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The Cytoplasmic Dynein Transport Machinery and its Many Cargoes

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Abstract

Cytoplasmic dynein-1 is an important microtubule-based motor in many eukaryotic cells. Dynein has critical roles both in interphase and during cell division. Here we focus on interphase cargoes of dynein, which include membrane-bound organelles, RNAs, protein complexes and viruses. A central challenge in the field is to understand how a single motor can transport such a diverse array of cargoes and how this process is regulated. The molecular basis by which each cargo is linked to dynein and its cofactor dynactin has started to emerge. Of particular importance for this process is a set of coiled coil proteins — 'activating adaptors' — which both recruit dynein–dynactin to their cargoes and activate dynein motility.

The microtubule cytoskeleton is responsible for long distance movements and spatial organization of intracellular vesicles, organelles, and large protein- and RNA-containing complexes in many eukaryotic cells. Microtubules are polarized structures with a minus and a plus end. In interphase cells microtubule plus ends are typically located near the periphery. Minus ends originate from microtubule organizing centres (MTOC), which are often located close to the nucleus, but are also found at other locations in the cell. In mitosis microtubules reorganize to form the spindle, with the microtubule minus ends focused at the two poles. The molecular motors, dyneins (minus-end-directed) and kinesins (primarily plus-end-

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directed), are responsible for many microtubule-based functions. Notably, plants and some algae lack dynein genes in their genome.

Dyneins were first discovered as the motors that drive flagellar beating in *Tetrahymena pyriformis*[1]. Subsequently, two dynein isoforms were found that are responsible for movement in the cytoplasm (cytoplasmic dynein-1) and cilia (cytoplasmic dynein-2)[2–5]. This review will focus on cytoplasmic dynein-1 (subsequently referred to as dynein). Dynein is an essential gene in a number of organisms, including *Dropsophila melanogaster* and mice[6,7] and mutations in the dynein transport machinery have been linked to neurological diseases. These include neurodegenerative disorders such as the Parkinson's-like Perry Syndrome, Spinal Muscle Atrophy with Lower Extremity Dominant (SMA-LED), Hereditary Motor Neuron disease, and Charcot-Marie-Tooth. They also include neurodevelopmental diseases such as lissencephaly **[G],** as well as other malformations of cortical development and intellectual disability[8].

Remarkably, a single dynein functions in the cytoplasm in animal cells, in contrast to the ~40 kinesins that perform related functions. This suggests dynein uses a different strategy to interact with its cargoes compared to kinesin. Here we address how a single dynein transports such a diversity of cargoes. We first discuss the structure of the dynein-based transport machinery. We then describe the main cargoes of dynein, which we group under four categories: membranes, RNAs, proteins, and viruses. We have limited this Review to interphase functions of dynein, as its mitotic and meiotic roles have been covered elsewhere[9].

The dynein transport machinery

After the discovery of dynein, it became clear that other factors were required for its activity. A large molecular weight complex, later named dynactin, was found to be necessary for vesicle movement along microtubules[10,11]. However, the two complexes only interacted weakly *in vitro*[12]. This interaction was shown to become stronger in the presence of an amino-terminal domain of BICD2 (BICD2-N), which is predominantly coiled coil[12]. BICD2 is the human homologue of *bicaudal-D,* which was originally identified as a polarity factor in *D. melanogaster*[13]. Recent studies demonstrated that BICD2-N dramatically activates the motility of isolated dynein–dynactin complexes to move long distances *in vitro*[14,15]. Additional coiled-coil-containing proteins have also been shown to activate dynein–dynactin motility (Table 1). We refer to these coiled-coil proteins as 'activating adaptors'. These proteins have the dual property of both activating motility and linking dynein–dynactin to their cargoes. Collectively, these results suggest the 'dynein transport machine' consists of 1) the dynein complex, 2) the dynactin complex, and 3) a coiled coil-containing activating adaptor (such as BICD2) (Fig. 1 and Table 1). Below we provide an overview of these three central components, as well as two additional regulators, Lis1 (PAFA1H1) and Nudel (NDE1 and NDEL1; collectively referred to as "Nudel" here), which associate with the dynein complex and are required for many dynein functions. Beyond activating adaptors, other connections between dynein and its cargoes have been shown to be involved in dynein transport (Box 1).

Structure of dynein

Human dynein is a 1.4 MDa complex composed of six different polypeptides all of which are present in two copies (Fig. 1a). There is a single dynein heavy chain gene (DHC; DYNC1H1) and two isoforms of each of the other components: the intermediate chains (DIC; DYNC1IC1 and 2), the light intermediate chains (DLIC; DYNC1LI1 and 2) and the three light chain families (DLCs): Robl (DYNLRB1 and 2), LC8 (DYNLL1 and 2), and Tctex (DYNLT1 and 3).

The DHC is 4634 amino acids long, containing a carboxy-terminal motor domain and an amino-terminal tail domain. Starting from the amino-terminus of the DHC, the 'tail' contains a dimerization domain (residues 1–200), followed by an extended region made up of nine helical bundles (residues 201–1420)[16–18] (Fig. 1b). The last helical bundle of the tail joins into the motor domain, which consists of the linker (itself also made of helical bundles), a ring of six AAA+ domains **[G]**, and a carboxy-terminal domain. The motor binds to its track via a microtubule binding domain (MTBD) at the end of a coiled-coil stalk that emerges from the AAA+ ring[19,20]. Dynein moves along microtubules by coupling ATP induced conformational changes in the AAA+ ring with bending and straightening of the linker[21].

The DIC contains a WD40 domain **[G]** that binds the DHC helical bundles 4 and 5, whereas the DLIC has a Ras-like domain **[G]** that contacts DHC helical bundles 6 and 7[16,18]. The DLIC is further anchored onto the DHC by amino- and carboxy-terminal helices (α1 and α13, respectively) that span out from the Ras-like domain and contact DHC helical bundles 8 and 5, respectively (Fig. 1b). The DICs have extended ~230 residue amino-termini that contact dimers of DLCs. One of these DLCs, Robl, binds both this amino-terminus and docks onto the WD40 domain of one of the DICs. The two DLICs have extended ~130 residue carboxy-termini (Fig. 1a), which contains two alpha helices (α14 and α15)[22]. The DLIC carboxy-termini contact activating adaptors and in some cases may also provide a direct link to cargo[23,24].

Structure of dynactin

The 1.1 MDa dynactin complex is composed of 23 subunits (11 different polypeptides; Fig. 1c)[25]. Its central feature is a short actin-like filament, which contains 8 copies of the actin related protein (Arp) 1 (ACTR1A and B), and 1 copy of ß actin (ACTB). The filament is capped at the barbed end **[G]** by the actin capping protein CapZ (CAPZA1 or CAPZA2, and CAPZB) and at the pointed end **[G]** by another actin related protein, Arp11 (ACTR10). Three other proteins p62 (DCTN4), p27 (DCTN6) and p25 (DCTN5) bind Arp11 to form a pointed end complex. A 'shoulder' domain sits on the filament near the barbed end. It is composed of 2 copies of $p150^{glued}$ ("p150"; DCTN1), four copies of p50/dynamitin ("p50"; DCTN2), and 2 copies of p24 (DCTN3). Extended peptides corresponding to the amino-terminus of p50 emerge from the shoulder and wrap around one side of the filament. The carboxy-terminus of p150 is buried in the shoulder and the amino-terminus forms a flexible extension with two stretches of coiled-coil (CC1 and CC2) interrupted by a globular domain. CC1 contains two halves, CC1a and CC1b, which form a hairpin structure. At the extreme

amino-terminus of p150 are the CAP-Gly and basic domains, which have been implicated in microtubule binding[26].

Activating adaptors

At the time of writing, eight activating adaptors have been shown to promote long distance movement of dynein–dynactin complexes in vitro (Table 1, Fig. 1d). There are no sequence motifs that are common to all of these activating adaptors. Instead the common features are 1) the presence of a long (> 200 residues) coiled coil, 2) a binding site for the DLIC carboxyterminus[23,24,27], and 3) a binding site for proteins (e.g. Rab6, Rab11, RZZ, FTS) that link the adaptors to their cargoes (Fig. 1d).

Activating adaptors contain at least three different types of binding sites for the DLIC carboxy terminus. BICD2, the BICD-related protein BICDL1 (also called BICDR1), and the kinetochore binding adaptor SPDL1 (Spindly) likely bind the DLIC via a motif referred to a "CC1-box" in their coiled coil[27]. The CC1-box contains an AAxxG sequence (where x denotes any amino acid). In contrast, HOOK3 and HOOK1 use a small "Hook domain", which is located amino-terminal to their coiled-coils[24]. The penultimate helix (α14) in the DLIC carboxy-terminus is the contact site for BICD2, SPDL1 and HOOK3[22]. The activating adaptor RAB11FIP3 (Rab11 Family-interacting protein 3) also binds the DLIC carboxy-terminus. The exact site of interaction is not yet known, but the region of RAB11FIP3 (residues 2–435[28]) that interacts with DLIC contains a pair of EF-hands **[G]**. Interestingly the same type of domain is also found in the activating adaptors Ninein (NIN) and Ninein-like (NINL), although these proteins have not yet been shown to bind the DLIC. All of the activating adaptors are known or predicted to be dimers.

