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Review Article

# Kinesin superfamily proteins (KIFs): Various functions and their relevance for important phenomena in life and diseases

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ABSTRACT

Kinesin superfamily proteins (KIFs) largely serve as molecular motors on the microtubule system and transport various cellular proteins, macromolecules, and organelles. These transports are fundamental to cellular logistics, and at times, they directly modulate signal transduction by altering the semantics of informational molecules. In this review, we will summarize recent approaches to the regulation of the transport destinations and to the physiological relevance of the role of these proteins in neuroscience, ciliary functions, and metabolic diseases. Understanding these burning questions will be essential in establishing a new paradigm of cellular functions and disease pathogenesis.



## Contents



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Most newly synthesized proteins in the cell are actively transported along cytoskeletal filaments to their appropriate destination by molecular motors. Proteins are transported in various membranous organelles and protein complexes, and mRNAs are carried in large ribonuclear protein complexes. Directional intracellular transport is most prominent in polarized cells, such as neurons and epithelial cells, and is fundamental for neuronal function and survival because most of the proteins required in the axon and nerve terminals must be transported from the cell body. Therefore, neurons are a good model system for studying intracellular transport. Among the molecular motors that are involved in intracellular transport, three large superfamilies have been identified—kinesins, dyneins and myosins.

Here, we focus on the role of the kinesin superfamily proteins (also known as KIFs) in the process of intracellular transport in various cell types. Based on observations made using electron microscopy, five major kinesin families were initially discovered in the mouse brain. It is now thought that there are 45 mammalian KIF genes, but there could be twice as many KIF proteins because multiple isoforms can be generated by alternative mRNA splicing. The KIFs are classified into 15 kinesin families, which are termed kinesin-1 to kinesin 14B according to the results of phylogenetic analyses (Fig. 1). These families can be broadly grouped into three types, depending on the position of the motor domain in the molecule: N kinesins have a motor domain in the amino terminal region, M kinesins have a motor domain in the middle region and C kinesins have a motor domain in the carboxy-terminal region. In general, N kinesins and C kinesins provide microtubule-plus-end- and minus-end-directed motilities, respectively, and M kinesins depolymerize microtubules into tubulin molecules [1,2].

This review focuses on several important questions regarding the role of KIFs in intracellular transport. Regarding the mechanisms of intracellular transport, studies have accumulated evidence related to the types of cargo that are transported by each KIF [2]. The second question is how these KIFs recognize and bind to these cargos. It has been clarified that KIFs typically use scaffold proteins and adapter proteins to recognize and bind to cargo although they can sometimes bind to their cargo directly. The cargo–motor relationship has a high level of specificity; however, there is redundancy in some cases. The third question is how cargo unloading is controlled: phosphorylation, Rab GTPase activity and $Ca^{2+}$ signaling were identified as their major mechanisms [1]. In this review, we focus on the fourth question, which is concerned with how the direction of transport is determined in relationship with the microtubule tracks. Furthermore, we introduce the emerging exciting roles of KIFs in the regulation of several important physiological processes in mammals, including the regulation of higher brain functions such as learning and memory, brain development, development of the body plan, and relationships with certain diseases.

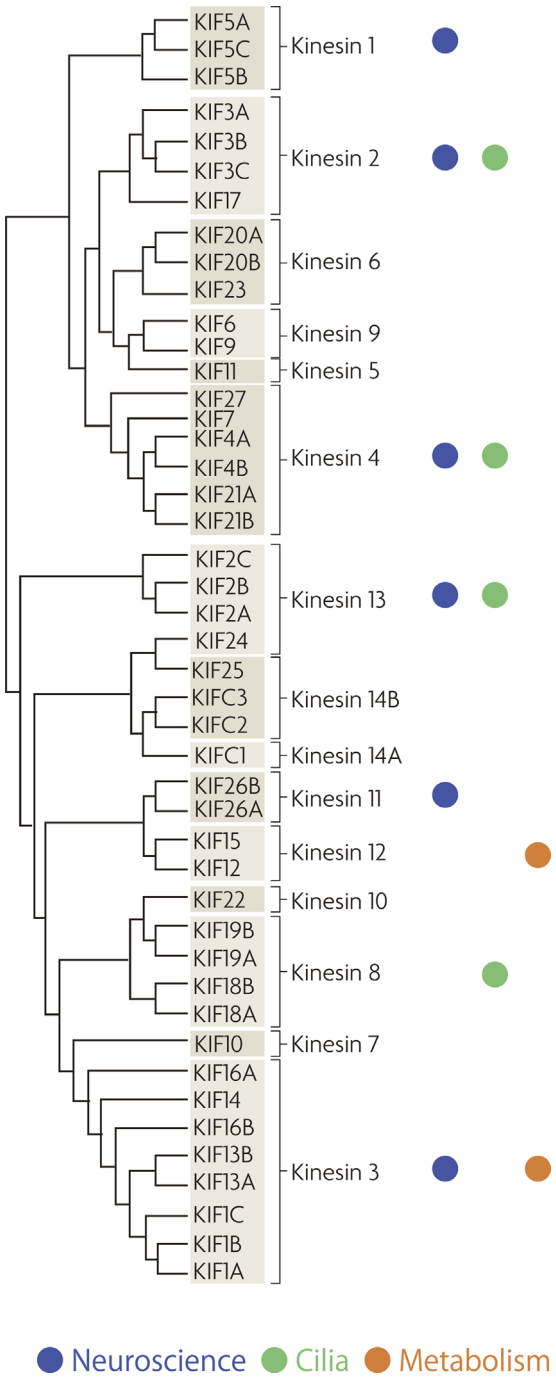


**Fig. 1 – Molecular phylogeny of mouse kinesin superfamily proteins (KIFs), classified into 15 subfamilies. The significance of each subfamily in neuroscience, ciliary function, and metabolic diseases are marked as indicated, according to the text. Reproduced and modified with permission from Ref. [1].**

