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Review

Molecular Motors in Neurons: Transport Mechanisms and Roles in Brain Function, Development, and Disease

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The kinesin, dynein, and myosin superfamily molecular motors have fundamental roles in neuronal function, plasticity, morphogenesis, and survival by transporting cargos such as synaptic vesicle precursors, neurotransmitter and neurotrophic factor receptors, and mRNAs within axons, dendrites, and synapses. Recent studies have begun to clarify the mechanisms of cargo selection and directional transport in subcellular compartments. Furthermore, molecular genetics has revealed unexpected roles for molecular motors in brain wiring, neuronal survival, neuronal plasticity, higher brain function, and control of central nervous system and peripheral nervous system development. Finally, it is also evident that molecular motors are critically involved in neuronal disease pathogenesis. Thus, molecular motor research is becoming an exciting frontier of neuroscience.

Introduction

Neurons develop a highly polarized structure composed of dendrites and an axon along the direction of the impulse propagation. Axons are frequently very long: in the case of motor neurons in the spinal cord, an axon is approximately 1 m long. Interestingly, most of the proteins necessary for the axon and synaptic terminals must be transported down the axon after synthesis in the cell body. The proteins are conveyed in various kinds of membranous vesicles and protein complexes in the axon and dendrites. In dendrites, mRNAs such as *CaMKIIα* mRNA, *Arc* mRNA, and *Fmr1* mRNA are transported, and protein synthesis occurs locally. Therefore, intracellular transport is fundamental for neuronal morphogenesis, function, and survival.

Molecular motors from the kinesin, dynein, and myosin superfamilies have been identified to transport these cargos (Cheney and Baker, 1999; Hirokawa, 1998; Karki and Holzbaur, 1999; Vale, 2003). In the axon and dendrites, microtubules and neurofilaments are the major longitudinal cytoskeletal filament (Figures 1A–1C). Kinesins and dyneins move along microtubules (Figures 2 and 3). In the synaptic regions, such as presynaptic terminals and postsynaptic spines, actin filaments form the major cytoskeletal architecture (Figures 1D–1F). Here, mainly myosins convey the cargos (Figures 2 and 3). In the axon and dendrites, transport occurs bidirectionally, from the cell body to the periphery (anterograde transport) and from the periphery to the cell body (retrograde transport). These directionalities of transport depend on the polarity of the rails (Figure 3). Microtubule rails have a polarity: in the axon and the distal dendrites, the plus end (the fast growing end) points distally, whereas in the proximal dendrites, the polarity is mixed. Actin filaments also have a polarity: the barbed end (the growing end) points to the plasma membrane in the presynaptic and postsynaptic regions.

Kinesin superfamily proteins (KIFs) comprise three major groups depending on the position of the motor domain within the molecule: N-terminal motor domain KIFs (N-KIFs), middle motor domain KIFs (M-KIFs), and C-terminal motor domain KIFs (C-KIFs) (Figure 4A). In mammals such as human and mouse, the total number of *Kif* genes is 45, including three M-*Kifs* (*Kif2a*, *Kif2b*, and *Kif2c*) and three C-*KIFs* (*Kifc1*, *Kifc2*, and *Kifc3*). *Kif* genes have been classified into 14 classes (Aizawa et al., 1992; Miki et al., 2001; Lawrence et al., 2004; Figure 4B).

N-terminal KIFs generally move toward microtubule plus ends, while C-terminal KIFs move toward minus ends. KIF2A and 2C are unique KIFs that depolymerize microtubules in an ATP-dependent manner. N-KIFs and C-KIFs are composed of a motor domain, a stalk domain and a tail region. The overall homology of the amino acid sequence among the motor domains is 30–60%, while the other parts exhibit significant divergence. The motor domain binds to microtubules and moves on them by hydrolyzing ATP, while in general the tail regions, and less frequently the stalk regions, recognize and bind to the cargo(s) (Hirokawa and Noda, 2008; Figure 5).