Cryo-EM structures have been solved for dynein and dynactin in complex with three different activating adaptors (BICD2, BICDL1 and HOOK3)[16,17]. These cryo-EM maps are at medium (BICDL1) to low (BICD2, HOOK3) resolution in the regions around the activating adaptors, but are sufficient to reveal the main ways in which the activating adaptors bring dynein and dynactin together. In all cases an ~250 residue coiled-coil of the activating adaptor runs along the length of the dynactin filament (Fig. 1e). Their amino termini lie close to the barbed end of the dynactin filament and their carboxy-termini contact the pointed end complex. The coiled-coils of the activating adaptors interact with dynactin slightly differently, especially toward the pointed end. This is consistent with the lack of conserved motifs in the coiled-coils of different activating adaptors. Interestingly, BICD2, HOOK3 and BICDL1 can all recruit two dynein dimers at a time[16,29], although for BICD2 the recruitment of a second dynein dimer appears to be less efficient[16]. The second dynein lies next to the first along the dynactin filament (Fig. 1e). These interactions mediated by activating adaptors recruit dynein to dynactin so that the individual DHCs bind in grooves between dynactin filament subunits[16,17]. Importantly, these interactions induce large conformational changes in dynein that align its motor domains so that both microtubule binding domains can bind microtubules[18]. This likely underlies how activating adaptors increase the ability of dynein to move over long distances. The ability to recruit two dyneins to one dynactin further enhances this effect[16,29].

Dynein and dynactin also interact via the amino-terminus of the DIC contacting CC1 of p150[30]. This interaction may reinforce the interactions described above. Alternatively, a recent report suggested that this DIC–p150 interaction inhibits dynein[31], raising the possibility that binding of an activating adaptor could disrupt this interaction.

The activation of dynein includes a number of steps in addition to binding activating adaptors. Dynein in isolation can exist in an inhibited form, referred to as the "phi particle"[32], which not only binds weakly to microtubules, but is also unable to bind dynactin and activating adaptors[18]. The mechanism by which the phi-particle opens up is not yet known.

In addition to the known activating adaptors there are a number of possible candidate activating adaptors (Table 1, Fig. 1d). These proteins contain long coiled-coils and co-immunoprecipiate with both dynein and dynactin. Sequence analysis suggests many of these putative activating adaptors have domains that bind the DLIC, although as of yet this has not been directly tested. TRAK1 (trafficking kinesin binding protein 1), TRAK2 and HAP1 (Huntington interacting protein 1) contain the CC1-box motif[27], whereas NuMA (Nuclear mitotic apparatus protein), CCDC88A/Girdin, CCDC88B/Gipie, and CCDC88C/Daple all contain Hook domains (Fig. 1d).

An interesting question is whether RILP (Rab interacting lysosomal protein) and JIP3 (CJun-amino-terminal kinase-interacting protein3) are activating adaptors. Like known activating adaptors, both proteins can interact with dynein and dynactin[33,34], with RILP directly binding to the DLIC[23,35]. While RILP and JIP3 both have regions of coiled-coil, they are not long enough to bind to dynein and dynactin in the same way as other activating adaptors (Fig. 1d). They may therefore fall into a category of non-activating adaptors (Box 1) that serve as links between the dynein complex and cargo without the activation function.

Dynein regulation by Lis1 and Nudel

Two other central regulators of dynein are Lis1 and Nudel. They have been linked to dynein function genetically in many organisms (reviewed recently in[36]). Lis1, a dimer of two β-propellers **[G]** binds directly to dynein's motor domain at two distinct sites[37,38]. Nudel proteins are coiled coil-containing proteins that interact with the DIC and LC8, as well as Lis1[39–41]. There is evidence that Nudel may tether Lis1 to dynein[38,40]. The molecular mechanism of Lis1mediated regulation appears to be complex as in vitro experiments have revealed a range of Lis1 functions including decreasing[38,42,43] and increasing velocity of the dynein motor[37,44,45]. Based on experiments using *Saccharomyces cerevisiae* dynein, the effects Lis1 exerts on dynein depend on the nucleotide state at dynein's 3rd AAA+ domain[37]. The function of Nudel also appears to be complex as it can both enhance[38,46] and oppose Lis1 function in vitro[42,43]. Lis1 — likely in complex with Nudel proteins — has been implicated in multiple cellular processes, including localizing dynein to microtubule plus ends, initiating cargo transport, and supporting the ability of dynein to transport high-load cargoes (reviewed recently in[36]).

Dynein cargoes

The remainder of this Review focuses on the wide range of cargoes that dynein transports (Fig. 2). Studies with dextrans suggested that, while 500kDa molecules can diffuse freely across a cell, complexes larger than 2MDa are confined and effectively immotile[47]. Thus, cargoes for dynein are typically large objects, such as organelles and ribonucleoprotein (RNP) or protein complexes. Dynein can also act while it is anchored at the cell cortex **[G],** where it can act as a tether and/or generate pulling forces. Although many of these cargoes move bi-directionally owing to the interplay between dynein and kinesin, here we focus on dynein-based motility. For each cargo we describe its physiological role and discuss the evidence for the involvement of dynein in its dynamics. We also describe the current state of knowledge for how each cargo is linked to dynein–dynactin, highlighting the role of known or candidate activating adaptors (Table 1, Fig. 1d and Fig. 2). Our focus will be on vertebrates, although results from other organisms, such as flies and filamentous fungi, are also discussed.

Membrane cargoes

There are many discrete membrane-bound compartments in eukaryotic cells. Some of these are marked by small GTPases of the Rab family. Rabs bind effector proteins to direct trafficking processes including membrane tethering, fusion, and movement mediated by molecular motors[48]. Disrupting dynein function (Box 2) alters the cellular localization or motile properties of many of these membrane compartments.

Endoplasmic reticulum.

The endoplasmic reticulum (ER) is a meshwork of membranes consisting of tubules and sheets. Tubules are particularly dynamic and their movements require dynein as they are inhibited by overexpression of the dynactin component p50, which is a classic method for disrupting dynein–dynactin function (Box 2)[49]. Similarly, overexpression of p50 showed that dynein–dynactin is responsible for transporting ER membranes in neuronal dendrites[50].

Dynein also moves vesicles originating from the ER, which is spread throughout the cell, to the cell centre. These vesicles coalesce to form the ERGIC (Endoplasmic Reticulum Golgi Intermediate Compartment), a precursor compartment of the Golgi. Evidence for this comes from visualization of a secreted viral protein (VSVG) that exits the ER and moves rapidly to the centre of the cell. This movement is disrupted by overexpression of p50[51] and dynein colocalizes with markers of the ERGIC compartment[52].

It is not yet clear how dynein associates with either the ER or the ERGIC. These interactions could either be direct, or mediated by attaching to another vesicle that then interacts with dynein. The latter process, called “hitchhiking”, has been observed in filamentous fungi[53]. In *Ustilago maydis* ER vesicles comigrate with early endosomes[54], a cargo that requires dynein for movement in this organism[55]. It remains to be seen if ER hitchhiking is conserved in mammalian cells.

Golgi.

The Golgi apparatus is made up of stacks of membranes typically positioned near the nucleus. However in some organisms and cell types, the Golgi stacks are dispersed throughout the cytoplasm. In Golgi stacks, secreted proteins move from the nuclear proximal cis-Golgi compartment through the stack to the trans-Golgi network (TGN). From the TGN components are transported in Golgi-derived vesicles to the plasma membrane or to other organelles such as endosomes and lysosomes.

Dynein plays a key role in Golgi positioning. The Golgi is dispersed by deletion of dynein in mouse cells[7], injection of anti DIC antibodies, or over-expression of p50[56] (Box 2). The BICD adaptors (BICD1 and BICD2), which are involved in Golgi vesicle movement (see below), are not involved in this process, as over-expression of a carboxy-terminal fragment of BICD2 displaces endogenous BICD2 but has no effect on Golgi morphology[57,58]. A candidate adaptor for dynein-based Golgi positioning is GOLGA3 (Golgin 160), as its knockdown leads to Golgi dispersal and it co-immunoprecipitates with both dynein and dynactin. When GOLGA3 is ectopically recruited to non-Golgi membranes, it drives their movement towards the centre of the cell (“relocation assay”, Box 2)[59], which would be consistent with it acting as an activating adaptor for dynein–dynactin. While GOLGA3 is rich in coiled-coils, it lacks any obvious DLIC interacting motif and the region of the protein used in the relocation assay is too short to activate in a BICD2-like manner. Therefore, it is an open question whether GOLGA3 is a true activating adaptor.

Dynein has been directly linked to the movement of Golgi-derived vesicles via activating adaptors of the BICD family. In addition to bridging the dynein–dynactin interaction, BICD2 binds the Rab6 GTPase and localizes to cytoplasmic vesicles and the TGN[57,58] (Fig. 3a). Rab6-marked vesicles have been implicated in intra-Golgi, endosome to Golgi, Golgi to ER and Golgiderived exocytic vesicle trafficking[48]. Over-expression of a carboxy-terminal fragment of BICD2 displaces endogenous BICD2 from Rab6 vesicles and causes them to accumulate at the periphery of the cell[57,58]. This is presumably due to kinesin-driven transport dominating when dynein– dynactin is removed from the Rab6 vesicles[60].

BICDL1 is another Golgi-associated activating adaptor, which also binds Rab6 and is predominantly associated with exocytic Golgi-derived vesicles[61]. Unlike BICD1 and BICD2, BICDL1 is expressed predominantly early in embryonic development in neural and kidney tissue and regulates neurite outgrowth[61]. A related isoform, BICDL2, binds to Rab13[61] and is also associated with post-Golgi trafficking[62]. The activating adaptor NINL and the candidate activating adaptor HOOK2 (Table 1), have both been implicated in trafficking Rab8-marked Golgi derived vesicles that are destined for the base of the primary cilium[63,64].

