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Review

Microtubule transport defects in neurological and ciliary disease

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Abstract. Microtubules are primarily responsible for facilitating long-distance transport of both proteins and organelles. Given the critical role of this process in cellular function, it is not surprising that perturbation of microtubule-based transport can lead to diverse phenotypes in humans, including cancer and neurodegenerative disorders such as Alzheimer or Huntington disease. Recent investigations have also indicated that defects in specialized microtubule-based transport systems, such as mutations affecting the transport of protein particles along the length of cilia (intraflagellar transport) can cause retinal dystrophy, polycystic kidney disease or more complex syndromic phenotypes, such as Bardet-Biedl syndrome. In this review, we discuss recent findings implicating defects in microtubule-associated transport and motor proteins in a variety of diseases, particularly the role of defective microtubular transport in neurological and ciliary disease. These defects frequently display phenotypic consequences that manifest as human disease yet do not cause organismal lethality.

Key words. Dynein; kinesin; intraflagellar transport; neurodegeneration; microtubule-associated proteins.

Introduction

Mammalian cells have three major types of filaments: microtubules, microfilaments and intermediate filaments. While the latter two fulfill structural and mechanical functions, with microfilaments also supporting myosin-based contractility and motility of the cell, microtubules serve as an intracellular network that facilitates the transport of cargo (such as proteins or even organelles) across long distances. Moreover, microtubules play a central role in the assembly of the mitotic spindle and thus in the progression of the cell cycle. Like microfilaments, which are composed of actin monomers, microtubules are polarized structures. They assemble from heterodimers of α- and β-tubulin in a GTP-dependent fashion, with the minus end originating at or near the microtubule-organizing center (MTOC) and the plus end protruding toward the cell periphery (fig. 1A). Depending on the bound nucleotide, this conformation allows incorporation of the heterodimers into the polymer (GTP-bound state) or prevents such polymerization (GDP-bound state). The ends of the microtubule differ in their rate of polymerization; the addition to the plus end is much more rapid than to the minus end (fig. 1B). When net growth on the plus end equals net shrinkage on the minus end, treadmilling occurs, resulting in overall constant length [1–6]. Microtubule dynamics play an important role in mitosis and the cell cycle, and interference with these dynamic processes can trigger apoptosis [7]. In nerve cell axons, microtubules show unipolarity, with the plus ends pointing in the direction of the synapse. In dendrites, however, only microtubules in the distant region display the same unipolarity, with the

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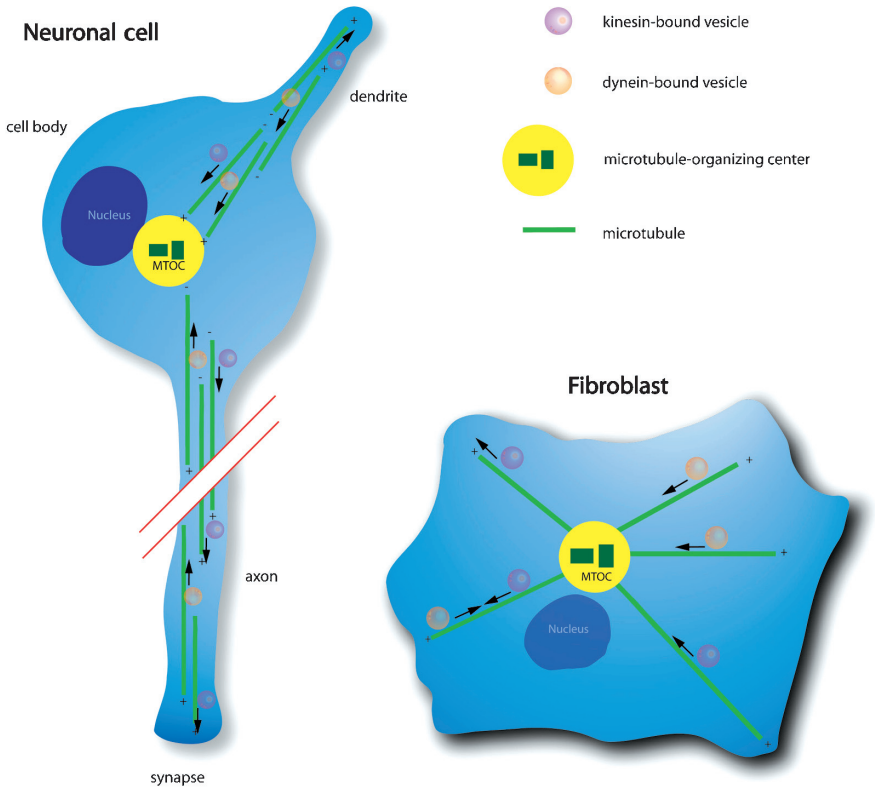

Figure 1. (*A*) Microtubule organization in neuronal cells and fibroblasts. In neuronal cells, microtubules show unipolarity, with the plus ends pointing in the direction of the synapse. Microtubules in dendrites, however, display similar unipolarity only in distant regions; the more proximal ones have mixed polarity. In fibroblasts, microtubules extend from their minus ends at or near the microtubule-organizing center (MTOC) to their plus ends, which project toward the cell periphery.