Dynein superfamily proteins comprise two major groups, cytoplasmic dyneins and axonemal dyneins; the latter also called ciliary or flagellar dyneins. Dyneins are mechanoenzymes that move along microtubules by hydrolyzing ATP. Cytoplasmic dynein is used for intracellular transport and consists of a huge protein complex of approximately 1.5 megadaltons, containing multiple polypeptide subunits: two heavy chains (~520 kDa) with ATPase activity and generating movement along the microtubules, two intermediate chains (~74 kDa), four intermediate light chains (~33–59 kDa) and several light chains (~10–14 kDa) (Karki and Holzbaur, 1999; Pfister et al., 2005; Figure 2). Furthermore, cytoplasmic dynein has an important associated protein complex called dynactin, containing $p150^{Glued}$, p62, dynamitin,

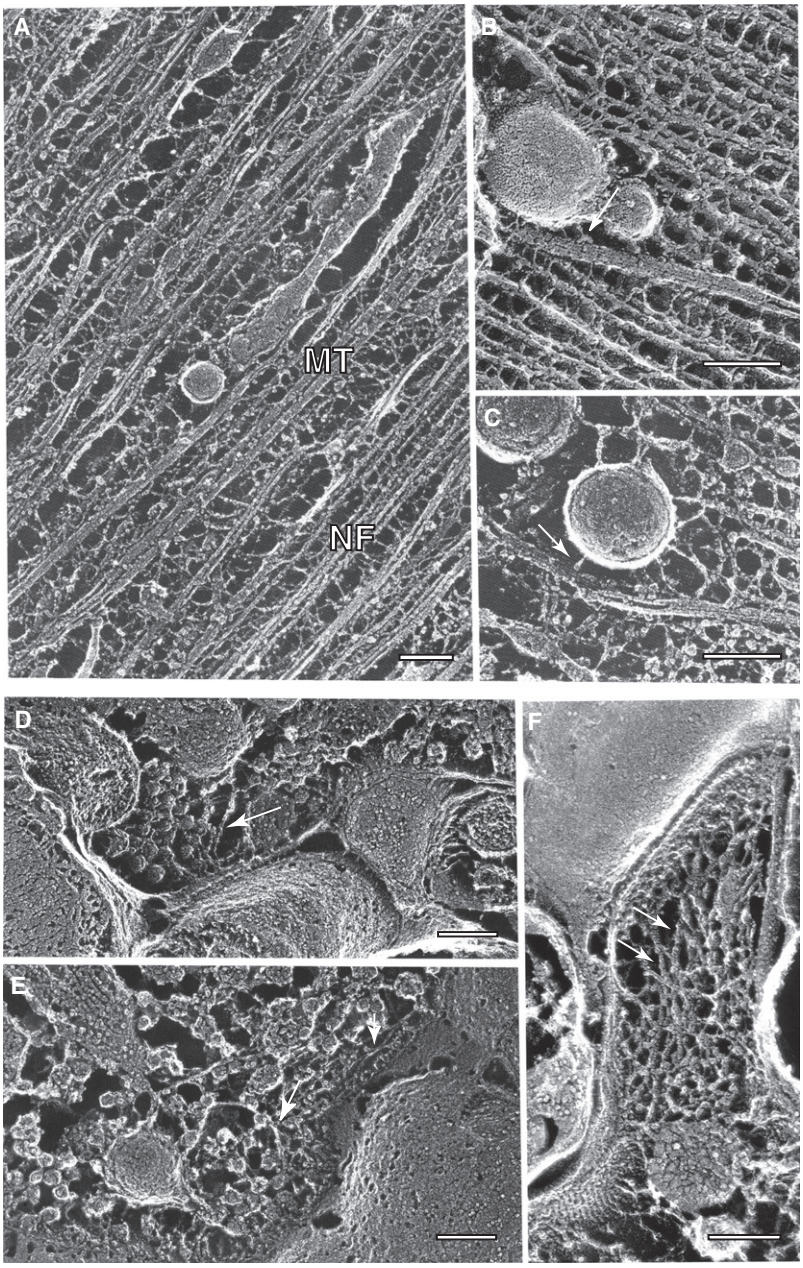

Figure 1. The Neuronal Cytoskeleton Revealed by Quick-Freeze Deep-Etch Electron Microscopy

(A) A low-magnification view of a neurite showing longitudinally arranged microtubule (MT) bundles and neurofilament (NF) bundles. Membranous organelles are observed close to the microtubules.