Endolysosomal system.

Endocytosis is the process of internalizing portions of the plasma membrane, which can contain receptors and their ligands. Internalized membranes are sorted to various destinations including recycling endosomes **[G]**, late endosomes **[G]**, multivesicular bodies

[G] (MVBs), the TGN, and the lysosome. Each compartment is marked by one or more Rab GTPases.

Dynein is required for trafficking throughout the endolysosomal system. For example, knockout of dynein in mouse cells disperses lysosomes and endosomes[7]. Overexpression of p50 disrupts early and late endosome and lysosome distribution[56], inhibits trafficking of signalling receptors from the cell surface towards the centre of the cell[65], and blocks transport of endosomes along nerve axons[66].

Early endosomes are marked with the Rab5 GTPase. Activating adaptors of the Hook family have been implicated in linking these vesicles to dynein. Hook was first shown to have a role in endocytic trafficking in *D. melanogaster*[67]. Experiments in filamentous fungi subsequently linked Hook to dynein, showing that a Hook homolog was required to link Rab5marked early endosomes to the dynein machinery[68,69]. Mammals have three Hook-related proteins (HOOK1, HOOK2 and HOOK3). HOOK1 and HOOK3 have been directly linked to dynein-driven movement of early endosomes in axons[70].

Hook proteins are part of a complex called FHF, named after its components FTS (AKTIP), Hook, and FHIP (FAM160A2)[68,71,72]. The GTP-bound form of Rab5 interacts with the FHF complex in both *D. melagoaster*[73] and human cell[70] extracts. In *Aspergillus nidulans* FHIP can bind to early endosomes in the absence of the other two components[72] and two-hybrid interaction studies with human proteins suggest that FHIP can bind directly to the GTP-bound form of Rab5[70]. This suggests the FHF complex binds directly to Rab5 on early endosomes via the FHIP component, and the Hook protein recruits the dynein–dynactin complex (Fig. 3b).

Another potential connection between dynein and early endosomes is via Huntingtin (Htt) and HAP1 (Box 1, Fig. 1d). Htt binds to the GTP-form of Rab5[73] and has been linked to the movement of signalling endosomes (see also below)[74], as well as other membranous cargoes. In addition, Htt binds dynein[75] and HAP1 binds dynactin[76]. HAP1 is a candidate activating adaptor based on its homology to other adaptors (Fig. 1d, Table 1). An intriguing question is whether both Htt/HAP1 and the FHF complex are found on the same early endosomes, or whether they provide alternate routes to recruit dynein–dynactin (Fig. 3b).

Late endosomes are marked with the GTPase Rab7. Rab7 forms a complex with the cholesterol sensor ORP1L (oxysterol-binding protein-related protein 1L) and RILP (Box 1)[77]. RILP binds to GTP-bound Rab7[78], directly binds the DLIC[23,35], and is required to recruit dynein and dynactin to late endosomes and lysosomes[34] (Fig. 3c). Interestingly the ORP1L–Rab7–RILP complex also interacts with the HOPS complex **[G]**[71], which is implicated in late endosome trafficking[79]. The HOPS complex binds to the Hook-containing FHF complex[80,81], raising the possibility that late endosomes also engage Hook proteins to link them to dynein[82] (Fig. 3c). If this is confirmed, it will suggest that, as with early endosomes, there are multiple ways in which dynein can be recruited to late endosomes. Late endosomes mature into lysosomes, which are found in a perinculear region in some cell types. This positioning has also been linked to dynein– dynactin[56] and there is evidence that

lysosome motility and positioning is mediated by the same factors that are used by late endosomes[83].

In addition to the adaptors described above, a number of other proteins have been implicated in dynein's association with the endolysosomal system, including JIP3[33,84], AnkyrinB[85], Snapin[86] and Spectrin[87] (Box 1, Figs. 3b and 3c). These proteins all lack long coiled-coils, suggesting they are not activating adaptors. This raises the question of whether these proteins act together with an activating adaptor or can provide an alternate means of activating dynein–dynactin.

A subset of endosomes contains receptors that signal in the cytoplasm after internalization. These endosomes, called signalling endosomes, have been well studied in neurons, where growth factors bind to receptors at the nerve synapse, undergo endocytosis, and are transported back along the axon to the cell body by dynein–dynactin. For example, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) bind to the receptor tyrosine kinases TrkA and TrkB, respectively[88]. These NGF–TrkA and BDNF–TrkB complexes colocalize with both Rab5 early endosomes[89] and Rab7 late endosomes in axons[90], suggesting that signalling endosomes may use the same adaptors as early and late endosomes.

Many cells also have an endosomal compartment near the MTOC that is a nexus for receptor recycling to the plasma membrane and is distinct from early endosomes. These recycling endosomes are marked by Rab11[91]. RAB11FIP3 is a Rab11 interacting protein that is required to maintain the structure of recycling endosomes[92] and is a dynein–dynactin activator in vitro[14] (Table 1 and Fig. 1d). RAB11FIP3 is also required to deliver membranes to cilia[93] and the cytokinetic furrow[94]. As with endosomes, other adaptors may also recruit dynein–dynactin to recycling endosomes. For example, JIP3 has been shown to have a role in the movement of recycling endosomes during cytokinesis[95].

Melanosomes.

Melanosomes are pigment-containing organelles related to lysosomes. In many vertebrates, their movements are regulated to control skin colour changes. In pigmented cells of *Xenopus laevis*, antibodies against the DLIC block melanosome movement towards the cell centre[96]. In zebrafish lacking the protein ninein-like (NINL), melanosome transport is severely impaired. NINL interacts with components of the dynein and dynactin complex as shown via mass spectrometry experiments[97,98], and human NINL is an activating adaptor[98], suggesting that NINL is the activating adaptor for melanosome motility.

Autophagosomes.

Autophagosomes are double membrane vesicles formed after engulfment of organelles and proteins destined for destruction by autophagy. They are marked with the ubiquitin-related protein LC3. In HeLa cells autophagosomes move to the cell centre and cluster with lysosomes[99]. In neurons, autophagosomes can form at the axon tip[100] and then fuse with LAMP1- or Rab7-marked late endosomes to initiate transport towards the cell body[100–102]. Autophagosomes can also form in the soma[103].

A role for dynein in autophagy came from the observation that overexpression of p50 or p150 CC1 (Box 2) impairs autophagic clearance[104]. Furthermore, injection of an anti-DIC antibody inhibits clustering of LC3 autophagosomes in HeLa cells[99] and p150 CC1 overexpression inhibits their movement in neurons[100]. Because moving autophagosomes can fuse with late endosomes, a Hook protein may be the activating adaptor for dynein-mediated autophagosome transport. There is also evidence that Htt and the candidate activating adaptor HAP1 are important for autophagosome motility[105]. The protein JIP1 (c-Jun N-terminal kinase interacting protein 1) is also necessary for autophagosome motility[105,106]. JIP1 is structurally unrelated to JIP3 and lacks any predicted coiled-coil, suggesting it is not an activating adaptor. Intriguingly, autophagosomes have different motile properties than endosomes and lysosomes[107]. It is not yet clear what accounts for these differences.

Mitochondria.

Mitochondria move bidirectionally along microtubules and pause frequently. Their motility can respond to changes in cell signalling or axon growth, for example, which can lead to their accumulation in areas with high metabolic requirements[108]. Mutations in *D. melanogaster* dynein impair movement of mitochondria in axons, suggesting a direct role of dynein in retrograde movement (that is from the periphery to the cell body) of mitochondria[109]. Both dynein and kinesin associate with mitochondria via Milton (TRAK 1 and 2 in humans), which binds to the mitochondrial outer membrane protein Miro (RHOT1 and RHOT2 in humans)[110]. TRAK proteins co-precipitate dynein and dynactin from brain extracts[111], suggesting they interact with the dynein motor. TRAK1 and TRAK2 contain a region with similarity to BICDL1 and HAP1[60], raising the possibility that the TRAK proteins are activating adaptors of dynein–dynactin for mitochondrial motility (Box 1, Fig. 1d).

Peroxisomes.

Peroxisomes perform a variety of metabolic functions, including the breakdown of fatty acids and metabolism of hydrogen peroxide. Peroxisomes are relatively evenly distributed in cells and only 10–15% of them are mobile in many cell types[112]. Overexpression of p50 disrupts peroxisome motility in mammalian cells[113]. However, to date no peroxisome-specific dynein–dynactin adaptor has been identified.

In filamentous fungi, where peroxisomes move in a kinesin- and dynein-dependent manner[114], they do so by hitchhiking on moving early endosomes[54,115]. Peroxisomes co-migrate with Rab5-marked early endosomes and require endosome motility for movement. In *Aspergillus nidulans*, PxdA, a long coiled-coil-containing protein is required for hitchhiking, and may act to tether the two organelles[115] (Fig. 3d). It is not clear if the hitchhiking mechanism is used for peroxisome motility outside of filamentous fungi.

Lipid droplets.

Lipid droplets serve as lipid storage compartments and also provide a source of membrane lipid precursors[116]. Like peroxisomes they show both diffusive and microtubule-dependent movements[117]. Genetic studies in *D. melanogaster* and filamentous fungi have implicated kinesin and dynein in the bidirectional motility of lipid droplets[54,118,119]. In *D. melanogaster*

BicD, which is related to the mammalian BICD proteins, has been shown to have a role in lipid droplet movement[120]. However, it is unclear if this role is direct and no other adaptor proteins have been identified for lipid droplets to date. In the filamentous fungus, *U. maydis* lipid droplets hitchhike on early endosomes, like ER vesicles and peroxisomes[54].