## Regulatory mechanisms of transport directions

Neurons are highly polarized cells possessing dendrites and a long axon. The differential transport of various types of membrane organelles and proteins into these polarized processes is fundamental for neuronal morphogenesis, function, and survival. Recently, it has been shown that a number of kinesin superfamily proteins, or KIFs, play significant roles in polarized transport [2]. GFP-VSV-G, beta-APP and GAP-43 are transported dominantly towards the axon by the kinesin-1 motor KIF5 whereas GFP-Kv2.1 is transported to the dendrites [3]. However, the homodimeric kinesin-2 motor KIF17 conveys NR2B-containing vesicles to the dendrites [4]. What controls this directional transport is a fundamental question in neurobiology.

As a basis of this mechanism, differences in the microtubule tracks between the axon and dendrites have been noted. In this regard, the KIF5 motor has been shown to have a binding preference to the microtubules in the initial segment of the axon (Fig. 2). Low-dose paclitaxel treatment causes the mis-sorting of KIF5 and axon membrane proteins to the tips of the dendrites. Microtubules in the initial segment of the axons showed a remarkably high affinity to EB1-YFP, which was known to bind to the tips of growing microtubules. These findings suggest unique features of the microtubule cytoskeleton that provide directional information for polarized axonal transport [3]. Indeed, this selective translocation of KIF5 is the earliest known marker of axonal identity, occurring before morphological differentiation [5]. Thus, how the microtubules in the axons differ from the microtubules in the dendrites and how KIF5 recognizes their differences came about as the next questions. Certain post-translational modifications of tubulin, such as tyrosination, were proposed to be important, whereas increasing tubulin acetylation without altering the levels of other tubulin modifications did not alter the selectivity of KIF5 accumulation in the polarized cells [6,7]. Thus, it remained unknown what caused KIF5 to recognize and bind preferentially to the axonal microtubules.

Recently, the significance of the differential nucleotide states of tubulin molecules in this polarized sorting has been proposed. An anti-GTP-tubulin antibody preferentially labeled the axonal microtubules. Super-resolution microscopy (photoactivated localization microscopy, PALM) combined with EM immunocytochemistry revealed that GTP-tubulin was localized at the KIF5 attachment sites. In addition, EB1, which binds preferentially to GTP microtubules in vitro, recognized the anti-GTP-tubulin-antibody-binding sites on axonal microtubules. Furthermore, the expression of the anti-GTP-tubulin antibody in neurons disrupted the selective accumulation of the KIF5 motor head in the axon tips. In vitro studies

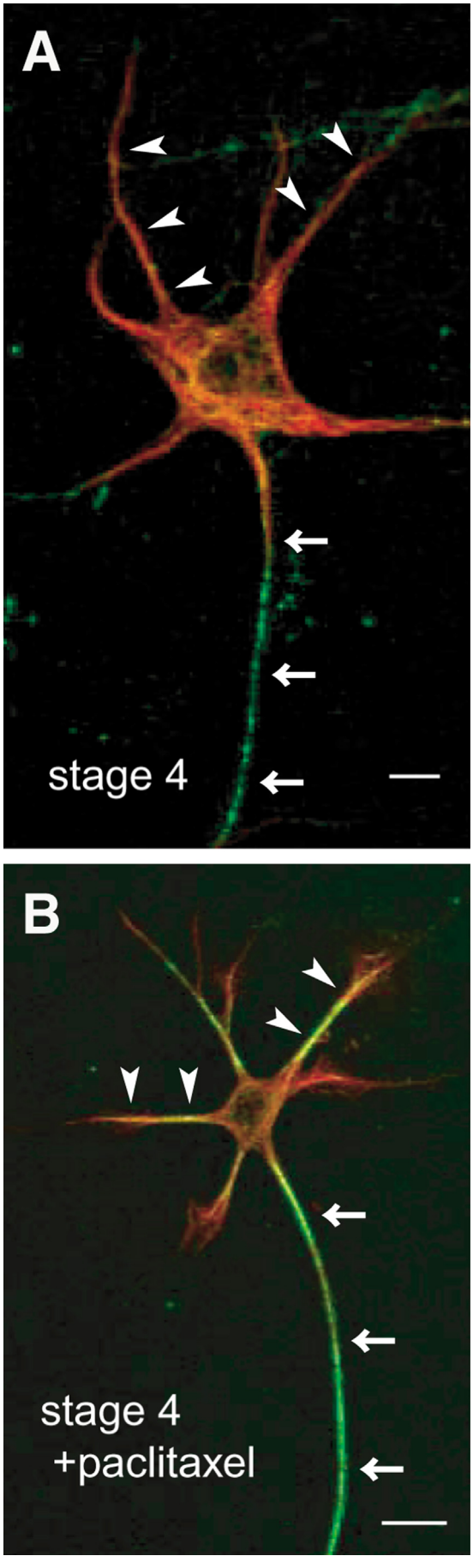


**Fig. 2 – Axon-specific localization of GTP-tubulin. The hippocampal neurons at stage 4 were labeled with an anti-GTP-tubulin antibody (green) and the dendritic marker anti-MAP2 antibody (red). Most of the GTP-tubulin was localized to the axon (arrows) and excluded from the dendrites (arrowheads) of normal neurons (A), but this preferential localization was not present in the neurons treated with 100 nM paclitaxel (B). Bars, 10 μm. Reproduced and modified with permission from Ref. [8] ©Nakata et al., 2011. Originally published in *J. Cell Biol.* doi: 10.1083/jcb.201104034.**

revealed an approximately threefold stronger binding of the KIF5 motor head to GTP microtubules than to GDP microtubules. These data collectively suggested that the abundance of GTP-tubulin in axonal microtubules may underlie selective KIF5 localization and polarized axonal vesicle transport [8].