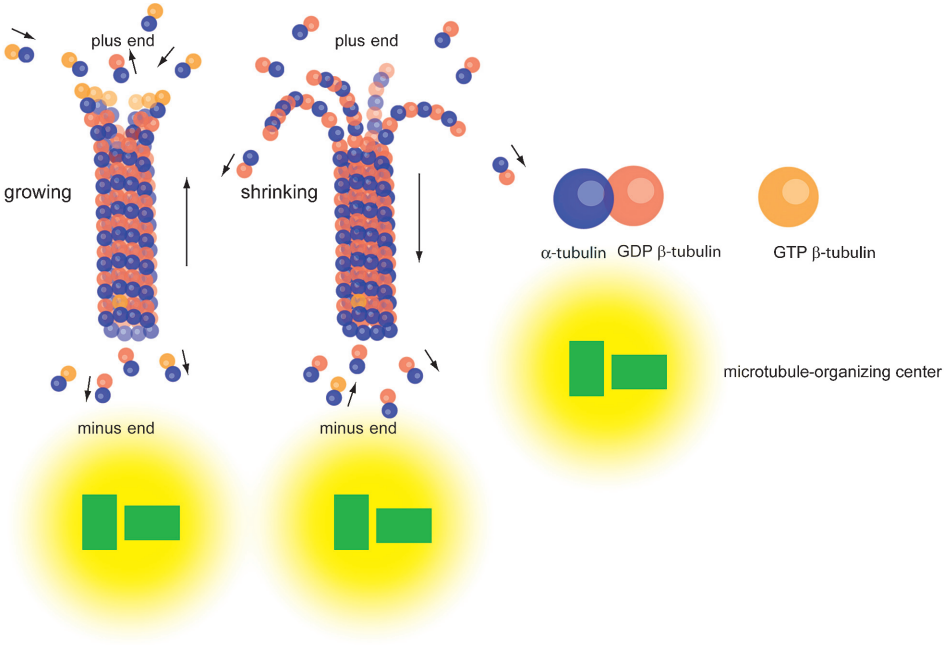

Figure 1. (*B*) Dynamic instability of microtubules. In the growing state, heterodimers of α-tubulin and GTP-bound β-tubulin bind to the plus end at a higher rate than GTP is hydrolyzed to GDP. In the shrinking state, GTP hydrolysis occurs at a higher rate than polymerization and promotes disassembly. The perpendicularly arranged pair of centrioles in the MTOC (green) is surrounded by pericentriolar material (yellow).

plus ends projecting toward the periphery; microtubules in the proximal region have mixed polarity (fig. 1B).

Next to the dynamic behavior of microtubules themselves, transport along the microtubule network is accomplished by microtubule-associated motor proteins and other microtubule-associated proteins (MAPs), which either actively move cargo along the microtubules (motor proteins) or serve as docking molecules to bind cargo to motor proteins [8]. We will refer to all proteins found to attach to microtubules, whether directly or as part of larger protein complexes, as MAPs. Microtubule-associated motor proteins are divided into two major families: kinesins and dyneins. Each consists of a globular motor domain that is connected to a rod-like structure. The motor domains exhibit binding sites for both ATP and microtubules and undergo repetitive cycles of binding, conformational change mediated by ATP-hydrolysis that leads to dissociation, and rebinding [9]. The motor domains typically share high sequence homologies; it is in the rodlike structures that proteins of the same family are less conserved and, thus, more diverse [9–11]. These substructures serve as the binding sites for cargo and enable the utilization of motor proteins in a multitude of intracellular transport processes. Members of the dynein family enable transport of cargo from the plus end of microtubules to the minus end, thus generally from the periphery of the cell to its center [9, 12]. By comparison, the kinesin superfamily (KIF) is much larger [9, 13]. Though similar in structure to each other, most known kinesin motors mediate transport from the minus end toward the plus end of microtubules, with the exception of the C-terminal kinesins, which facilitate transport in the minus-end direction [9, 13]. Perturbations of microtubule transport functions can lead to human genetic disease, particularly in the central nervous system, where neuronal function is dependent on the transport of cargo across significant distances (up to 1 m in humans). Defective microtubule-based movement, organization and polarization can also be found underlying a broader range of human phenotypes, including disorders of ciliary function. Considering the fundamental role of microtubule-based transport, relatively few examples of human disease caused by microtubule transport dysfunction are known to date. Since medical genetics is still a fairly young discipline, this rarety might be a mere stochastic effect. However, it might reflect the fundamental importance of directed and organized transport in many cell types and the possibility that such transport defects are incompatible with life. Of those diseases linked to defective microtubular transport, most manifest in cells that require active transport, e.g. neurons. In other cells, diffusion might be able to compensate for the defects in active transport. In this review, rather than focus on the cellular mechanism of microtubule transport, a subject discussed extensively in several recent articles [10, 11, 14], we will focus on the phenotypic consequences of mutations affecting microtubule transport. We will place particular emphasis on neurons and ciliated cells,

Table 1. Dynein motors and associated proteins mutated in human disease.

Protein	Localization	Putative function	Associated disease	Reference
Axonemal dynein heavy chain 11 (DNAH11)	axonemal in cilia and flagella, primarily in testis and trachea	retrograde transport	situs inversus viscerum, primary ciliary dyskinesia	136
Axonemal dynein heavy chain 5 (DNAH5)	axonemal in cilia and flagella, primarily in in testis and trachea	retrograde transport	primary ciliary dyskinesia	137
Axonemal dynein intermediate chain 1 (DNAI1)	axonemal in cilia and flagella, primarily in testis and trachea	retrograde transport	primary ciliary dyskinesia, Kartagener syndrome	138
Dynactin (DCN1)	microtubule-associated dynein/dynactin complex	retrograde transport	lower motor neuron degeneration	30
Lissencephaly 1 (LIS1)	colocalizes and interacts with dynein/dynactin	regulation of retrograde movement of cytoplasmic dynein and tubulin	isolated lissencephaly	139
Huntingtin (Htt)	interacts with huntingting associated protein 1 (HAP1) and $p150^{Glued}$	vesicular (BDNF) transport	Huntington disease	38
Dynein light chain Tctex1	dynein motor	retrograde transport	polio	51
Dynein light chain Tctex1/RP3	direct interaction with herpes simplex virus 1 capsid protein VP26	retrograde transport	herpes	52