Nuclei.

Dynein-dependent movement and positioning of nuclei occurs in many organisms ranging from yeast to humans. In mitosis dynein positions the spindle, which ultimately leads to nuclear positioning[121,122]. In interphase cells dynein also has direct roles in nuclear movement or positioning. Early demonstrations of this include defects in nuclear positioning in filamentous fungi with mutations in dynein or dynactin subunits[123,124] and defects in the movement of pronuclei **[G]** in *Caenorhabditis elegans* embryos depleted of dynein or dynactin[125]. In vertebrate cells dynein is responsible for the movement of nuclei during cell migration[126,127], interkinetic nuclear migration **[G]** in neural progenitor cells[128], and distributing and positioning nuclei in developing muscle cells (myoblasts)[129,130].

These different nuclear movements can be driven by dynein that is directly connected to the nucleus or by cortically anchored dynein pulling on microtubules emanating from MTOCs. A number of proteins have been identified as being important for linking dynein to the cell cortex or nuclear membrane. In mitosis NuMA and the LGN complex anchor dynein to the cortex[131]. In interphase, dynein is anchored to the nucleus by BICD2 via the nucleoporin RANBP2[132,133]. The nucleoporin Nup133 and the dynein regulator Nudel also have a role in localizing dynein to the nucleus[132,134]. In some cell types dynein may be recruited by different mechanisms. For example, Par6 is required for dynactin localization to the nuclear envelope in myotubes, and its depletion reduces the movement of recently fused myoblast nuclei within myotubes[133]. In *C. elegans* a protein related to the Hook family of activating adaptors, Zyg-12, is important for attaching dynein to the nuclear membrane[135].

RNA cargoes

Subcellular localization of mRNAs is a mechanism to locally control gene expression in many organisms[136]. The role of dynein in RNA localization was discovered in *D. melanogaster*[137], where mutations in the DHC or injection of antibodies against the DHC or p50 all lead to defects in mRNA localization in fly syncytial blastoderm **[G]**[138]. In mammalian cells there is no direct evidence for the role of dynein in RNA localization, although the DIC co-immunoprecipitates with the RNA binding proteins Staufen[139] and La[140].

mRNAs are transported in complex with proteins, as ribonucleoprotein particles (RNPs). In *D. melanogaster*, the localization of many RNAs requires BicD and the formation of transport competent mRNP complexes requires the RNA-binding protein Egalitarian (Egl). Egl binds directly to RNA and the carboxy-terminal cargo-binding domain of BicD, thus linking RNA to the dynein transport machinery[141]. As an example, the dynein–dynactin–BicD–Egl complex has an essential role during oogenesis in flies by controlling the localization of *oskar* and *bicoid* mRNAs, which are involved in anterior–posterior axis determination of the embryo[142]. These mRNAs, packaged as mRNPs, are transported from

nurse cells **[G]** into the oocyte along polarized microtubule arrays, requiring dynein, dynactin, BicD, and Egl for movement[143,144]. Once inside the oocyte, *bicoid* continues to require dynein to maintain its localization[145]. BicD also contributes to RNA localization in fly neurons, where it interacts with the RNA-binding factor, Fragile X mental retardation protein (FMRP)[146]. BicD and FMRP interact and move together bidirectionally in fly neurons, and both proteins are required for normal levels of dendritic branching **[G]**[146].

In filamentous fungi, RNAs are distributed by hitchhiking on early endosomes[147]. For example, in *U. maydis* mRNA-containing polysomes **[G]** are distributed throughout the cytoplasm by their association with dynein and kinesin-driven early endosomes[148,149]. It remains to be explored if hitchhiking is used by higher eukaryotes as a means to distribute or localize mRNA transcripts.

Protein cargoes

Aggresomes and misfolded proteins.

Misfolded proteins are processed by either chaperones, which refold them, or the ubiquitin-proteasome system, which removes them by proteolysis. When these pathways are overwhelmed, cells temporarily sequester these toxic protein species. The misfolded proteins are transported to juxtanuclear structures known as aggresomes that can be eventually processed by autophagy[150]. Overexpression of p50 (Box 1) prevents the formation of aggresomes, implicating dynein–dynactin in their formation[151,152]. Three pathways have been reported to recognize misfolded proteins and connect them to dynein– dynactin. The first depends on HDAC6, which links polyubiquitylated proteins to dynein– dynactin[153]. The precise protein–protein interactions underlying the connection of HDAC6 to dynein–dynactin are not known. A second pathway uses SQSTM1 to link polyubiquitylated proteins to dynein through an interaction with the DIC[153]. HDAC6 and SQSTM1 interact with each other[154], although depletion of HDAC6 increases the amount of SQSTM1 that interacts with dynein, suggesting that HDAC6- and SQTSM1-dependent pathways might act competitively[155]. A third pathway uses the Hsp70 co-chaperone BAG3 to couple misfolded proteins to the dynein–dynactin complex. This pathway does not require ubiquitylation to target proteins to the aggresome[156]. The BAG3–dynein interaction is bridged by the 14–3-3 protein **[G]**, which interacts with BAG3 and the DIC[157]. No known activating adaptor has been so far implicated in aggresome formation.

Transcription factors.

Although small proteins can move quickly by diffusion, there is evidence that some are transported by dynein. For example, transcription factors are translated locally in axons in response to nerve injury and then transported in a retrograde direction along microtubules. This relocalizes them to the nucleus where they activate a transcriptional response[158]. The transcription factor STAT3 immunoprecipitates with dynein and disruption of microtubules prevents its accumulation in the nucleus in response to axon damage[159]. The connection between dynein and STAT3 may involve importins **[G]**, as a peptide that blocks the STAT3 interaction with importin reduces the ability of STAT3 to immunoprecipitate with dynein[159,160].

Intermediate filaments and microtubules.

Intermediate filaments are cytoskeletal components that contribute to cell shape, motility and organelle positioning[161]. Dynein participates in the subcellular distribution of vimentin intermediate filaments. Vimentin moves along microtubules[162], and overexpression of p50 (Box 1) redistributes vimentin from the perinuclear region to the cell periphery[163]. In addition, vimentin co-immunoprecipitates with dynactin[164]. Depletion of the DHC also impairs the retrograde motility of intermediate filaments present in neurons, known as neurofilaments[165]. This might reflect a direct interaction of dynein with some neurofilaments, as neurofilament-M interacts with the DIC[166].

It has also been shown that dynein can contribute to the movement of microtubules. Cell body-originating microtubules are transported into developing axons in rat neuron cultures via a process that is blocked by expression of p50 (Box 1)[167]. Because these dynein-dependent microtubule movements are anterograde (in the opposite direction from normal dynein transport in the axon) it suggests that the microtubules move by sliding over dynein anchored to the cortex[165]. Cortically anchored dynein also drives the formation of a uniformly polarized microtubule network in *D. melanogaster* neurons[168].

Centrosomal components.

Centrosomes are the sites of microtubule nucleation and typically anchor microtubule minus ends[169]. Dynein has a role in transporting proteins to the centrosome. For example, expression of the CC1 domain of the dynactin subunit p150 (Box 2) disrupts the localization of CDK5RAP2 (also known as CEP215) to the centrosome[170]. CDK5RAP2 is required for γ-tubulin **[G]** localization and microtubule polymerization[171]. CDK5RAP2 contains a long region of predicted coiled-coil and co-immunoprecipitates with the DIC, although further work will be required to determine if it is an activating adaptor for dynein cargos destined for the centrosome. There is evidence that the known or candidate activating adaptors, NIN, NINL and HOOK2 are enriched at the centrosome[172–174]. These proteins have a role in nucleating microtubules, suggesting that they may transport factors required for this process to centrosomes.

Centriolar satellites are smaller motile structures that contribute material to centrosomes and are important for ciliogenesis[175]. Dynein interacts with components of satellites[176], and overexpression p50 (Box 1) disperses them[177]. In neuroblastoma cells, the activating adaptor HOOK3 localizes to and is important for the function of centriolar satellites, raising the possibility it activates dynein–dynactin to drive the movement of satellite components towards the MTOC[178].

Finally, dynein also has a role in tethering centrosomes to the nucleus. Depletion of BICD2 or RANBP2, which are located on the nucleus, severs the tight association of centrosomes and the nucleus[133].

Viruses

There are seven classes of viruses and members from every class use dynein for some aspect of their life cycle (Table 2). The most common roles are related to viral replication. For

example, DNA and RNA viruses that replicate in the nucleus use dynein motility to reach it[179–182]. Some retroviruses, which reverse transcribe their RNA genomes into DNA in the cytoplasm, use dynein to deliver the DNA to the nucleus for integration into the nuclear genome[183]. In addition some DNA and RNA viruses that replicate in the cytoplasm in "perinuclear factories" also require dynein to accumulate at these sites[184–188].

In addition to using dynein to reach their site of replication, some viruses use dynein at other stages of their life cycles. Rabies virus uses dynein for motility along neural axons, which allows it to spread from the site of infection to other parts of the nervous system[189]. Dengue virus uses dynein during the assembly of new viral particles[188]. Hepatitis C virus triggers dynein-dependent clustering of lipid droplets at the MTOC, which are then incorporated into newly formed viral particles[190]. Hepatitis B virus uses dynein to cluster mitochondria close to the nucleus, perhaps to provide energy for its replication[191]. Finally, there is evidence that Influenza virus requires dynein to disassemble the viral capsid to release its RNA to the cytoplasm. HDAC6 is also required for this release step, suggesting that HDAC6 serves as a dynein adaptor in this context[192].