The next questions were concerned with how GTP microtubules differ from GDP microtubules and how KIF5 recognizes and binds preferentially to GTP microtubules. Microtubule dynamics are regulated through guanosine triphosphate (GTP) hydrolysis by beta-tubulin. Using cryoelectron microscopy (cryo-EM), a structure of microtubules stabilized with a GTP analog, GMPCPP, was resolved at an 8.8-angstrom resolution by using a novel cryo-EM image reconstruction algorithm. Significant differences were detected between GMPCPP and the GDP-taxol microtubules at the contacts between tubulins both along the protofilaments and between neighboring protofilaments, contributing to the stability of the microtubules. These findings suggest the structural basis not only for the regulatory mechanism of microtubule dynamics but also for the recognition of the nucleotide state of microtubules by microtubule–binding proteins such as KIF5 and EB1 [9].

In addition, another interesting mechanism has been proposed for directional transport, which is a selective filter for cytoplasmic transport at the axon initial segment. In cultured hippocampal neurons, an ankyrin-G- and F-actin-dependent structure emerged in the cytoplasm of the axon initial segment (AIS) within 2 days after the axon/dendrite differentiation. This structure was imposed as a selective filter for the diffusion of macromolecules and the transport of vesicular carriers into the axon [10]. Axonal entry was allowed for KIF5-driven carriers of the synaptic vesicle protein VAMP2 but not for KIF17-driven carriers of the dendrite-targeting NMDA receptor subunit NR2B. Comparisons of transport rates between the chimeric forms of KIF17 and KIF5B, with the motor and cargo-binding domains switched, and between KIF5 loaded with VAMP2 versus GluR2 suggest that the axonal entry of vesicular carriers depends on the transport efficacy of the KIF-cargo complexes. This selective AIS filtering could also contribute to preferential trafficking and segregation of cellular components in polarized neurons [10]. A further structural analysis of cytoplasmic selective AIS filtering is necessary. Because certain cargoes such as GluR2 and mRNAs with large protein complexes could also regulate their own transporting directions [11,12], there should be multiple factors synergistically working together that control the directionality of transport. Further studies will be required to solve the entire mechanism.

## Relevance of KIFs for biological phenomena in life

In the latter half of this review, we will look at the major physiological relevance of KIFs that has been revealed by recent studies involving molecular genetics. As depicted in the phylogenetic tree of KIFs (Fig. 1), we will mainly focus on the KIFs that are crucial to neuroscience, cilia function, and metabolism.

### KIFs and regulation of higher brain function, learning and memory

As we have discussed in the last section, neuronal KIFs transport synaptic vesicle precursors and transmitter receptors such as glutamate receptors and GABA receptors and mRNAs to fundamentally regulate neuronal functions. Indeed, molecular genetics studies have recently discovered that KIFs' functions include controlling higher brain functions such as learning and memory.

The homodimeric kinesin-2 motor KIF17 transports the N-methyl-D-aspartate (NMDA) receptor subunit 2B (NR2B) in dendrites [11]. Disruption of the murine *Kif17* gene inhibited the NR2B transport and was accompanied by decreased transcription of the *Nr2b* gene, resulting in a loss of synaptic NR2B. In *Kif17*$^{-/-}$ hippocampal neurons, the NR2A levels also decreased because of an accelerated ubiquitin-proteasome-system-dependent degradation. Accordingly, NMDA receptor-mediated synaptic currents, early and late long-term potentiation, long-term depression, and CREB responses were attenuated in the *Kif17*$^{-/-}$ neurons, concomitant with a hippocampus dependent memory impairment in knockout mice. In wild-type neurons, CREB is activated by synaptic inputs, which increase the levels of KIF17 and NR2B. Thus, KIF17 differentially maintains the levels of NR2A and NR2B, and when synapses are stimulated, the NR2B/KIF17 complex is upregulated on demand through CREB activation. These KIF17-based mechanisms for maintaining NR2A/2B levels could underlie multiple processes in learning and memory in vivo [13].

KIF17-dependent modulation of NMDA receptor trafficking is crucial to regulate synaptic transmission. $Ca^{2+}$/calmodulin-dependent protein kinase IIA phosphorylates the tail domain of KIF17 and controls NR2B transport by changing the KIF17–cargo interaction in vitro [14]. The mechanisms of regulation of NR2B transport in vivo and its physiological significance were first uncovered by mouse-knockout/transgenic-rescue approaches. Transgenic mice carrying wild-type KIF17 (TgS) or KIF17 with dephosphomimetic S1029A (TgA) and phosphomimetic S1029D (TgD) mutations, respectively, in a *Kif17*$^{-/-}$ background were generated. Interestingly, both of the TgA/*Kif17*$^{-/-}$ and TgD/*Kif17*$^{-/-}$ mice exhibited reductions in synaptic NMDA receptor levels because of their inability to load/unload NR2B onto/from KIF17, respectively, leading to impaired neuronal plasticity, CREB activation, and spatial memory. The expression of GFP-KIF17 in TgS/*Kif17*$^{-/-}$ mouse neurons counteracted the synaptic and behavioral defects of the *Kif17*$^{-/-}$ mice. These results suggest that phosphorylation-based regulation of the NMDA receptor transport is critical for learning and memory in vivo [15].