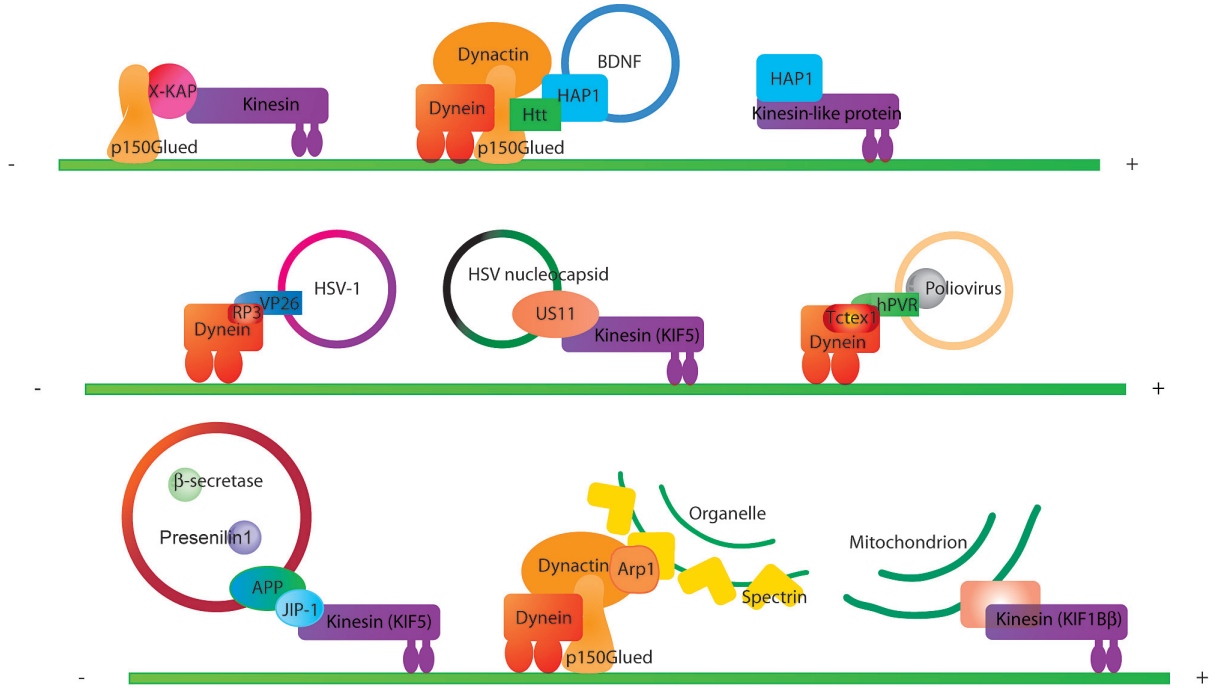

Figure 2. Protein complexes formed with members of the dynein or kinesin family. In the upper panel, two members of the kinesin protein family form complexes, one with kinesin-associated protein X-KAP and p150^{Glued} and the other one with huntingtin-associated protein. Also depicted is the protein complex formed with dynactin and the proteins playing a role in Huntington disease. The middle panel shows dynein- and kinesin-associated complexes formed with viral proteins. Finally, the lower panel depicts kinesin-associated complexes that play a role in Alzheimer disease (APP etc.) and Charcot-Marie-Tooth disease type 2A, as well as dynein/dynactin complexes that are involved in organelle transport.

which appear to be especially susceptible to transport perturbation.

Dynein defects

Of the 15 members of the dynein protein family known in vertebrates, most are axonemal, reflecting their roles in ciliary and flagellar movement [10, 15]. There are two cytoplasmic forms of dynein. Cytoplasmic dynein 1 fulfills roles in the transport of membranous organelles, chromosome behavior, mitotic spindle orientation, and nuclear and cell migration [10]. In contrast, cytoplasmic dynein 2 shows a much more restricted distribution and a narrower range of functions: it is specific to ciliated cells and limited to a variety of motile and immotile ciliary structures. Closer investigation has associated cytoplasmic dynein 2 with cilia and the Golgi apparatus [16, 17]. Therefore, this protein is likely responsible for general cargo transport from the distal to the proximal end of axonemal structures, as well as for vesicle transport from the endoplasmic reticulum to the Golgi apparatus.

Dynein requires interaction with the large dynactin complex for its activation [18–21], an interaction that increases the processivity and efficiency of the motor [15, 22]. Dynactin also participates in cargo binding via its largest subunit, the polypeptide p150^{Glued}, which binds both microtubules and the dynein intermediate chain [15, 20, 23]. Moreover, the dynactin complex contains the Arp1 filament, which has been shown to bind the spectrin matrix found on organelles and therefore potentially mediates cargo attachment [24–26] (fig. 2). Interestingly, the dynactin complex can be disrupted by overexpression of its 50-kDa dynamitin subunit, which causes both dynein and dynactin to be displaced from mitotic kinetochores [27]. The role of dynactin has been complicated by the recent finding that the complex binds not only to the dynein intermediate chain but also to kinesin II in *Xenopus laevis* [28] (fig. 2). This interaction has been shown in coimmunoprecipitation experiments using several different monoclonal and polyclonal antibodies raised against kinesin II. It has been demonstrated that dynactin plays a role in bidirectional melanosome transport along microtubules [28]. The p150^{Glued} component and the *Xenopus* kinesin II-associated protein KAP interact, but p150^{Glued} does not bind XKAP and the dynein intermediate chains at the same time, which was also established in coimmunoprecipitation experiments [28]. This observation implicates a novel regulatory mechanism that controls the direction of motility.

Mutations in the dynein or dynactin subunits have been implicated directly in the pathogenicity of motor neuron

disease (MND), one of the most common human neurodegenerative diseases [29, 30]. Mice overexpressing dynamitin, and thus disrupting the dynactin complex [27], develop a late-onset, progressive motor neuron degenerative disease characterized by decreased strength and endurance, motor neuron degeneration and loss, and denervation of muscle [31]. This model confirmed the hypothesis that a specific targeted disruption of microtubule transport is sufficient to cause MND. Commonly, neuronal transport is divided into slow and fast axonal transport [32]. Since slow axonal transport may result from the dual activity of the opposing motors kinesin and dynein [33], disruption of the dynein/dynactin interaction would essentially eliminate this form of transport and lead to axonal degeneration. The relevance of these findings to human disease was shown when a single-point missense mutation in DCTN1 ($p150^{Glued}$ subunit of dynactin) was found to be the likely cause of disease in a family with a slowly progressive autosomal dominant form of lower MND without sensory symptoms [30]. The G59S mutation occurs in the highly conserved Cytoskeleton-associated protein glycine-rich (CAP-Gly) motif of the polypeptide, which is critical for microtubule binding. Structural modeling studies suggest that the serine residue is likely to impair the proper folding of the microtubule-binding domain through steric hindrance, and it has been demonstrated that this distortion leads to a moderate decrease in binding affinity [15]. This is consistent with the late disease onset and the relatively mild disease progression observed in this kindred.