The connections between viruses and dynein during viral particle transport can either be direct or indirect. Examples of viruses that use direct interactions include Herpes Simplex Virus and Pseudorabies Virus[193]. In these cases, the viral inner tegument proteins (which are attached to the capsid) are required for dynein binding[194]. The prime candidate for interaction with dynein is pUL36, which is a potential activating adaptor of dynein, as it is active in a relocation assay (Box 2)[195]. Adenoviral particles may also travel by direct interaction with dynein after infection and may use this transport to reach the nucleus[196]. The adenovirus capsid protein, hexon, immunoprecipitates with dynein and interacts with both DLIC and DIC[197]. The interaction with dynein is stimulated by phosphorylation of the DLIC Ras-domain[35], suggesting a direct interaction with dynein. However, the role of dynactin in adenoviral intracellular transport is less clear, as dynactin did not immunoprecipitate with hexon[197], but p50 overexpression (Box 1) blocked nuclear accumulation of the adenovirus[196]. There is also evidence that other viruses interact directly with dynein–dynactin[183,187,198].

Examples of indirect dynein-based transport involve viruses that move intracellularly within endosomes. Adeno-associated viral particles, for example, which move along neural axons, colocalize with Rab7 vesicles[180]. Rabies viral particles also move within vesicles and in this form are transported along neuronal axons[189]. Their dynein-directed movement depends on the envelope glycoprotein, as it was shown that incorporating this protein into retroviral capsids allows retrograde transport of retroviral particles along axons[199]. How the viral glycoprotein regulates dynein is a mystery, as it is localized within the moving endosome rather than on its cytoplasmic face.

Conclusions and perspectives

While a vast number of dynein cargoes have been described, there are likely to be many more. For example, recent proteomic experiments have identified a number of putative new cargoes linked to dynein by the BICD1, BICD2, HOOK1, HOOK3, NIN or NINL activating

adaptors[98]. Here we have focused largely on cargoes that dynein translocates along microtubules, but dynein can also function anchored at the cell cortex, where it can capture the plus ends of dynamic microtubules[200]. New dynein "cargoes" may include specific cortical sites that anchor dynein, as suggested by studies that find dynein on the cortex at adherens junctions[201] and focal adhesions[202], and the numerous cortically localized proteins found in the dynein interactome[98].

This large number of dynein cargoes raises many questions related to how dynein achieves cargo specificity. What molecular interactions will mediate binding of dynein to new cargoes? Do some cargoes hitchhike rather than recruit dynein directly[53]?

In this Review we have emphasized the role of activating adaptors in dynein–dynactin motility. A question for the future will be to determine if all dynein cargoes, including viruses, require an activating adaptor. Reconstitution experiments will be required to verify if all current candidate activating adaptors (i.e. BICD1, HOOK2, CCDC88A, CCDC88B, CCDC88C, TRAK1, TRAK2, NUMA, and HAP1) are indeed able to activate dynein–dynactin motility. If there are fewer activating adaptors than cargoes, how does dynein achieve cargo specificity? Additional proteins that are not activating adaptors are likely required to regulate dynein. For example, as discussed above, the dynein–dynactin interacting proteins, RILP, JIP3 and Htt may be involved in adding cargo specificity to an already activated dynein–dynactin complex.

There may also be mechanisms to activate dynein that do not require activating adaptors. Presumably these factors will also release dynein from its autoinhibited "phi" conformation[18]. It is also possible that large clusters of dynein motors could overcome the need for activating adaptors or even for the interaction with dynactin, as dynein groups can processively move beads in vitro in the absence of both dynactin and any activator[203].

Finally, while we have focused on dynein-based movements in this Review, many cargoes move bi-directionally[204]. Some cargoes that move bidirectionally can switch directions rapidly implying that there is coordination between opposite polarity motors. What regulates this coordination? Do activating adaptors, some of which can also bind kinesins[61,98,205], have a role in this process?

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Biography

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Andrew Carter is a programme leader at the Medical Research Council Lab of Molecular Biology (MRC LMB), Cambridge, UK. He was a postdoctoral fellow with Ron Vale at the University of California, San Francisco, USA and a graduate student at the MRC LMB, Cambridge, UK with Venki Ramakrishnan. His lab studies the structure and mechanism of dynein based transport.

Glossary terms

Lissencephaly
Derived from Greek for “smooth brain”, lissencephaly is a spectrum of developmental disorders characterized by defective neuronal migration and the resulting lack of brain folds and grooves.

Cell cortex
The cytoplasmic face of the plasma membrane.

AAA+ domain
An “ATPase associated with diverse cellular activities” domain is a highly conserved ATPase fold.

WD 40 domain
A structural domain formed from WD40 repeats, themselves composed of approximately 40 amino acids and often ending in tryptophan (W), followed by aspartic acid (D).

Ras-like domain
A protein domain with sequence similarity to the GTPase domain of Ras.

Barbed end
When actin filaments are decorated with myosin motor domains and visualized by electron microscopy the barbed end is the end where myosins can be seen protruding; similar nomenclature is used to refer to the equivalent end of the Arp1 minifilament in dynactin.

Pointed end

When actin filaments are decorated with myosin motor domains and visualized by electron microscopy the pointed end is the end where myosins cannot be seen protruding; similar nomenclature is used to refer to the equivalent end of the Arp1 minifilament in dynactin.

EF-hands
A helix-loop-helix protein structural domain that often confers a protein with calcium-binding ability.

β-propellers
A protein structural domain characterized by 4–8 wedge-shaped beta sheets arranged similarly to the blades on a propeller.

Recycling endosomes
Endocytic vesicles characterized by the presence of the protein Rab11, which direct the anterograde trafficking of materials to the cell surface.

Late endosomes
Pre-lysosomal endocytic vesicles with lower internal pH relative to early endosomes, and characterized by the presence of the protein Rab7.

Multivesicular bodies
Late endosomes that contain multiple internalized vesicles.

HOPS complex
The "homotypic fusion and vacuole protein sorting complex" is a multisubunit membrane tethering complex that participates in organelle fusion events within the endolysosomal system in concert with Rab proteins.

Pronuclei
Refers to the distinct egg and sperm nuclei that are present within a single cell at the onset of fertilization before the fusion of their genetic material.

Interkinetic nuclear migration
The cell cycle-dependent movement of nuclei observed in neural progenitor cells.

Syncytial blastoderm
Drosophila melanogaster early embryos comprise a syncytial blastoderm, which is characterized by multiple nuclei residing in a shared cytoplasm, and is the result of multiple nuclear divisions in the absence of cytokinesis.

Nurse cells
A group of fifteen polyploid *Drosophila melanogaster* ovarian cells that share a cytoplasm with each other and the developing oocyte and function to support the development of the oocyte by providing nutrients and biomolecules (mRNAs and proteins) through intercellular connections called ring canals

Dendritic branching

The process by which a dendrite, the portion of neuron that receives signals from other cells, forms the cellular projections it contributes to synapses.

Polysomes
The complex formed by two or more ribosomes simultaneously engaged in translation along the length of a single messenger RNA.

14–3-3 protein
A conserved family of adaptor proteins that interact with diverse proteins and regulate their function through, for example, altered localization, activity, or stability

Importins
Proteins that recognize and deliver proteins with nuclear localization signals into the nucleus through nuclear pores.

γ-tubulin
Tubulin family member that, as a component of γ-tubulin ring complexes, templates nascent microtubules.

SNARE
Proteins that are anchored to either donor or acceptor membranes, mediating fusion between distinct membranes.

BLOC-1 complex
(biogenesis of lysosome-related organelles complex-1) A multi-subunit protein complex that contributes to membrane tubulation, which is important for sorting and organelle biogenesis in the endolysosmal system.

Total internal reflection microscopy
This microscopy techniques results in illumination of only a region approximately 100 nm from the coverslip surface, allowing high signal-to-noise ratios to be achieved, which makes it feasible to image and track single molecules.

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Box 1 |

Other connections between dynein and its cargo.

In addition to the activating adaptors or candidate activating adaptors (Table 1) a number of other links between dynein–dynactin and its cargoes have been reported. Here we present some prominent examples.

RILP is required for dynein–dynactin recruitment to Rab7 lysosomes[34]. Because RILP interacts with the HOPS complex it may be involved in linking dynein–dynactin to Rab7 (Fig. 3c). Purified RILP co-precipitates with purified dynein DLIC1, suggesting a direct interaction with the complex[23,35].

Huntingtin (Htt) and ***Huntingtin-associated-protein1*** (HAP1) associate with membrane vesicles[75] and are transported in neurons along microtubules[206]. Htt is linked to signalling endosomes[74] and autophagosomes[105]. Htt and HAP1 knockdown decreases retrograde movement of autophagosomes[105]. Htt binds purified dynein[75], suggesting a direct interaction that does not require dynactin. HAP1 co-immunoprecipitates with p150 from brain lysate[76,207]. HAP1 contains a coiledcoil and has sequence similarity to TRAK and BICDL1[60] (Fig. 1d, Table 1), raising the possibility that it is a BICD-like activating adaptor.

c-Jun N-terminal kinase (JNK) interacting proteins (JIPs) are implicated in the motility of dynein–dynactin cargoes. JIP1 depletion inhibits retrograde transport of amyloid precursor protein[208] and autophagosomes[106] in neurons. JIP3 co-immunoprecipitates with dynactin and colocalizes with dynein and dynactin on vesicles in neurons[33]. JIP1 lacks coiled-coils, whereas JIP3 contains two short stretches of coiled coil (Fig. 1d). JIP4 is closely related to JIP3 and shares the same domain architecture.