Glutamatergic synapses are highly energy-dependent, and it was recently reported that the same transcription factor, nuclear respiratory factor 1 (NRF-1), co-regulates energy metabolism (via its regulation of cytochrome *c* oxidase and other mitochondrial enzymes) and synaptic proteins for glutamatergic transmission (NR1, NR2B, GluR2, and nNOS). Furthermore, the hypothesis that NRF-1 also transcriptionally regulates KIF17 was tested. By means of an in silico analysis, electrophoretic mobility shift and supershift assays, in vivo chromatin immunoprecipitation assays, promoter mutations, and real-time quantitative PCR, it was found that NRF-1 (but not NRF-2) functionally regulates the *Kif17* gene but not the *Kif1a* gene. NRF-1 binding sites on the *Kif17* gene are highly conserved among mice, rats, and humans. The silencing of NRF-1 with small interference RNA blocked the upregulation of *Kif17* mRNA and proteins (and of *Nr1* and *Nr2b*) induced by KCl-mediated depolarization whereas overexpressing NRF-1 rescued these transcripts and proteins from being suppressed by TTX. Thus, NRF-1 co-regulates oxidative enzymes that generate energy and neurochemicals that consume energy related to

glutamatergic neurotransmission, such as KIF17, NR1, and NR2B, thereby ensuring that energy production matches energy utilization at the molecular and cellular levels [16].

A primary determinant of the strength of neurotransmission is the number of AMPA-type glutamate receptors (AMPARs) at the synapses. However, the mechanistic understanding of how the number of synaptic AMPARs is regulated has been elusive. It was shown that UNC-116, the *C. elegans* homolog of the vertebrate kinesin-1 heavy chain (KIF5), modifies synaptic strength by mediating the rapid delivery, removal, and redistribution of synaptic AMPARs. Furthermore, the real-time imaging of the transport of *C. elegans* AMPAR subunits in vivo demonstrated that glutamate-gated currents were diminished in *unc-116* mutants because heteromeric GLR-1/GLR-2 (GluR1/GluR2) receptors did not reach the synapses in the absence of UNC-116/KIF5-mediated transport, although homomeric GLR-1 AMPARs can diffuse to and accumulate at synapses. Thus, this study supports a model in which the ongoing motor-driven delivery and removal of AMPARs controls not only the number but also the composition of synaptic AMPARs and thus the strength of synaptic transmission [17].

The levels of KIF-based axonal transport appear to be both dynamically modulated by and able to modulate the higher brain functions, reflecting the change in brain activities. Environmental enrichment causes a variety of effects on brain structure and function. Brain-derived neurotrophic factor (BDNF) plays an important role in enrichment-induced neuronal changes; however, the precise mechanism underlying these effects remains uncertain. Recently, a specific upregulation of the kinesin-3 motor KIF1A was observed in the hippocampus of mice kept in an enriched environment in vivo and in hippocampal neurons in vitro. BDNF increased the levels of KIF1A and of KIF1A-mediated cargo transport. An analysis of $Bdnf^{+/-}$ and $Kif1a^{+/-}$ mice revealed that a lack of KIF1A upregulation resulted in a loss of enrichment-induced hippocampal synaptogenesis and learning enhancement. In addition, KIF1A overexpression promoted synaptogenesis via the formation of presynaptic boutons. These findings demonstrate that KIF1A is indispensable for BDNF-mediated hippocampal synaptogenesis and learning enhancement induced by environmental enrichment. This is a new molecular-motor-mediated presynaptic mechanism underlying experience-dependent neuroplasticity [18].

Doublecortin (Dcx), which is a growing family of microtubule-associated proteins (MAPs) involved in neuronal migration and process outgrowth, is essential for the function of KIF1A, which traffics synaptic vesicle precursors. Neurons lacking Dcx and/or its structurally conserved paralogue, doublecortin-like kinase 1 (Dclk1), showed impairment in the KIF1A-mediated transport of Vamp2, which is a cargo of KIF1A, resulting in a decreased run length. Human disease-associated mutations in the Dcx linker sequence (e.g., W146C and K174E) altered the KIF1A-mediated Vamp2 transport by disrupting the Dcx/KIF1A interactions without affecting Dcx-microtubule binding. Dcx specifically enhances the binding of the ADP-bound KIF1A motor domain to microtubules. Cryo-electron microscopy and subnanometer-resolution image reconstruction revealed the kinesin-dependent conformational variability of microtubule-bound Dcx and suggested a model for MAP-motor crosstalk on microtubules. Alteration of the kinesin run length by MAPs represents a previously undiscovered mode of control of kinesin transport and provides a mechanism for the regulation of microtubule-based transport by local signals [19].

## KIFs and brain development

KIFs control brain development in a fundamental manner. Through interactions with microtubules, KIFs can play multiple roles in neuronal function and development. During neuronal development, postmitotic neurons develop primary axons extending toward targets whereas other collateral branches remain short. Although the process of collateral branching is important for the correct wiring of the brain, the mechanisms involved are not well understood. $Kif2a^{-/-}$ mouse brains showed multiple phenotypes, including aberrant axonal branching because of overextension of the collateral branches. In the growth cones of $Kif2a^{-/-}$ neurons, microtubule-depolymerizing activity decreased. Moreover, at $Kif2a^{-/-}$ cell edges, individual microtubules showed abnormal behavior. Based on these results, KIF2A was proposed to regulate the microtubule dynamics at the growth cone edge by depolymerizing microtubules to play an important role in the suppression of collateral branch extension during brain development [20].