Several inherited neurodegenerative disorders, including Huntington disease (HD), have been linked to polyglutamine (poly Q) expansions [34]. In HD, the causative gene, huntingtin (*Htt*), has been shown to be expanded within the open reading frame. Yeast-2 hybrid screening and glutathione *S*-transferase (GST)-pulldown experiments revealed that wild-type Htt binds both huntingtin-associated protein 1 (HAP1) and the $p150^{Glued}$ subunit of dynactin (fig. 2) and seems to play a role in axonal transport [35, 36]. Symptoms of HD consist mainly of characteristic uncontrolled movements, changes in personality and progressive dementia; patients die within 10–20 years of onset. The neuropathology comprises significantly dysfunctional neurons as well as loss of neurons, especially the medium spiny neurons of the striatum [37]. Motor and cognitive defects have been observed in both patients and murine models of the disease before any neurodegeneration is detected [38]. It is therefore likely that the loss of neurons is a consequence of neuronal dysfunction. The aforementioned polyQ expansion linked to HD impairs the Htt protein, a brain-enriched protein shown to be essential for embryonic development and neurogenesis [39, 40]. Mice lacking Htt show an increased rate of programmed cell death, implying that Htt possesses antiapoptotic properties, which also seem to be necessary in adults, since the late inactivation of Htt in a conditional mouse model leads to progressive neurodegeneration [41]. Significantly decreased levels of brain-derived neurotrophic factor (BDNF) have been observed in the brains of HD patients [42]. Although Htt is found in the nucleus, it is present in much higher concentrations in the cytoplasm, where it associates with vesicular structures and microtubules. In particular, Htt interacts with HAP1, which is transported in axons (fig. 2). Moreover, it interacts with the $p150^{Glued}$ dynactin subunit [36, 43] and thus affects fast axonal transport [44, 45]. However, the molecular pathogenic mechanisms were not established until recently.

Both decreased BDNF expression [46] and impaired BDNF transport could provide an explanation for the HD phenotype. BDNF is produced by cortical neurons and is subsequently transported to the striatum, where it serves as a prosurvival factor for striatal neurons [47, 48]. In concordance with its antiapoptotic properties, Htt enhances vesicular transport of BDNF along microtubules [38], a process that involves both HAP1 and the $p150^{Glued}$ subunit of dynactin. Importantly, polyQ expansion of Htt leads to a significantly higher binding affinity to HAP1, as demonstrated in GST-pulldown experiments, and to a reduced association of key components of the motor proteins with microtubules [38, 43], which indicates that alteration of the Htt/HAP1/$p150^{Glued}$ complex correlates with reduced interaction of motor proteins with microtubules. BDNF transport is attenuated both in the disease context and by reducing the levels of wild-type Htt [38]. Strikingly, a reduced association of the kinesin heavy chain with microtubules in the HD knockin mouse has also been observed [38], which is relevant to the proposed interaction between HAP1 and a kinesin-like protein; this protein shows a 99% identity to human kinesin heavy chain isoform 5C, a neuron-specific kinesin [36, 49] (fig. 2). Consequently, HAP1 could interact directly not only with $p150^{Glued}$ but also with kinesins and, as demonstrated for $p150^{Glued}$ itself, could participate in anterograde and retrograde transport vesicles. Seemingly, the separation between kinesin-mediated anterograde movement and dynein-mediated retrograde movement is not as complete as was once believed.

In the mouse model, the early course of HD is characterized by a loss of function in Htt mediated transport, which is due to a direct effect of polyQ expansion on the ability of Htt to interact properly with HAP1 [38, 50]. The later stage of HD is marked by the accumulation of neuritic aggregates that contribute to reduce further axonal transport, resulting in a feedback mechanism [38]. The fact that transport is reduced but not completely blocked or stopped could explain the slow progress of HD.

In addition to inherited disease, normally functioning motor proteins can be utilized in other mechanisms of disease. For example, given their direction of axonal

transport, dyneins are prime targets for the entry of pathogens into the cell. Indeed, several viruses use dynein-interacting proteins for transport toward the nucleus, e.g. poliovirus and herpes simplex virus 1 (HSV-1). It has been established recently that the light chain of dynein, Tctex-1, interacts directly with the cytoplasmic domain of the human poliovirus receptor (hPVR) [51]. In a pulldown experiment with purified epitope-tagged Tctex-1 and a purified construct of GST and the cytoplasmic domain of hPVR (CPα), Tctex-1 precipitated with the GST construct. The dynein light chains Tctex-1 and RP3 have also been shown to interact with the HSV-1 capsid protein VP26 [52] (fig. 2). Both candidates resulted from a yeast-2 hybrid screen involving a library of HSV capsid and tegument structural genes, with dynein subunits as bait, and were confirmed as interaction partners in GST-pulldown experiments. This interaction is sufficient for retrograde transport of viral capsids in a cellular model. However, in the case of HSV-1, the migration of unenveloped HSV nucleocapsids within infected neurons also utilizes microtubule-associated motor proteins: the HSV tegument protein US11 has been shown to interact with the heavy chain of conventional kinesin (KIF5) in oligohistidine pulldown experiments [53] (fig. 2).

Kinesin defects

KIF proteins can be divided into three major types, based on the position of their motor domain, i.e. N-terminal, middle or C-terminal. Accordingly, these types are referred to as N-, M- and C-kinesins [9, 13]. KIF proteins of the human and mouse genomes have been categorized into 14 classes, 11 of which comprise the N-kinesins, two the C-kinesins and the remaining one the M-kinesins. KIF proteins of other species can also be grouped into these classes.

Loss of function mutations in kinesins impede neuronal function, although the resulting phenotype is distinct from that of dynein-based mutations. For instance, patients with Charcot-Marie-Tooth disease type 2A (CMT2A), a form of inherited peripheral neuropathy, carry a loss of function mutation in the gene encoding KIF1B [54]. This KIF protein is involved in the transport of mitochondria (fig. 2). Interestingly, the tail domains of the two isoforms, KIF1Bα and KIF1Bβ, share little or no homology [54], which suggests that the cargos of KIF1Bα and KIF1Bβ might be distinct. CMT2A patients share a missense mutation in the motor domain of the protein. Further investigations revealed both decreased ATPase activity and decreased motility, suggesting that haploinsufficiency of this motor protein is responsible for CMT2A [54].