Ankyrin B (AnkB) knockout mice show reduction in the speed of fast axonal transport of early endosomes, lysosomes, mitochondria and synaptic vesicles. AnkB binds the lipid PI(3)P on membrane cargoes and directly contacts the pointed-end complex of dynactin[85].

Sorting nexins (SNX) are a large family of membrane-associated proteins that contain a lipid binding PX domain. Affinity tagged SNX5 and SNX6 co-precipitate with dynein and/or dynactin from human cell lysates[209,210].

Spectrin is a peripheral membrane protein that co-immunoprecipitates with dynactin[87]. While a two-hybrid screen reported an interaction between spectrin and Arp1[211], the structure of the dynein– dynactin–BICD2 complex shows little fully exposed Arp1, which would be available for binding[17].

Snapin, a SNARE **[G]** interacting protein that is part of the BLOC-1 complex **[G]**[212], has been implicated in the retrograde movement of late endosomes and suggested to be a dynein adaptor[86]. Snapin is required for dynein to localize to late endosomes and GST-snapin co-precipitates with dynein and dynactin components from brain lysate[86]. However, because these in vitro experiments were done in the absence of other BLOC-1 complex members, they should be revisited.

Direct cargo binding to dynein. In addition to its interaction with activating adaptors, the DLIC can form direct interactions with cargoes, such as the adenoviral hexon protein[35], pericentrin[213] and Par3[214]. The dynein light chains LC8 and Tctex bind motifs found in many proteins, leading to the idea that DLCs directly recruit proteins to dynein. However, because these motif binding sites on the DLCs bind to the DIC amino-terminus, the current consensus is that this is not the case[215]. Many of the DLC binding motifs likely recruit LC8 or Tctex for dynein-independent functions, such as dimerization. However, there is some evidence for cargoes connecting to dynein via DLCs, including some viruses[181], rhodopsin[216,217], and the Rho GEF Lfc (ARHGEF2)[218]. Additional structural studies will be required to determine if peptides from these proteins can bind to DLCs that are already in complex with the DIC amino-terminal peptides; NMR mapping experiments suggest that this may be possible[218,219].

Box 2 |

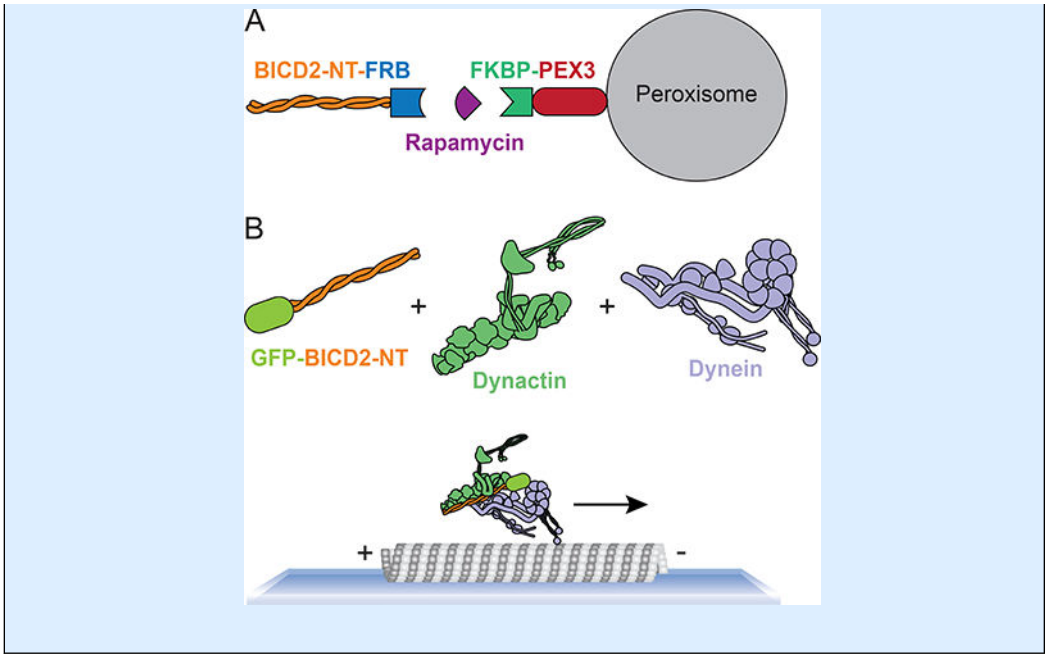
Methods to study dynein function and activation

Components of the dynein machinery have been depleted using RNA interference and CRISPR methods and genetic studies have revealed the functions of many components. Several other widely used methods have been important for determining if dynein or dynactin are involved in a process of interest. Over-expression of dynactin components, such a dynamitin/p50[220] (Fig. 1c) or one of the coiled coil segments (CC1) of p150[221] (Fig. 1c) result in the disruption of many dynein–dynactin-dependent processes. The exact mechanism of disruption is not completely clear, but probably involves disruption of the dynein–dynactin interaction[222]. Antibodies raised against the DIC (Fig. 1a) have also been extensively used to block dynein function in cell-free systems or systems amenable to antibody injection[223].

A number of methods have been used to provide evidence that a dynein adaptor is an activating adaptor. All activating adaptors co-immuoprecipitate with dynein and dynactin, providing an initial suggestion that a candidate adaptor could be an activating adaptor[98]. Cell-based “relocation assays” have also been used to provide evidence for dynein–dynactin activation[224,225]. In these experiments, a candidate activator is targeted to a largely non-motile organelle, such as the peroxisome. Any increase in minus-end-directed peroxisome motility provides indirect evidence that a candidate adaptor could be an activating adaptor. For example, the amino-terminus of BICD2 can be fused to the rapamycin-binding domain FRB. FKBP, which also binds rapamycin, is fused to an organelle targeting protein, such as the peroxisomal protein PEX3. In the presence of rapamycin BICD2 enhances peroxisome motiltiy[225] (see figure part a).

In vitro motility experiments can also provide indirect evidence for activating adaptors. For example, candidate activators can be used to immunoprecipitate dynein and dynactin from cell lysates or tissue extracts and then the motile properties of the immunoprecipitated complex can be assessed using single-molecule motility assays[14,98]. A variation of this method is to visualize dynein or dynactin directly in lysates without prior immunoprecipitation[226].

The gold standard for determining if a candidate adaptor is a dynein–dynactin activator is to reconstitute motility from purified components, as has been done for BICD2, BICDL1, HOOK3, NIN and NINL[14–16,24,98]. In this approach each protein or protein complex is purified separately and at least one component is tagged with a fluorescent marker. Motility is then monitored using total internal reflection microscopy **[G]**. Bond fide activators lead to processive dynein–dynactin motility (see figure part b).