In brain development, apoptosis is a physiological process that controls the final number of neurons. It was reported that the activity-dependent prevention of apoptosis in juvenile neurons is regulated by the kinesin-4 motor KIF4A. The C-terminal domain of KIF4A is a module that suppresses the activity of poly (ADP-ribose) polymerase-1 (PARP-1), which is a nuclear enzyme known to maintain cell homeostasis by repairing DNA, thus serving as a transcriptional regulator. When neurons are stimulated by membrane depolarization, calcium signaling mediated by CaMKII induces the dissociation of KIF4A from PARP-1, resulting in the upregulation of PARP-1 activity, which supports neuronal survival. After dissociation from PARP-1, KIF4A enters the cytoplasm from the nucleus and moves toward the distal part of the neurites in a microtubule-dependent manner. This study suggested that KIF4A controls the activity-dependent survival of postmitotic neurons by regulating PARP-1 activity in brain development [21].

Radial glial progenitor cells exhibit bidirectional cell-cycle–dependent nuclear oscillations. The purpose and underlying mechanism of this unusual 'interkinetic nuclear migration' are poorly understood. The basis for this behavior was studied by live imaging of the nuclei, centrosomes and microtubules in embryonic rat brain slices, coupled with the use of RNA interference (RNAi) and the myosin inhibitor blebbistatin. Nuclei migrate irrespectively of centrosomes and unidirectionally away from or toward the ventricular surface along the microtubules, which are uniformly oriented from the ventricular surface to the pial surface of the brain. RNAi directed against cytoplasmic dynein specifically inhibited nuclear movement toward the apical surface. An RNAi screen of kinesin genes identified KIF1A as the motor for basally-directed nuclear movement. These observations provide direct evidence that KIFs are involved in nuclear migration and neurogenesis and suggest that a cell-cycle–dependent switch between distinct microtubule motors drives interkinetic nuclear migration [22].

## KIFs related to cilia function

Cilia and flagella are unique cellular protrusions that principally function in fluid flow generation and signal transduction. The heterotrimeric kinesin-2 complex KIF3A/KIF3B/KAP3 performs the most essential role in ciliogenesis by transporting structural components to the tips of cilia, a process defined as intraflagellar transport (IFT) [23,24]. Mouse mutants lacking kinesin-2 or IFT

components display a disorganized left-right determination of the internal organs [24], accompanied in part by other signs of ciliopathy, such as polycystic kidneys [25]. Ciliogenesis in the ventral node, which is an embryonic organ, is a key element of this phenomenon. The ventral node is a transient triangular concave structure on the ventral midline surface of the embryo at the early somite stage. Interestingly, monocilia on the ventral node rapidly rotate clockwise around a posteriorly-tilted axis, generating leftward surface fluid flow (nodal flow) [24]. Extracellular vesicles called nodal vesicular parcels (NVPs) were found to be secreted from the cell surface protrusions FGF-signal-dependently, transferred to the left, and trapped at the left periphery of the node, where they deposit their contents [26]. This leftward flow may induce effects such as left-specific calcium elevation and the expression of left-specific genes, which is the basis of the asymmetrical development of the internal organs.

Primary cilia detect extracellular signals through membrane receptors and channels. The outer segment of a vertebrate photoreceptor cell represents the most elaborate of all primary cilia, containing extraordinarily large amounts of the visual receptor protein, opsin. Because of its high abundance, opsin potentially represents a good model for the study of ciliary membrane receptor trafficking, including their transport. The movement of ciliary opsin was analyzed to test whether the highly conserved intraflagellar transport (IFT), as driven by KIF3, is required. Results showed that opsin can enter and move along the primary cilium of a nonphotoreceptor cell, suggesting that it can be recruited by the common anterograde IFT system of cilia. Fluorescence recovery after a photobleaching (FRAP) analysis of the cilia of these cells showed that the motility of ciliary opsin was comparable to that of the IFT protein, IFT88. Moreover, the movement of opsin in these cilia and in the cilia of mouse rod photoreceptor cells was reduced significantly when KIF3A was deficient. These studies therefore provide evidence from a live-cell analysis that the conserved KIF3 is required for the normal transport of opsin along the ciliary plasma membrane [27].

The homodimeric kinesin-2 motor, KIF17, is also detected in cilia, in addition to KIF3. How these motors and their cargoes gain access to the ciliary compartment is poorly understood. A ciliary localization signal (CLS) in the KIF17 tail domain that is necessary and sufficient for ciliary targeting was identified. Similarities between the CLS and classic nuclear localization signals (NLSs) suggest that similar mechanisms regulate nuclear and ciliary import. It was hypothesized that the ciliary targeting of KIF17 is regulated by a ciliary-cytoplasmic gradient of the small GTPase Ran, with high levels of GTP-bound Ran (RanGTP) in the cilium. Consistent with this theory, the cytoplasmic expression of GTP-locked Ran (G19V) disrupts the gradient and abolishes the ciliary entry of KIF17. Furthermore, KIF17 interacts with the nuclear import protein importin-β2 in a manner that is dependent on the CLS and inhibited by RanGTP. Thus, it was proposed that Ran has a global role in regulating cellular compartmentalization by controlling the shuttling of cytoplasmic proteins into nuclear and ciliary compartments [28].