The heterozygous *kif1B*$^{+/-}$ mouse model resembles the symptoms of the disease, whereas homozygous *kif1B*$^{-/-}$ mice die within 30 min after birth [54]. Transfecting cultured *kif1B*$^{-/-}$ neurons with KIF1Bα and KIF1Bβ, respectively, revealed that KIF1Bα, but not KIF1Bβ, was able to reverse the neuronal loss phenotype [54]. The *kif1B*$^{+/-}$ mice showed progressive muscle weakness and motor discoordination in behavioral tests. After demyelination of the nerves had been ruled out, it appeared that defects in neuronal axons most likely contributed significantly to the peripheral neuropathy of *kif1B*$^{+/-}$ mice [54]. The observation that distal muscles are damaged earlier and more severely than proximal muscles (the 'distal-first' theory of axonal neuropathies) can be explained at least partially by the idea that longer axons need higher levels of motor proteins. Alternatively, they may depend on

Table 2. Kinesin motors and associated proteins mutated in human disease.

Protein	Localization	Putative function	Associated disease	Reference
Amyloid precursor protein	colocalizes with kinesin I light chain, β-secretase and presenilin 1	kinesin I membrane receptor	cerebroarterial amyloidosis familial Alzheimer disease presenile dementia	140 141 142
Presenilin 1	colocalizes in same membrane compartment as β-secretase and APP	regulation of γ-secretase activity, Notch signaling	familial Alzheimer disease frontotemporal dementia Pick disease of the brain	143 144 145
KIF1B	kinesin subunit	axonal transport predominantly in differentiated nerve cells	Charcot-Marie-Tooth disease type 2A	54
KIF21A	kinesin subunit	plus-end directed transport	fibrosis of extraocular muscle	146
τ protein	microtubule-associated protein enriched in axons	regulation of intracellular neuronal transport (especially anterograde transport)	frontotemporal dementia frontotemporal dementia with parkinsonism Pick disease pallidopontonigral degeneration supranuclear palsy	147 148, 149 150 151 152

active transport more heavily than shorter axons do because diffusion is not sufficient.

Kinesin-based defects can also be found in other neurological phenotypes, the most prominent of which is Alzheimer disease (AD), the most common cause of human dementia. The end stage of AD is marked by extracellular plaques of amyloid peptide, neurofibrillary tangles (NFTs) composed of hyperphosphorylated τ protein and decreased density of cholinergic neurons in the basal forebrain [55]. The amyloid peptide plaques consist mainly of Aβ, the proteolytic cleavage product of amyloid precursor protein (APP) [56]. Studies of familial AD (FAD) link the disease to mutations of the gene encoding for APP [14]. Interestingly, patients with trisomy 21 are prone to develop AD, potentially because of trisomy for the *APP* gene, located on chromosome 21q11 [57]. Other studies have identified mutations in the genes encoding presenilin 1 (PS1) and presenilin 2 (PS2), which play a role in APP processing [58]. The presenilins are cleaved into N- and C-terminal fragments and as such form part of a macromolecular complex with γ-secretase activity. In addition to APP, substrates of this complex are Notch 1, ErbB-4 and E-cadherin. PS1 is, in turn, a substrate of glycogen synthase kinase-3 β (GSK3β) [59–61], which also phosphorylates β-catenin, the microtubule-interacting τ protein, and kinesin light chains [62, 63]. It has been shown that PS1 mutations can lead to increased GSK3β activity and thus to increased KIF5 phosphorylation levels [64]. This may lead to the release of KIF5 from membrane-bound organelles essential for neuronal function, such as synaptic vesicles or mitochondria. PS1 mutations can thus deregulate GSK3β activity and lead to a reduction in fast anterograde transport. A new cyclin-dependent kinase 5 (CDK5)-dependent pathway for regulating GSK3 activity and kinesin-driven motility in neurons has only recently been identified [65]. Inhibition of CDK5 activity leads to activation of GSK3 by protein phosphatase 1, phosphorylation of kinesin light chains by GSK3 and detachment of kinesin from transported cargo.

Detailed investigations of the mechanism of axonal transport and APP trafficking have revealed that APP interacts with the tetratricopeptide repeat (TPR) 1 domain of the kinesin light chain subunit and that the levels of interaction between KIF5 and APP vary among different combinations of light and heavy chains [66]. These experiments involved the study of steady-state protein levels in sciatic nerve axons, dorsal root ganglia and corpa callosa from *APP*$^{-/-}$ and wild-type mice. APP is a transmembrane protein whose binding site for complex formation with KIF5 is located near the C-terminus (fig. 2) [67]. As recently determined in GST pull down experiments, the interaction of APP and the kinesin light chain is mediated by the scaffold protein C-jun-amino-terminal kinase-interacting protein 1 (JIP-1) [68]. Other studies suggested that APP serves as a KIF5 membrane receptor that mediates the axonal transport of β-secretase and PS1, indicating that APP is located in the same axonal membrane compartment as β-secretase and PS1 [66]. The processing of APP to amyloid-β by secretases can therefore occur in an axonal membrane compartment transported by KIF5. It is possible that cleavage of APP in response to axonal damage or blockage might cause Aβ deposition in axons, owing to the release of KIF5 from moving vesicles in which Aβ is generated.