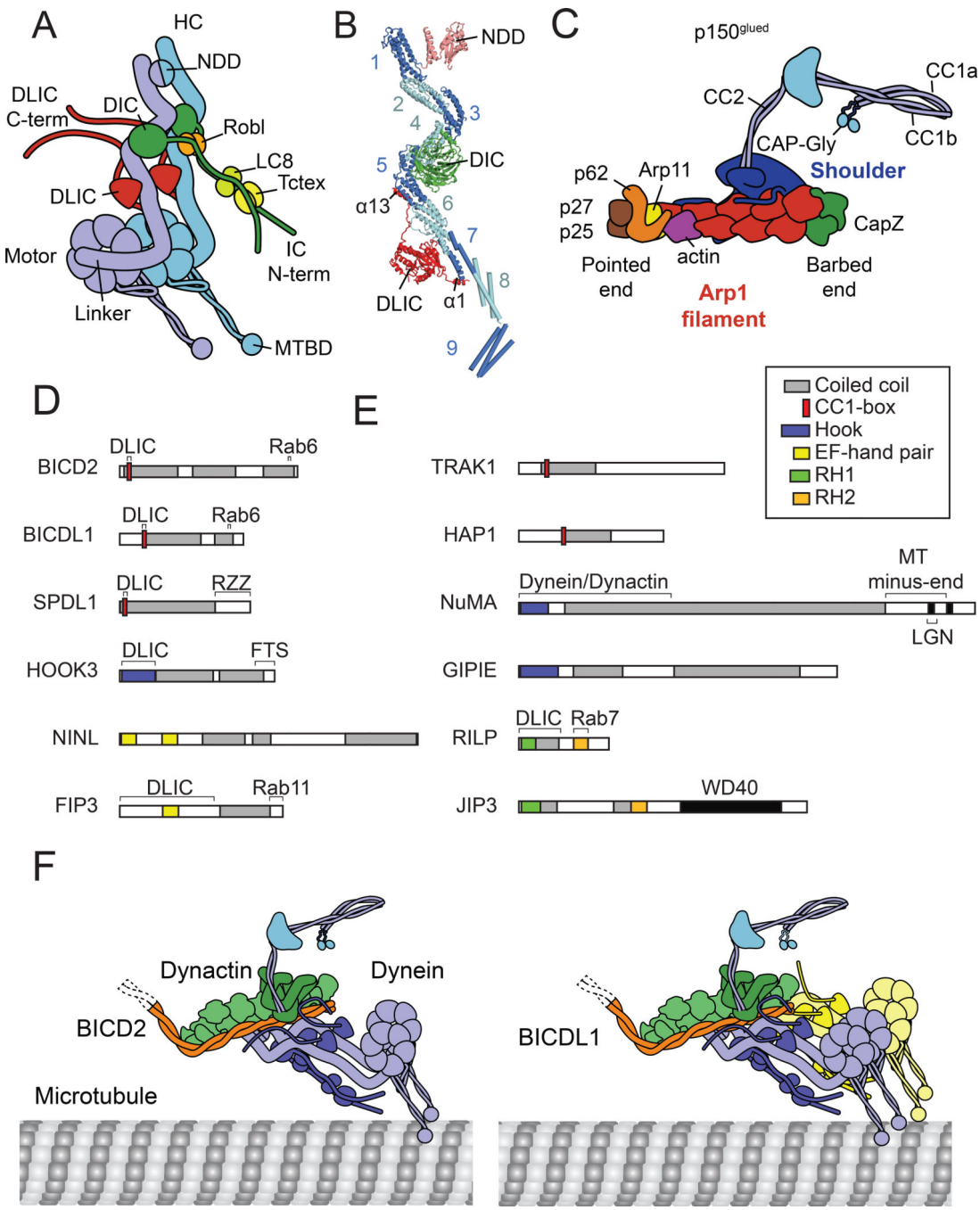


Figure 1 |. The dynein transport machinery.

a | Cartoon of cytoplasmic dynein-1. The two dynein heavy chains (DHCs) are linked together by an amino-terminal dimerization domain (NDD) and have a carboxy-terminal motor domain with a microtubule binding domain (MTDB) at the end of a long anti parallel coiled-coil stalk. The intermediate chains (DIC) have extended amino-termini that bind dimers of the light chains Roadblock (Robl), LC8 and Tctex. The light intermediate chain (DLIC) has an extended carboxy-terminus. **b** | Structure of the dynein tail[16,18] (PDBs 6F1T and 5NVU) showing the amino-terminal dimerization domain (NDD) and nine helical

bundles (1–9; neighbouring bundles are shown in different shades of blue to distinguish them) in the DHC and depicting interactions of DHC with DIC and DLIC. The DIC WD40 domain binds bundles 4 and 5, whereas the Ras-like domain of DLIC binds to bundles 5 and 7, using its amino- and carboxy-terminal helices (α1 and α13). The DIC and DLIC extended termini are not shown. The structure of helical bundles 8 and 9 is approximate. **c** | Dynactin is built around a filament of eight actin related proteins (Arp1). At the barbed end are capping proteins (CapZ). At the pointed end is an actin monomer, another actin related protein (Arp11) and a complex of three proteins (p62, p27 and p25). The shoulder domain binds the filament via extended amino-terminal peptides of p50/dynamitin. The p150 component extends from the shoulder, containing stretches of coiled-coil (CC2, CC1b and CC1a). At the amino-terminus of p150 are the basic and CAP-Gly domains that can interact with microtubules. **d** | Domain structure of known and candidate activating adaptors (see also Table 1). Reported sites of interactions are indicated above each cartoon. Key shows domains identified in the literature or by InterPro. RH1 and RH2, RILP homology 1 and 2. **e** | Dynein–dynactin–activator complexes on microtubules. The activating adaptors BICD2 or BICDL1 run along the dynactin filament and recruit the dynein heavy chains. BICD2 preferentially recruits one dynein dimer (left), whereas BICDL1 recruits two dimers (right).

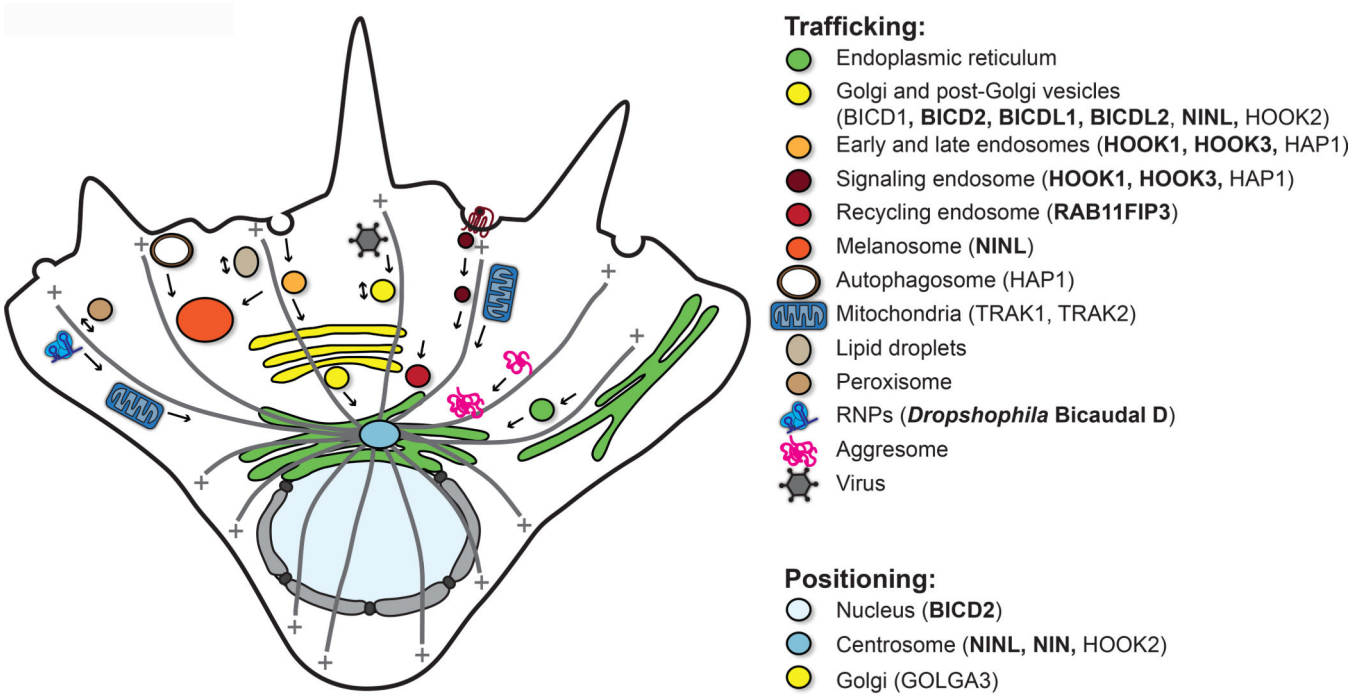


Figure 2 |. Many cargoes of dynein and their activating adaptors.

Many of the dynein cargoes discussed in this Review. Some cargoes are trafficked along microtubules, while in other cases the role of dynein is to position them. Known activating adaptors are marked with a star. Candidate activating adaptors are also listed.

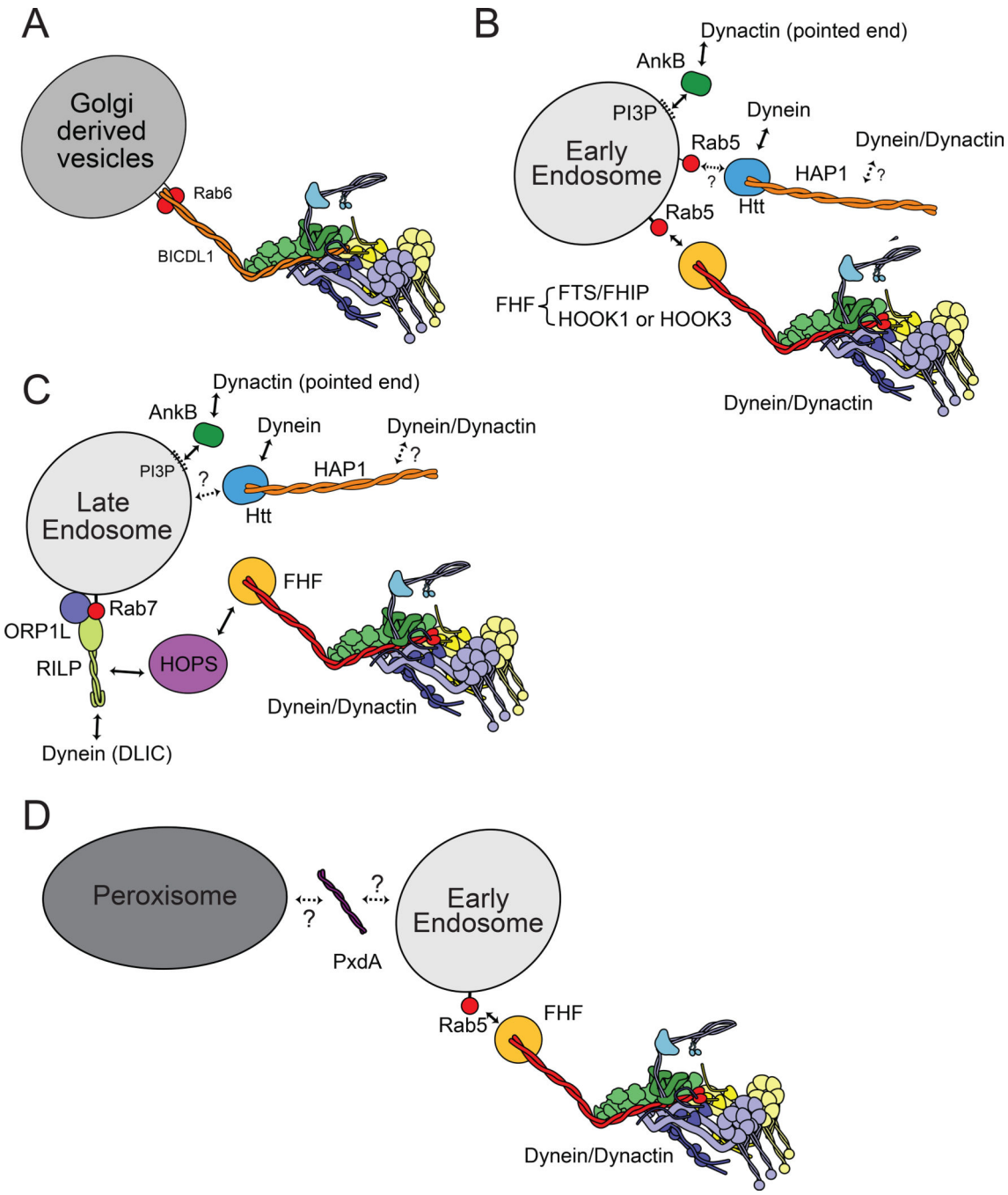


Figure 3 |. Mechanisms linking dynein and dynactin to membrane cargoes.