Other than these kinesin-2 motors, more new KIFs have been detected recently in cilia, and their functions have been uncovered. Cilia control the homeostasis of the mammalian body by generating fluid flow. It has long been assumed that ciliary length-control mechanisms are essential for proper flow generation because fluid flow generation is the function of ciliary length. However, the molecular mechanisms of ciliary length control in mammals remain elusive. KIF19A was identified and reported to regulate ciliary length by depolymerizing microtubules at the tips of cilia. *Kif19a*$^{-/-}$ mice displayed hydrocephalus and female infertility phenotypes because of abnormally elongated cilia that cannot generate proper fluid flow. KIF19A localized to cilia tips, and recombinant KIF19A controlled the length of microtubules polymerized from axonemes in vitro. KIF19A had ATP-dependent microtubule-depolymerizing activity mainly at the plus end of microtubules. These results indicated a molecular mechanism of ciliary length regulation in mammals, which plays an important role in the maintenance of the mammalian body [29].

Another new KIF controlling cilium architecture was reported. Mammalian hedgehog (Hh) signal transduction requires a primary cilium, a microtubule-based organelle, and the Gli–Sufu complexes that mediate Hh signaling, which are enriched at the cilia tips. KIF7/Costal-2, a kinesin-4 family protein, is a conserved regulator of the Hh signaling pathway and is responsible for a human ciliopathy. KIF7 localizes to the cilium tip, the site of the microtubule plus ends, where it limits cilium length and controls cilium structure. Purified recombinant KIF7 binds to the plus ends of the growing microtubules in vitro, where it reduces the rate of microtubule growth and increases the frequency of microtubule catastrophe. KIF7 is not required for normal intraflagellar transport or for trafficking Hh pathway proteins into cilia. Instead, a central function of KIF7 in the mammalian Hh pathway is to control cilium architecture and to create a single cilium tip compartment, where Gli–Sufu activity can be precisely regulated [30,31].

KIF24 shares homology with the kinesin-13 subfamily of motor proteins and specifically interacts with CP110 and Cep97, which are centrosomal proteins that play a role in regulating centriolar length and ciliogenesis. KIF24 preferentially localizes to mother centrioles. The loss of KIF24 from cycling cells results in aberrant cilia assembly but does not promote the growth of abnormally long centrioles, unlike the depletion of CP110 and Cep97. The loss of KIF24 leads to the disappearance of CP110 from mother centrioles, specifically in cycling cells that are able to form cilia. KIF24 is able to bind and depolymerize microtubules in vitro. Ectopically expressed KIF24 specifically remodels centriolar microtubules without significantly altering cytoplasmic microtubules. Thus, these studies have identified a centriolar KIF that specifically remodels a subset of microtubules, thereby regulating cilia assembly. These studies also suggest mechanistic differences between the regulation of microtubule elongation associated with centrioles and cilia [32].

## KIFs and diseases

It has been known that congenital and acquired malfunctions of certain KIFs cause diseases, and studies of the defects of KIFs' functions have uncovered the pathogenesis of certain diseases. The following recent studies revealed the relationship between KIFs and diseases. A number of KIFs have been deeply involved in tumorigenesis and caricinogenesis [33]; however, this subject will not be discussed in this review because of space limitations.

### *KIFs and nervous system diseases*

KIF5 (also known as kinesin-1) family members, KIF5A, KIF5B, and KIF5C, are microtubule dependent molecular motors that are important for neuronal function. Among the KIF5s, KIF5A is neuron specific and highly expressed in the central nervous system. However, the specific roles of KIF5A remain unknown. Conditional

*Kif5a* knockout mice, in which KIF5A protein expression was postnatally suppressed in neurons, were established. Epileptic phenotypes were observed as electroencephalogram abnormalities in knockout mice because of an impairment in $GABA_A$ receptor ($GABA_AR$)-mediated synaptic transmission. The cell surface expression of $GABA_AR$ in knockout neurons was reduced. Importantly, KIF5A specifically interacted with the $GABA_AR$-associated protein (GABARAP), which is known to be involved in $GABA_AR$ trafficking. KIF5A regulated the neuronal surface expression of $GABA_ARs$ via an interaction with GABARAP. These results provide an insight into the molecular mechanisms of KIF5A, which regulates inhibitory neural transmission, and clearly show that its defect causes epilepsy [34].

Mice deficient in the kinesin-3 motor KIF13A (*Kif13a*$^{-/-}$ mice) exhibited elevated anxiety-related behavioral phenotypes because of a reduction in serotonin 5-$HT_{1A}$ receptor (5-$HT_{1A}$R) transport. The cell-surface expression level of 5-$HT_{1A}$R was reduced in KIF13A-knockdown neuroblastoma cells and *Kif13a*$^{-/-}$ hippocampal neurons. A biochemical analysis showed that the forkhead-associated (FHA) domain of KIF13A and an intracellular loop of $5HT_{1A}$R serve as the interface between the motor and cargo vesicles. A minimotor consisting of the motor and FHA domains was able to transport $5HT_{1A}$R-carrying organelles in an in vitro reconstitution assay. Collectively, these results suggest a role for this molecular motor in anxiety control [35].