(B and C) Short cross-bridges (arrows), structural candidates for KIFs, are observed between membranous vesicles and microtubules. Note the structural differences in these cross-bridges.

(D and E) Cytoskeletal structures in the presynaptic terminals. Actin filaments (arrows) are extending toward and associating with the presynaptic membrane.

(F) Cytoskeletal structures in a postsynaptic spine. Actin filaments (arrows) form the major cytoskeletal elements that extend toward the postsynaptic membrane.

The scale bars represent 100 nm.

actin-related protein (Arp) 1, CAPZα and CAPZβ, p27, and p24. Dynactin regulates dynein activity and the binding capacity of dynein for its cargos (Schroer, 2004; Figure 2). Compared with the diversity in the kinesin and myosin superfamilies, cytoplasmic dyneins have only two heavy chain family members, cytoplasmic dynein heavy chain 1 (Dync1h1) and cytoplasmic dynein heavy chain 2 (Dync2h1) (Tanaka et al., 1995; Pfister et al., 2006). Dync1h1 mainly serves in minus end-directed cytoplasmic transport and Dyhc2h1 mainly functions in retrograde intraflagellar transport (May et al., 2005). Dync1h1 can acquire a variety of cargo associations through direct binding or recruiting alternative forms of dynein subunits including multiple light intermediate chains, intermediate chains, light chains (Tctex1, Roadblock, and LC8 subfamilies), and dynactin complexes, while kinesins and myosins have diverged into huge superfamilies and use their own tail regions for recognition and binding of cargos.

Myosin superfamily motor proteins bind to actin and use the energy of ATP hydrolysis to generate force and movement along actin filaments (Figure 2). They are classified into 18 classes (Foth et al., 2006). They play significant roles in cell movement, muscle contraction, cytokinesis, membrane trafficking, and signal transduction. Most myosins form a dimer and consist of a motor domain, a neck region, and a tail region.

Various cargos including membranous vesicles, protein complexes, and mRNAs with large protein complexes are transported in the axon, dendrites, and pre- and postsynaptic regions by these motors (Figure 3, Table 1). In this review, we will introduce recent progress regarding the following questions. (1) What kind of cargo(s) does each motor transport? (2) How does the motor recognize and bind its cargo(s)? (3) How does the motor regulate loading and unloading of the cargo(s)? (4) How is the activity of the motor regulated in terms of velocity and binding to microtubules? (5) How is bidirectional transport regulated? (6) How is the fast transport of membranous organelles and the slow transport of cytoplasmic proteins regulated? (7) How is the direction of transport in axons versus dendrites determined? (8) What is the biological significance of the motor function at the whole-body level? (9) To what diseases does disturbance in motor function relate, and how is the motor involved in the pathogenesis of those diseases? The primary mechanisms of intracellular transport in neurons have been elucidated for certain motors, such as their cargos, direction, and velocity of transport and the mechanisms of cargo recognition, loading, and unloading (Table 1). In addition, the mechanisms of directional transport in the axon

