factors, patterns to their organization have begun to emerge from the most extensively studied cases (Fig. 3). Nuclei have been found to behave as dynein cargo under a variety of physiological conditions. In cultured mammalian cells, dynein is targeted to the late G2-prophase nuclear envelope, where it contributes to nuclear envelope breakdown[61,74,75]. Two apparently independent and non-redundant mechanisms for nuclear envelope recruitment have been implicated in this behaviour, involving chains of protein–protein interactions, each initiated by distinct nucleoporins[62,76,77] (Fig. 3).

Dynein also controls nuclear migration in neural progenitor cells in the developing central nervous system[56,78,79], potentially involving related or alternative dynein–nuclear-envelope recruitment mechanisms. LIS1 and dynactin have each been found to be necessary for nuclear migration in radial glial neural progenitors[78–80]. It is uncertain whether these factors are recruited by mechanisms involved in nuclear envelope breakdown in non-neuronal cells; it is also unclear how NudE– or NudEL–LIS1 and dynactin regulation is coordinated. Recent work indicates that NudE and dynactin compete for overlapping sites within the dynein intermediate chains[63], ensuring that individual dynein molecules cannot be occupied by both regulators. Given this situation, independent mechanisms for dynein cargo recruitment at the nuclear envelope might be required to permit both dynactin and LIS1 regulation. Finally, nesprins, which recruit dynein to the nuclear envelope in diverse systems[81], have also been implicated in nuclear migration during brain development[82], and it will be of interest to further explore specific roles of nesprin in nuclear envelope breakdown and neuronal migration.

Dynactin and NudE–LIS1 each participate in lysosome and late endosome transport. Dynactin is recruited to these structures through RILP (Rab7-interacting lysosomal protein; ref. 83; Fig. 3). However, dynein recruitment is independent of RILP (ref. 37), suggesting that the effects of dynactin inhibition[34,35,54] reflect a role in dynein motor regulation. ZW10, a protein initially implicated in dynactin and dynein recruitment to mitotic kinetochores, is also involved in lysosome motility[84]. Whether it serves specifically in lysosomal recruitment of dynactin or dynein is uncertain, although it acts independently of RILP (ref. 37). Spectrin and another Rab7 interactor, ORP1L (oxysterol-binding protein homologue 1L), are also needed for proper lysosomal distribution[83], but how these results relate to dynein recruitment or activation remains an important issue for further studies.

NudE and NudEL are essential for normal lysosome transport[85,86], but the role of LIS1 has been controversial[54,86,87]. Recent work has revealed that LIS1 inhibition interferes with axonal transport of large (but not small) lysosomes and late endosomes[54], supporting a role for LIS1 in transport under high resistance conditions. NudE/NudEL inhibition interferes more generally with lysosome behaviour[54,85], perhaps reflecting a role in lysosomal dynein recruitment.

Dynein recruitment to the Golgi apparatus exhibits some features common to lysosomes and late endosomes, such as the involvement of another small GTPase, Rab6 (refs 88,89) and ZW10 (refs 84,90; Fig. 3). The BicD (bicaudal D) family proteins also have important roles as dynein adaptors on Rab6 cargoes[91] (Fig. 3). Although the function of dynein at the Golgi apparatus is well-established, its specific roles at discrete stages of Golgi maturation are only partially understood[92].

The mitotic kinetochore is a well-known site for cytoplasmic dynein recruitment, but the underlying regulatory mechanisms remain incompletely understood. There are numerous recruitment partners and dynein may play multiple roles at this structure[57,93,94]. Phosphorylation may help orchestrate kinetochore dynein behaviour[93,95].

Finally, viruses represent an emerging and diverse group of dynein cargo. Dynein has been found to interact directly with adenovirus; dynactin and NudE also interact with the virus, albeit indirectly through dynein[39]. Nonetheless, dynactin is clearly involved in regulating dynein transport in this system, perhaps providing the clearest indication for discrete roles of dynactin in recruitment and regulation.

Conclusions

How generally these mechanisms apply to the broad range of additional organellar and macromolecular dynein cargo remains to be fully worked out, as does the functional relationship between dynactin and NudE–LIS1 in diverse dynein roles. Whether the latter proteins are recruited to lysosomes, nuclei and other organelles under load, constitutively or in response to developmental or physiological cues, remains to be explored. The emerging structural complexity of the dynein motor domain raises important questions regarding its interactions with extramolecular regulatory factors. LIS1 modulates the interaction of dynein with microtubules at the pre-power-stroke stage of the cross-bridge cycle, but the details of the underlying mechanism remain to be determined. Of equal interest is the mechanism responsible for dynactin regulation.

The mechanisms through which cytoplasmic dynein attaches to its diverse cellular cargoes are complex, and have emerged only gradually. Many questions remain about the details of dynein cargo recruitment, which should shed light on more general issues such as cell-cycle control of dynein behaviour. The identification of distinct modes of dynein motor regulation has expanded our understanding of how one motor protein contributes to such a broad range of cellular activities, from very rapid vesicular transport to a variety of very high-load functions.

Note added in proof: Since submission of this article, a further report of a role for LIS1 in axonal transport[102] and evidence for limited coordination between yeast cytoplasmic dynein motor domains[103,104] have been published.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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