Cytoplasmic protein transport in axons ('slow axonal transport') is essential for neuronal homeostasis and involves KIF5, which is also the motor for membranous organelle transport ('fast axonal transport'). However, both molecular mechanisms of slow axonal transport and the difference in the usage of KIF5 between slow and fast axonal transport have been elusive. It was shown that slow axonal transport depends on the interaction between the DnaJ-like domain of the kinesin light chain in the KIF5 motor complex and Hsc70, which scaffolds between cytoplasmic proteins and KIF5. The DnaJ-like domain is located within the tetratricopeptide repeat, which can bind to membranous organelles; competitive perturbation of this domain in squid giant axons disrupted cytoplasmic protein transport and reinforced membranous organelle transport, indicating that the domain might have a function as a switchover system between slow and fast transport by Hsc70. Transgenic mice overexpressing a dominant-negative form of the domain resulted in a delay in slow transport and an acceleration of fast transport to reveal an optic axonopathy. These findings provide a basis for the regulatory mechanisms of intracellular transport and its intriguing implications in neuronal dysfunction, such as glaucomatous optic neuropathy [36].

The microtubule tracks are deeply involved in intracellular transport by KIFs. Mutations in tubulin, the major constituent of microtubules, result in neuronal diseases. An analysis of β-tubulin mutations that cause neuronal diseases have identified mutations that strongly inhibit the axonal transport of vesicles and mitochondria. These mutations are in the H12 helix of β-tubulin and change the negative charge on the surface of the microtubule. This surface is the interface between the microtubules and KIFs. The binding of axonal transport KIFs to microtubules is dominant-negatively disrupted by these mutations, which alters the localization of KIFs in neurons and inhibits axon elongation in vivo. In humans, these mutations induce broad neurological symptoms, such as the loss of axons in the central nervous system and peripheral neuropathy. Thus, this study identified the critical region of β-tubulin that is required for axonal transport and suggested a molecular mechanism for human neuronal diseases caused by tubulin mutations [37].

Recently, unexpected functions of KIFs have been uncovered. New kinesin-11 motor KIF26A is such an example. KIF26A is an atypical KIF member because it lacks ATPase activity. Mice with a homozygous deletion of *Kif26a* developed a megacolon with enteric nerve hyperplasia. *Kif26a*$^{-/-}$ enteric neurons showed hypersensitivity for GDNF-Ret signaling because KIF26A suppressed GDNF-Ret signaling by competitively excluding the direct binding of Grb2, which is an essential component of GDNF/Akt/Erk signaling. Therefore, it was proposed that the unconventional kinesin KIF26A plays a key role in enteric nervous system development by repressing a cell growth signaling pathway, and its defect causes megacolons [38]. This is a clear and exciting example demonstrating that KIF plays an important and unexpected role as a factor of the signal transduction cascade.

Schizophrenia (SCZ) is one of the most disabling psychiatric disorders. It is thought to be a result of a complex interplay between polygenic and various environmental risk factors, although recent reports on genomic copy number variations suggested that a fraction of the cases could result from variably penetrant de novo variants. The gene encoding KIF17 involved in the glutamatergic synapse was shown to be a candidate gene for SCZ. KIF17 was resequenced in a cohort of individuals with sporadic SCZ. Additional populations included autism spectrum disorder, nonsyndromic mental retardation, and control subjects. Functional validation of the human mutation was performed in developing zebrafish. A de novo nonsense truncating mutation in KIF17 was found in one patient with SCZ. No de novo or truncating KIF17 mutations were found in the additional samples. The pathogenic nature of this mutation was discovered by knocking down its expression in zebrafish embryos, which resulted in a developmental defect. This study suggested that the disruption of KIF17, although rare, could result in a schizophrenia phenotype, which emphasizes the possible involvement of rare de novo mutations in this disorder [39].

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder of motor neurons that typically develops in the 6th decade of life and is uniformly fatal, usually within 5 years. To identify genetic variants associated with susceptibility and phenotypes in sporadic ALS, a genome-wide SNP analysis in sporadic ALS cases and controls was performed. SNP rs1541160 within the *KAP3* gene (encoding a kinesin-associated protein for KIF3) yielded a genome-wide significant result. Homozygosity for the favorable allele (CC) conferred a 14.0-month survival advantage. Sequence, genotypic and functional analyses revealed that there was a linkage disequilibrium between rs1541160 and SNP rs522444 within the *KAP3* promoter and that the favorable alleles of rs1541160 and rs522444 correlated with reduced KAP3 expression. No SNPs were associated with the risk of sporadic ALS, the site of onset, or the age of onset. A variant within the *KAP3* gene that was associated with decreased KAP3 expression and increased survival in sporadic ALS was identified. These findings support the view that genetic factors modify phenotypes in this disease and that KIFs are determinants of motor neuron viability [40].

The ocular motility disorder "congenital fibrosis of the extraocular muscles type 1" (CFEOM1) is caused by heterozygous mutations that alter the motor and third coiled-coil stalk of KIF21A. *Kif21a* knockin mice were generated that harbored the most common human mutation to develop CFEOM. The developing axons of the oculomotor

nerve's superior division stalled in the proximal nerve; additionally, the growth cones enlarged, extended excessive filopodia, and assumed random trajectories. Inferior division axons reached the orbit but branched ectopically. A gain-of-function mechanism was established, and it was found that human motor or stalk mutations attenuate KIF21A autoinhibition, providing in vivo evidence for mammalian kinesin autoregulation. The structural microtubule-associated protein MAP1B was found as a KIF21A-interacting protein, and the *Map1b*$^{-/-}$ mice developed a CFEOM-like phenotype. The interaction between KIF21A and MAP1B is likely to play a critical role in the pathogenesis of CFEOM1 and highlights a selective vulnerability of the developing oculomotor nerve to perturbations of the axon cytoskeleton [41].