This hypothesis was tested in *Drosophila* by observing the phenotypic variations of loss or overexpression of APP-like protein (APPL) [69]. Both loss and overexpression of APPL gave rise to an axonal transport phenotype manifesting an accumulation of transported components in axons. Overexpression of APPL titrates KIF5 away from other axonal cargo and should therefore produce a phenotype similar to that produced by loss of APPL, resulting in stalled vesicular transport. Formation of axonal accumulations is dependent on the presence of the APP C-terminus; deletion of the C-terminus completely reversed this phenotype. The effects of APPL overexpression were augmented dramatically by genetic reduction of KIF5 [66]. In comparison, reduction of kinesin levels to 50% by deleting one of two copies of either the kinesin light chain (*klc*) or the kinesin heavy chain (*khc*) gene does not lead to any phenotype in wild-type *Drosophila* [66]. Similarly, reduction of cytoplasmic dynein levels to 50% by deleting either the dynein light chain or the dynein heavy chain gene (*dlc* or *dhc*) ordinarily produces no phenotype; in an animal overexpressing APPL, however, reduction of dynein levels leads to suppression of axonal accumulations [66]. A possible explanation for this is that the reduced rate at which vesicles and organelles moved by dynein are transported leads to stalled or accumulated vesicles. Alternatively, reduction of dynein-mediated transport contributes to vesicle stalling because of kinesin-driven activity. It has been observed that vesicles or organelles that exhibit net anterograde movement experience periodic retrograde transport due to the presence of kinesins and dyneins on the same vesicle or organelle [70]. Therefore, reduction of dynein levels could attenuate vesicle stalling by restoring movement balance. Given the viability of *Appl* and *APP* deletions, it is likely that there are several independent KIF5-driven vesicular axonal transport pathways in *Drosophila* and mammals. While loss of APPL causes organelle jams, their frequency is considerably less than in kinesin or dynein mutants that presumably block all pathways. This finding is consistent with the hypothesis that APPL is part of a minor pathway.

The NFTs characteristic of end-stage AD contain aggregates of hyperphosphorylated and/or misspliced τ protein, a substrate of GSK3β. Thus, increased activity of GSK3β is associated not only with increased levels of Aβ

and phosphorylated kinesin light chains but also with hyperphosphorylation of τ, a MAP expressed mainly in neurons of the central nervous system and thought to play a role in the assembly and stabilization of neuronal microtubules, as well as in the transport of organelles along axons and dendrites. Genetic linkage studies revealed a weak linkage of τ polymorphisms in early-onset AD, while no association could be established in late-onset AD [71, 72]. Overall, τ seems to be implicated in several neurodegenerative diseases, especially those including parkinsonism or dementia. [73–75] Although a direct connection between τ polymorphisms and parkinsonism has not been found, the τ haplotype seems to represent a susceptibility factor in sporadic cases of Parkinson disease as well as AD [76]. If a specific haplotype in the τ gene represents a risk factor for a number of neurodegenerative disorders, it is conceivable that these disorders share a common mechanism involving τ function.

Defects of intraflagellar transport

Microtubules make up cilia and flagella, cellular structures that are of central importance in a variety of developmental processes. Among vertebrates, primary cilia consist of a 9 + 0 axoneme, a structure of nine outer microtubules. Motile cilia have a 9 + 2 axonemal core structure in which two central microtubules are encircled by nine outer microtubules. Nearly all mammalian cells form cilia, and the ciliary apparatus is connected to cell cycle progression and proliferation [77, 78]. Sensory and motile axonemes are differentiated longitudinally into two domains: the middle segment and the distal segment, consisting of nine doublet and nine singlet microtubules, respectively. The centrosome is assembled by a pair of centrioles; it divides during mitosis, forming the spindle poles. Importantly, dividing cells disassemble cilia, so only nonmitotic or postmitotic cells are ciliated [79]. Centrioles can convert to basal bodies by generating a transition zone, a specialized structure essential for the correct assembly of cilia and flagella. The transition zone serves as a docking site for intraflagellar transport (IFT) proteins and their motors [80–82]. Similarly, basal bodies can convert to centrioles that serve as the microtubale-organizing center (MTOC) in animal and algal cells.

Recent studies have implicated directly cilia and basal bodies in several developmental processes, including left-right asymmetry [83], heart development [84], maintenance of the renal epithelium [85] and respiratory function [86]. Nodal cilia in early development trigger the molecular cascade that leads to visceral asymmetry in vertebrates [87]. In addition to generating force for the motility of sperm cells and single-celled organisms and for the transport of fluids over epithelial cells, cilia and flagella also play a part in sensory perception [79].

Since ciliary and flagellar proteins are synthesized in the cell body, they must be transported to the tip of the axoneme. This is achieved by IFT, an ordered and highly regulated anterograde and retrograde translocation of polypeptide complexes (IFT particles) along the length of the ciliary axoneme. IFT was first described in *Chlamydomonas reinhardtii* and has been found to be essential for the assembly of motile and sensory cilia in many organisms, including mice and humans [88, 89]. In scanning electron microscope (SEM) images, IFT particles appear as regions of electron-dense material located between the flagellar membrane and the B-subfiber of the outer doublet microtubules of the underlying flagellar axoneme [90]. Anterograde transport is dependent on kinesin, while retrograde transport is mediated by cytoplasmic dynein 1b [9, 12]. Recently, it was shown that anterograde movement in the sensory cilia of *Caenorhabditis elegans* neurons exhibits two rates: it moves more slowly along the middle segment (0.7 μm^{-1}) than along the distal segment (1.3 μm^{-1}) [91]. Two candidate anterograde motors were identified: the kinesin II heterodimer (KIF3A) and homodimeric osm-3-kinesin. It was shown that cilia in osm-3 mutants lack distal segments and that osm-3-kinesin moves along the full length of the axoneme at the same two rates as IFT particles, whereas kinesin II never enters the distal segment [91]. The double mutant worms confirmed the hypothesis that kinesin II and osm-3-kinesin have redundant roles in controlling IFT along the middle segment of cilia, whereas osm-3-kinesin, but not kinesin II, controls IFT along the distal segment. It was reported previously that *Kif3a*$^{-/-}$ mice lack primary cilia and therefore fail to establish left-right asymmetry [92]. This raises a question as to the generality of the observation made in *C. elegans*, since there appear to be differences in transport mechanisms between nodal cilia in mice and sensory cilia in *C. elegans*.

Interestingly, some of the proteins involved in regulation of the IFT machinery and control of flagellar assembly, disassembly, and length are homologs of signaling proteins and proteins involved in control of the mitotic spindle apparatus [93]. Lf4p, for example, is a MAP kinase implicated in flagellar shortening [94]. CrEB1 is a member of the microtubule plus-end tracking EB1 protein family and seems to promote dynamic instability at the flagellar tip [95]. This could influence turnover rates and general flagellar assembly. In addition, ciliary motility seems to be impaired, along with some separate functions requiring an intact cilium, such as ciliary membrane ion channels.