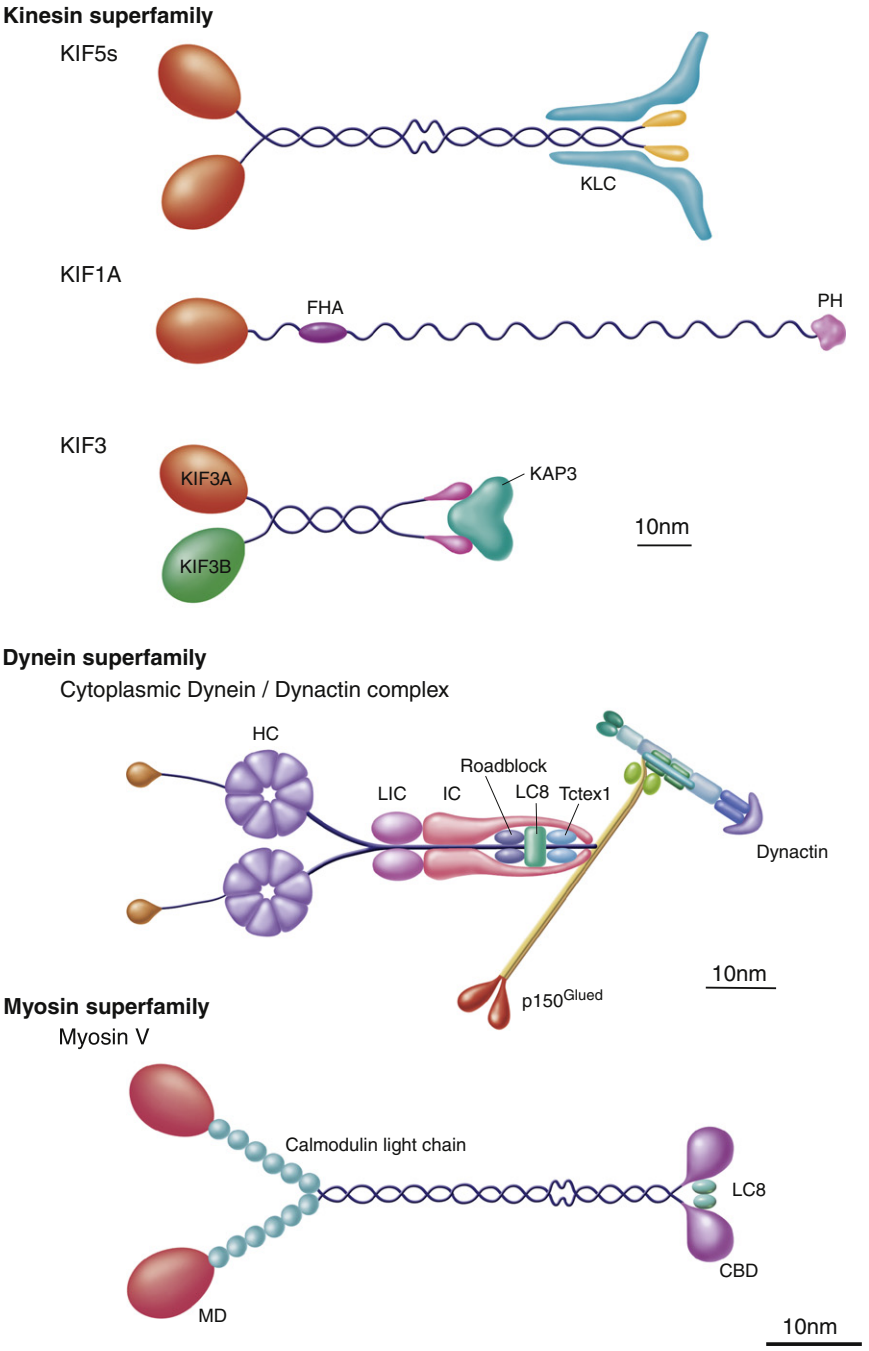

Figure 2. Structure of Motor Proteins

(Top) Kinesin superfamily proteins. Kinesin 1 consists of two KIF5s and two KLCs. KIF1A is a unique monomeric motor. KIF3A, KIF3B, and KAP3 form a tetramer.

(Middle) Cytoplasmic dynein. Cytoplasmic dyneins consist of heavy chains, light intermediate chains, intermediate chains, and light chains. To transport cargos, cytoplasmic dynein binds to the dynactin complex.