Mechanisms controlling microtubule dynamics at the cell cortex play a crucial role in cell morphogenesis and neuronal development. Another study reported a role of KIF21A as an inhibitor of microtubule growth at the cell cortex. In vitro, KIF21A suppresses microtubule growth and inhibits catastrophes. In cells, KIF21A restricts microtubule growth and participates in organizing microtubule arrays at the cell edge. KIF21A is recruited to the cortex by KANK1, which coclusters with liprin-α1/β1 and the components of the LL5β-containing cortical microtubule attachment complexes. These studies provide mechanistic insight into cortical microtubule regulation and suggest that altered microtubule dynamics contribute to CFEOM1 pathogenesis [42].

*KIFs and metabolic diseases*

Two KIFs, the kinesin-1 motor KIF13B and the kinesin-12 motor KIF12, were discovered to play unexpected fundamental roles and were significantly related to the pathogenesis of metabolic diseases. Multifunctional low-density lipoprotein (LDL) receptor-related protein 1 (LRP1) recognizes and internalizes a large number of diverse ligands, including LDL and factor VIII. However, little was known about the regulation of LRP1 endocytosis. It was shown that KIF13B, in an unexpected and unconventional way, enhances the caveolin-dependent endocytosis of LRP1. KIF13B was highly expressed in the liver and was localized on the sinusoidal plasma membrane of hepatocytes. *Kif13b*$^{-/-}$ mice showed elevated levels of serum cholesterol and factor VIII, and knockout MEFs showed a decreased uptake of LDL. Exogenous KIF13B, which was initially localized on the plasma membrane with caveolae, was translocated to the vesicles in the cytoplasm with LRP1 and caveolin-1. KIF13B bound to hDLG1 and utrophin, which, in turn, bound to LRP1 and caveolae, respectively. These linkages were required for the KIF13B-enhanced endocytosis of LRP1. Thus, it was proposed that KIF13B, working as a scaffold, recruits LRP1 to caveolae via the LRP1–hDLG1–KIF13B–utrophin–caveolae linkage and enhances the endocytosis of LRP1; conversely, its defect causes hypercholesterolemia [43].

A new KIF, KIF12, was found to be related to type 2 diabetes. Pancreatic β cell injury as a result of excess-nutrition-mediated oxidative stress is a typical etiology of diabetes caused by nutritional excess (beta cell lipotoxicity), but its precise mechanism remains largely elusive. KIF12 knockout mice suffer from hypoinsulinemic glucose intolerance because of increased beta cell oxidative stress. Using this model, an antioxidant signaling cascade involving KIF12 as a scaffold for the transcription factor Sp1 was identified. It was demonstrated that KIF12 forms a complex with heat shock protein Hsc70 and its transcriptional factor Sp1 to maintain their levels and plays an antioxidative role through peroxisome biogenesis in beta cells. KIF12-mediated stabilization of nascent Sp1 appeared to be essential for proper peroxisomal function by enhancing Hsc70 expression, and the pharmacological induction of Hsc70 expression with teprenone counteracted the oxidative stress. Because KIF12 is transcriptionally downregulated by chronic exposure to fatty acids, this antioxidant cascade involving KIF12 and Hsc70 is proposed to be a critical target of nutritional excess in beta cells in diabetes [44].

### KIFs and regulation of development

It has been discovered that KIFs play important roles in regulating development such as the determination of the left/right asymmetry of our body, as discussed earlier [45]. Recent studies further revealed that KIFs control early development and organogenesis. The kinesin-3 motor KIF16B/Rab14 complex acts in biosynthetic Golgi-to-endosome traffic of the fibroblast growth factor receptor (FGFR) during early embryonic development. *Kif16b*$^{-/-}$ mouse embryos failed in developing epiblast and primitive endoderm lineages and died in the periimplantation stage, similar to results previously reported for FGFR2 knockout embryos. KIF16B directly associated with the Rab14-GTP adapter on FGFR-containing vesicles and transported these vesicles toward the plasma membrane. To examine whether the nucleotide state of Rab14 serves as a switch for transport, Rab14-GDP overexpression was performed. This dominant negative approach reproduced the entire putative sequence of KIF16B or FGFR2 deficiency: impairment in FGFR transport, FGF signaling, basement membrane assembly by the primitive endoderm lineage, and epiblast development. These data provide one of the first pieces of genetic evidence that microtubule-based membrane trafficking directly promotes early development and stem cell survival [46].

The kidney develops through reciprocal interactions between two precursor tissues, which are the metanephric mesenchyme and the ureteric bud. The zinc finger protein Sall1 is essential for ureteric bud attraction toward the mesenchyme. The kinesin-11 motor KIF26B was revealed to be a downstream target of Sall1, and the disruption of this gene causes kidney agenesis because of impaired ureteric bud attraction. In the KIF26B-null metanephros, compact adhesion between the mesenchymal cells adjacent to the ureteric buds and the polarized distribution of integrin-α8 were impaired. This resulted in the failure of maintenance of GDNF, which is a critical ureteric bud attractant. Overexpression of KIF26B in vitro caused increased cell adhesion through interactions with nonmuscle myosin. Thus, KIF26B was suggested to be essential for kidney development through facilitating the adhesion of mesenchymal cells adjacent to the ureteric buds [47].

## Concluding remarks

Determining the location of biological molecules is fundamental to cellular functions. Molecular motors, particularly KIFs, are critical enzymes for such determination processes. The molecular mechanisms of the precise regulation of the transport destination and the biological significance of each kinesin have been gradually unveiled using cell biological and molecular genetic approaches. In the near future, further studies of KIFs will uncover

more exciting new functions of KIFs and also their relevance for health and diseases.

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