One of the best-characterized diseases linked to ciliary dysfunction is polycystic kidney disease (PKD). Although PKD may occur sporadically as part of abnormal development, or may be acquired during adult life, most forms are hereditary [96]. These inherited PKDs include autosomal dominant and autosomal recessive PKD,

nephronophthisis and medullary cystic disease. The most common form is autosomal dominant PKD (ADPKD), occurring in 1 in 800 live births. Patients usually present with significantly enlarged kidneys, hypertension, hematuria, polyuria and flank pain. They are also prone to recurrent urinary tract infections and renal stones. ADPKD is caused by mutations in *PKD1* [97] (85–90% of cases) and *PKD2* [98] (10–15% of cases). The protein products of these two genes, polycystin-1 and polycystin-2, are found on renal tubular epithelia. They are thought to interact with one another to form a Ca^{2+} channel in the plasma membranes of the primary cilia. Autosomal recessive PKD, by contrast, is much rarer and results from a mutation in a single gene, *PKHD1* [99]. The gene product of *PKHD1* is also localized to the primary cilia; therefore, ciliary dysfunction seems to underlie this form of PKD as well [100].

In both autosomal dominant and autosomal recessive PKD, apoptosis is abnormally persistent and can destroy much of the normal renal parenchyma, thereby allowing cystic epithelia to proliferate. Interestingly, mice with inactivated inhibitors of apoptosis (bcl-2 or activating protein 2β) were observed to develop PKD [96]. Both autosomal dominant and autosomal recessive PKD patients suffer from altered polarity of membrane proteins, including aberrant location of Na^+/K^+-ATPases, epidermal growth factor (EGF) receptors, cathepsin B, matrix metalloproteinase 2 and E-cadherin [96].

The kidney primary cilia are normally bent by mechanical stimulation or fluid flow and thus induce a rise in intracellular Ca^{2+} levels [85, 101, 102]. Kidney epithelial cells with polycystin defects proliferate excessively, fail to differentiate fully and form cysts [96]. Thus, epithelial kidney cilia have been proposed to play a role in growth control and differentiation.

Mouse models with impaired Tg737 [103] (a mouse homolog of IFT88 in *Chlamydomonas* and polaris in *C. elegans*) or cpk (cystin) [104] were shown to have abnormal ciliary structure or function and to develop PKD. The encoded proteins colocalize with polycystin-1 and -2 in collecting tubule cilia; polaris (the gene product of *Tg737*) localizes specifically to the basal bodies, as well as along cilia and flagella [104], and has been implicated in left-right patterning [105]. In addition, *Chlamydomonas* strains lacking IFT88 do not form flagella.

Certain specialized cell types, such as photoreceptor cells, rely almost completely on IFT for intercompartmental communication. The outer segments of photoreceptor cells are linked to the inner segments via the connecting cilium. Approximately 2000 molecules are transported through the connecting cilium each minute. Motor proteins and particles involved in IFT are localized around the basal bodies and in the cilia of vertebrate rod and cone cells. It is therefore not surprising that IFT plays a role in intersegmental transport in photoreceptors. Impairment of IFT will therefore manifest in photoreceptor cells, and thus loss of vision. Transport defects are strongly implicated in the pathogenesis of retinitis pigmentosa and blindness due to retinal degeneration. Conditional *Tg737* or *Kif3a*$^{-/-}$ mice accumulate opsin in the inner segments of their photoreceptor cells [103, 106].

Bardet-Biedl syndrome (BBS) is a rare genetic disorder characterized primarily by such diverse symptoms as retinal dystrophy, obesity, polydactyly, renal and gonadal malformations, and learning disabilities [107]. To date, eight causative genes (*BBS1* through *BBS8*) have been identified [108–116], although in some cases, three disease-causing alleles have to be present in order to manifest as BBS [107, 108, 117–121]. Recent genetic and molecular evidence indicates that ciliary defects underlie the BBS pathology and implicates microtubule defects in this broad clinical phenotype. Cloning of *BBS8* established the initial link between impaired ciliary function and BBS [112]. BBS8 contains eight TPR motifs and has similarity to a prokaryotic domain, pilF, involved in twitching mobility and type IV pilus assembly. In addition, one patient with homozygous null *BBS8* mutations presented with situs inversus, a defect of left-right axis determination known to be caused by dysfunction of nodal cilia [122]. Finally, BBS8 localizes specifically to ciliated tissues in mammals and *C. elegans*, an observation also found to be true for bbs-1, bbs-2, bbs-4 and bbs-7 [112]. Subsequent work showed that the BBS proteins are necessary for ciliary function (but not for biogenesis), since loss-of-function mutations in *bbs-7* and *bbs-8* in *C. elegans* cause structural and functional ciliary defects, including shortened or otherwise abnormal cilia and chemosensory abnormalities [123]. In wild-type *C. elegans*, BBS proteins localize predominantly at the base of cilia and undergo bidirectional movement along the ciliary axoneme. In this respect, they represent a novel class of proteins that participate in, and are required for, IFT. Experimental data suggest that kinesin motors and dynein motors are fully functional in the absence of BBS7 or BBS8 and that the structural platform for IFT remains intact [123]. Thus, BBS proteins may either facilitate incorporation of IFT proteins into the final motor-IFT particle complex at the transition zone or interact directly with different IFT proteins.

Analyses of the BBS protein complex have indicated a direct link to microtubule-based transport and dynamics. In a yeast-2 hybrid screen using BBS4 as bait, pericentriolar material 1 (PCM1) was identified as an interaction partner [124]. PCM1 is a 228-kDa autoantigen that is recognized by anticentrosome serum and that localizes with centrosomal satellites throughout the cell cycle, except during metaphase and anaphase, when it becomes cytosolic [125]. PCM1 seems to play a role in the biogenesis, function and maintenance of both centrosomes

and cilia, since in most animal cells the centrosome is surrounded by electron-rich pericentriolar material. PCM1 is one of the main constituents of this material and seems to be involved in its microtubule-regulatory function [125]. A series of in vitro experiments showed that BBS4 is necessary to recruit PCM1 to the centrosome, probably by acting as an adaptor between PCM1 and the dynein/dynactin motor complex [124]; upon repression of the BBS4 signal, using RNA interference, PCM1 became dispersed in the cytosol. In all cells showing loss of the BBS4 messenger RNA (mRNA) signal, the microtubule network was either a disorganized array emanating crudely from the outer edges of the nucleus or an extensive dispersal, forming bundles near the cell periphery. The physiological relevance of these data was substantiated by studies of the olfactory sensory cilia of *Bbs1*$^{-/-}$ and *Bbs4*$^{-/-}$ knockout mice, where loss of either BBS protein led to PCM1 mislocalization. In *Bbs1*$^{-/-}$ mice, PCM1 was trapped in the neuronal cell body and correlated with a disorganized microtubular dendritic network [126]. In *Bbs4*$^{-/-}$ mice, however, PCM1 was restricted to the dendritic knob, which correlated with shorter dendritic microtubule bundles. These data provided additional evidence that the BBS proteins are necessary for ciliary function and, importantly, demonstrated that perturbation of the microtubule network also has a profound effect on the function of apical dendrites in the central nervous system.