(Bottom) Myosin superfamily. Myosin V consists of two heavy chains. The neck domain of myosin V binds to calmodulin light chains. Light chain 8 binds to the tail region of the heavy chain.

versus dendrites are beginning to be unraveled. Furthermore, molecular genetic studies have revealed quite unexpected roles for motors in higher brain function, brain wiring, activity-dependent neuronal survival, suppression of tumorigenesis, and central nervous system (CNS) and peripheral nervous system (PNS) development (Tables 2 and 3). In particular, we will focus on the neuronal roles of KIF1A, KIF1Bα and KIF1Bβ, KIF2A, KIF3, KIF4, KIF5s, KIF13B, KIF17, KIF26A, and KIFC2 from the kinesin superfamily; cytoplasmic dynein and dynactin; and myosin I, myosin II, myosin V, myosin VI, myosin VII, and myosin X from the myosin superfamily.

The Mechanisms of Intracellular Transport: Motors, Cargos, Recognition, Binding, and Unloading of Cargos

The molecular motors mostly associate with their cargos through adaptor proteins (Figure 5 and Table 1). How certain cargoes are recognized by the motors is summarized in Table 1. Recent studies have revealed that the binding and unloading of cargos from the motors, or the rails, are strictly regulated by multiple mechanisms (Figure 6). In this section, we will explore the major mechanisms of intracellular transport in neurons.

KIFs and Axonal Transport

There are two types of transport in the axon: fast transport of membranous organelles and slow transport of cytosolic proteins and cytoskeletal proteins. In terms of the fast transport, various cargo vesicles are conveyed by distinct KIFs, although the functions of each KIF are sometimes redundant. Cargos transported down the axon include synaptic vesicle precursors (KIF1A and KIF1Bβ), presynaptic membrane or active zone vesicles (KIF5), mitochondria (KIF1Bα/KIF5), amyloid precursor protein (APP)-containing vesicles (KIF5), APOER2 vesicles (KIF5), TrkB vesicles (KIF5), plasma membrane precursors (KIF3), and phosphatidylinositol 3,4,5-triphosphate (PIP_3) vesicles (KIF13B). KIF5 has been identified also as a slow transport motor (Figures 3 and 5 and Table 1).

KIF1A and KIF1Bβ. The kinesin 3 family members KIF1A and KIF1Bβ are similar molecular motors that transport components of synaptic vesicles, which are called synaptic vesicle precursors and contain synaptic vesicle proteins such as synaptophysin, synaptotagmin, and Rab3A (Okada et al., 1995a; Zhao et al., 2001). Synaptic transmission is an important feature of neurons