a | Dynein– dynactin associates with Golgi-derived vesicles using the activating adaptors BICD2 or BICDL1 depending on the cell type. Both BICD2 and BICDL1 bind, via their carboxy-terminal coiled-coils, to a dimer of the small GTPase Rab6. Rab6 binds to Golgi-derived membranes via its prenyl tails, as do other Rabs[48]. **b** | Early endosomes recruit dynein–dynactin via the activating adaptors HOOK1 or HOOK3. These adaptors bind the FTS and FHIP proteins to form the FHF complex. FHIP is reported to bind directly to the early endosome marker Rab5. Rab5 also binds Htt, which is linked to HAP1, another

potential activating adaptor. The PI3P binding protein ANK-B binds the pointed end of dynactin and is also important for early endosome transport. How these and other dynein–dynactin adaptors work together is unknown. **c** | Late endosomes are marked with Rab7, which binds RILP and the cholesterol sensor ORP1L. RILP binds the DLIC. RILP also binds the HOPS complex, which interacts with the FHF complex, raising the possibility that HOOK proteins also link dynein–dynactin to late endosomes. As with early endosomes, other potential dynein–dynactin links have been reported for the movement of late endosomes. **d** | In filamentous fungi some cargos (peroxisomes, ER, lipid droplets, and RNPs) associate with the dynein transport machinery indirectly by hitchhiking on early endosomes, which can directly recruit the transport machinery via the Hook-containing FHF complex (see part b). PxdA is a putative tether that links peroxisomes to early endosomes although how it interacts with both peroxisomes and early endosomes is unknown.

Table 1 |

Activating adaptors and candidate activating adaptors for dynein–dynactin.

Activator or candidate activator	Evidence	Cargo
Confirmed activators (active in in vitro motility assays)		
BICD2	Reconstituted motility[14,15], relocation assay [224]	COP1-independent Golgi-to-ER vesicles[58], Golgi vesicles[57], nuclear pore complexes[133]
BICDL1 (BICDR1)	Reconstituted motility [16]	Rab6 vesicles[61]
SPDL1 (Spindly)	Co-IP motility[14]	Kinetochore[227]
HOOK1	Lysate motility and relocation assay[226]	Rab5 early endosomes[70] Clathrin-independent cargoes[228]
HOOK3	Reconstituted motility[24], Co-IP motility[14], lysate motility and relocation assay [226]	Rab5 early endosomes[70], Golgi [229]
NIN (Ninein)	Reconstituted motility[98]	Unknown
NINL (Ninein-like)	Reconstituted motility[98]	MICAL3 and RAB8A containing vesicles[63]
RAB11-FIP3	Co-IP motility[14]	Recycling endosomes[28]
Candidate activators		
BICD1	Co-IP[230]	COP1-independent Golgi-to-ER vesicles[58], microtubule arrays[230]
BICDL2 (BICDR2)	Homology to BICD proteins[61]	Rab13 vesicles[61]
HOOK2	Homology to Hook proteins	Centrosomal proteins[174], spermatid intramanchette trafficking[231]
CCDC88A (Girdin)	Co-IP[98]	Unknown
CCDC88B (Gipie)	Co-IP[232]	Secretory lysosomes (lytic granules)[232]
CCDC88C (Daple)	Co-IP[98]	Unknown
NUMA	Co-IP[233]	Minus ends of microtubules in the spindle[131,234]
TRAK1	Co-IP[111]	Mitochondria[111]
TRAK2	Co-IP[111]	Mitochondria[111]
HAP1	Co-IP[75,76,207]	Many membrane cargos[75]

Each activator or candidate activator is listed along with its cargo(s). Cargos are defined by their reliance on dynein or dynactin for movement or localization. We have not included known activator interacting proteins where there is not yet evidence for dynein–dynactin involvement for their trafficking.

Table 2 |

Viruses interacting with dynein during their life cycle.

Virus	Presence of the viral envelope	Replication site	Role of dynein in viral life cycle	Evidence for dynein involvement
Class 1 (dsDNA)				
Herpes Simplex Virus (HSV)	Env	Nuc	Transport (direct)	HSV movement requires microtubules[235], p50-blocks movement[235]
Pseudorabies virus	Env	Nuc	Transport (direct)	GFP-capsids move retrograde in axons [236], pUL36 on mitochondria relocates them to perinuclear regions[195]
Adenovirus	Non-Env	Nuc	Transport (vesicles)	Virus does not co-localize with endosomes by electron microscopy, p50 blocks perinuclear accumulation[196]
Polyomavirus	Non-Env	Nuc	Transport (vesicles?)	p50-blocks virus at cell periphery[237]
Bovine papliomaviruses	Non-Env	Nuc	Transport (vesicles)	Transport in endosomes. Viruses remain at the periphery with Nocodazole treatment[238]
Vaccinia virus (Pox virus)	Env	Cyt	Assembly (direct)	p50-blocks perinuclear accumulation of newly assembled virus particles[186]
African swine fever virus	Env	Cyt	Assembly (?)	p50-blocks viral replication at perinuclear regions[184]
Class II (ssDNA)				
Adeno-associated virus (parvovirus)	Non-Env (replication defective)	Nuc	Transport (vesicles)	Axonal transport of labelled virus in Rab7 vesicles[180]
Circovirus	Non-Env	Nuc	Transport (vesicles)	Nocodozaole disrupts perinuclear accumulation[179]
Canine parvovirus	Non-Env	Nuc	Transport (direct?)	Anti-dynein antibody reduces perinuclear accumulation[198]
Class III (dsRNA)				
Reoviruses (e.g. rotavirus)	Non-Env	Cyt	Transport (vesicles)	Viral particles in endosomes accumulate in perinuclear regions[185]
Class IV (+ssRNA)				
Dengue virus (Flavivirus)	Env	Cyt	Transport (vesicles) & Assembly (vesicles)	Virus colocalizes with endosomes and accumulates in perinuclear regions. Subsequently newly

Virus	Presence of the viral envelope	Replication site	Role of dynein in viral life cycle	Evidence for dynein involvement
				synthesized E-protein accumulates in perinuclear regions (p50 blocks it)[188]
Hepatitis C (Flavivirus)	Env	Cyt	Cell organization	HCV clustering of lipid droplets in perinuclear regions[190] requires viral protein NS5A and dynein[239]
Class V (-ssRNA)				
Influenza virus	Env	Cyt	Transport (vesicles)	Anti-dynein antibody inhibits rapid endosome transport to perinuclear regions[182]
Rabies virus	Env	Cyt	Transport (vesicles)	Long distance tracking of labelled virus[189], Rabies envelope-G protein can confer retrograde transport[199]
Hantaan virus	Env	Cyt	Transport (direct)	p50 blocks perinuclear accumulation of nucleocapsid (N) protein from virus or recombinantly expressed[187]
Class VI (ssRNA-RT)				
Human foamy virus	Env	Cyt&Nuc	Transport (vesicles)	p50 blocks perinuclear accumulation of virus or Gag protein alone[183]
Mason-Pfizer monkey virus	Env	Cyt&Nuc	Transport (direct)	p50 blocks perinuclear accumulation of Gag protein[240]
Class VII (dsDNA-RT)				
Hepatitis B	Env	?	Cell organization	Triggers dynein clustering of mitochondria in perinuclear regions[191]

Viruses are listed by class: classification based on nucleic acid (DNA or RNA), strandedness (ss–single stranded, ds-double stranded), sense (+ strand or − strand), and whether they use a reverse transcriptase (RT). Dynein is involved in different aspects of the viral life cycle, irrespective of whether the viruses are enveloped (Env) or non-enveloped (Non-Env), or whether they replicate in the nucleus (Nuc) or cytoplasm (Cyt). Roles of dynein can include transport of viruses to the perinuclear region during infection (via a direct connection or by transporting them in endosomes). Dynein can also transport components during assembly of new viruses, or can have a role reorganizing the cell in response to viral infection. Evidence for the role of dynein in viral infection is accumulation near the nucleus (perinuclear). Further support comes from showing that the viral components are dispersed, or fail to accumulate, when nocodazole is used to depolymerize microtubules, p50 is over-expressed (p50-block), or an anti-dynein antibody is injected. Direct visualization of viruses moving in the retrograde direction in axons also indicates a role for dynein.