Microtubule defects and phenotypic modification

In addition to causality in the classical Mendelian sense, MAPs are attractive candidates for exerting a modifier effect on human phenotypes. For example, a variant in MAP1a, a protein involved in vesicle and organelle trafficking [127, 128], has been associated with a more severe hearing phenotype in *tubby* mice [129]. While *tub*$^{-/-}$ in AKR/J, CAST/Ei and 129P2/OlaHsd backgrounds have no observable hearing loss, *tub*$^{-/-}$ mice in the C57/BL6 background are essentially deaf. This difference has been attributed to a *moth*1 (modifier of tubby hearing 1) allele in the C57/BL6 strain by virtue of genetic evidence mapping the locus [130]. The *Map1a* complementary DNA (cDNA) derived from B6 background mice differed in 12 single nucleotides of the open reading frame from that derived from AKR/J mice [129]. Further sequencing of the 129P2/OlaHsd and CAST/Ei alleles of *Map1a* revealed 10 amino acid changes and a shorter Ala-Pro repeat motif than that found in B6 mice [129]. A transgenic mouse carrying an exogenous protective allele from the 129P2/OlaHsd background showed significantly improved auditory brainstem response thresholds compared with B6 *tub*$^{-/-}$ littermates, except for high-frequency (32 kHz) hearing [129]. It was also shown that the BL6 allele of *Map1a* moderately reduces the binding affinity of MAP1A to postsynaptic density protein 95 (PSD95) [129]. PSD95 plays a role in the synaptic strengthening involved in learning and memory [131]. However, the exact role of MAP1a in hearing and its modifying role in the tubby phenotype are still unclear, since there is no evidence of direct physical interaction between the two proteins [132].

The tip of the iceberg

The accelerated pace of discovery of microtubule functions has profound implications for understanding human pathology. Notably, defects in microtubule structure, organization, or transport manifest in neurons and in other types of postmitotic cells, such as ciliated renal cells. Although this might be a stochastic observation, it is quite possible that there are biological reasons for this preference. The most obvious is that loss of microtubule plasticity or transport in mitotic cells might be incompatible with life. For example, *Kif3a*$^{-/-}$ mice are not viable [92]. It is also possible that in non-neuronal cells diffusion, rather than active transport, might provide sufficient compensation for the loss of organized traffic. Finally, given the size of the MAP family, functional redundancy should be considered. For instance, recent evidence suggests that kinesin-mediated transport in the middle segments of cilia is mediated by two members of the kinesin family [91].

Besides further elucidating the role of MAPs in neurological and ciliary disease, initial hints suggest that future research will expand on their involvement in a variety of seemingly unrelated processes, especially development. This will invariably lead to the direct or indirect association of MAPs with more diverse human phenotypes. For example, recent studies have indicated that IFT plays a central role in vertebrate Hedgehog signaling, since two embryonic lethal mouse mutations were found in the mouse orthologs of IFT proteins IFT172 (Wim) and IFT88 (fxo, a hypomorphic allele of polaris). Further genetic analysis showed that Wim and Polaris, as well as the IFT motor KIF3A, are required for Hedgehog signaling at a step downstream of Patched 1 (the Hedgehog receptor) and upstream of direct targets of Hedgehog signaling [133]. However, whether the Sonic hedgehog (Shh) signal is transduced through the cilium or whether some ciliary proteins serve both a cytoplasmic and a ciliary microtubular function in cells remains to be established.

The identification of a number of motor proteins and systematic dissemination of their cargo have provided important insight into basic biological systems, which in turn has facilitated the identification of numerous human disease phenotypes. At the same time, it will pose a challenge to systematically explore the phenotypic manifestations of microtubule dysfunction and their implications in

cellular function. New techniques will need to be developed to facilitate more generalized approaches that take into account the functions of all known MAPs and the functional characterization of newly identified MAPs. Investigations of the Hedgehog signaling pathway [133] point in the general direction of future scientific endeavors, although a more systematic library-like screen is likely appropriate for more narrowly focused questions. Since knocking out specific MAP members might lead to organismal lethality in some or many cases, conditional knockouts [103] or spatially constrained RNA interference [134] will need to be used to dissect the complex phenotypes a little further.

Hitherto, the common link between ciliary and cytoplasmic microtubule dysfunctions has been elusive. Already it seems clear that at least some proteins fulfill dual roles in both cilary function and cytoplasmic microtubule transport. The apical polarity determinant Crb3, for example, has recently been shown to be required for ciliogenesis [135]. Both Crb3 and the planar cell polarity complex Par3/Par6/aPKC bind to the kinesin subunit KIF3A [135].

While ciliary dysfunction seems to play a role predominantly in developmental processes (e.g. left-right asymmetry [122]), cytoplasmic microtubule transport dysfunctions apparently manifest as degenerative diseases following seemingly normal development (e.g. neurodegenerative diseases such as HD [38]). The retinal phenotype of ciliary diseases such as BBS, however, can be interpreted as degenerative and therefore exemplify a bridge between both phenotypes. Both manifestations might be sides of the same coin: while degenerative phenotypes are directly linked to insufficient transport (e.g. BDNF [38]), as manifested by accumulation of inclusion bodies, developmental phenotypes may result from improper propagation of signals or function of cilia. At this time, it is unknown whether this impaired function stems from defective transport of important components (e.g. signaling) or from lack of correct structural assembly; however, additional studies in this vibrant area of research are certain to address these issues.

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