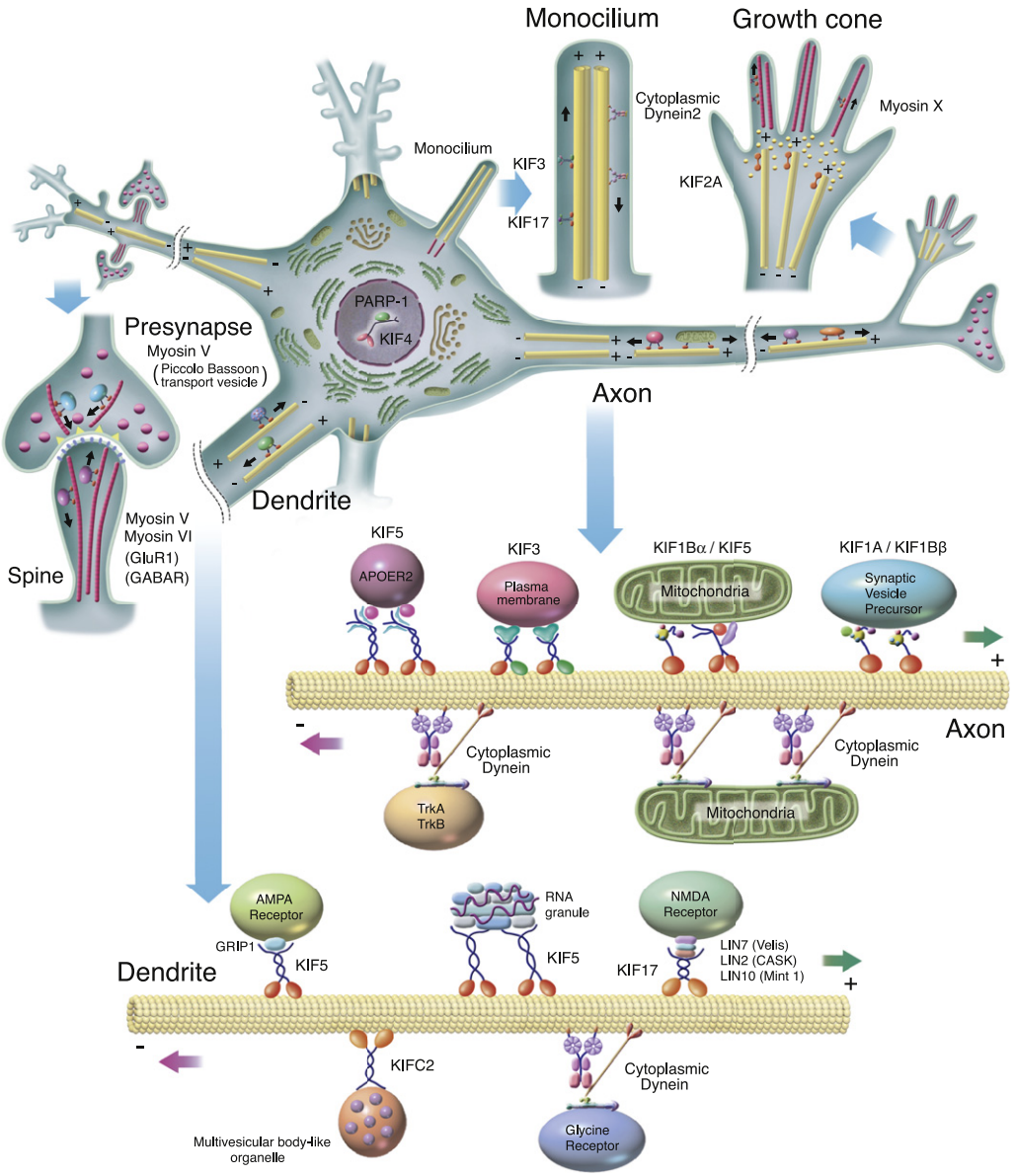

Figure 3. Intracellular Transport in Neurons

Various KIFs transport membranous organelles anterogradely in axons and dendrites, whereas cytoplasmic dynein 1 and KIFC2 transport retrograde cargos. In neuronal cilia, anterograde transport is performed by KIF3 and KIF17, while retrograde transport is performed by cytoplasmic dynein 2. In short-range transport, such as transport in the pre- and postsynapses and growth cone filopodia, the myosin family proteins function as the molecular motors.

that propagates nerve impulses between neurons and target cells. Functionally mature synaptic vesicles are generated by endocytosis at the synaptic plasma membrane. Prior to that, synaptic vesicle precursors must be transported from cell bodies to the synapse. KIF1A or KIF1Bβ contains a C-terminal pleckstrin homology (PH) domain and a conserved stalk domain. It has been suggested that the PH domain is required but not sufficient for cargo transport (Klopfenstein et al., 2002; Klopfenstein and Vale, 2004). Although the PH domains of KIF1A and KIF1Bβ have a preference for binding to phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2), this phospholipid is mainly localized to the plasma membrane. Thus, the PH domain is considered insufficient to bind to specific cargo organelles. This specificity is provided by adaptor proteins binding to the stalk domain. DENN/MADD has recently been identified as such an adaptor protein (Niwa et al., 2008; Figures 5A and 6B). The death domain of DENN/MADD binds to the stalk region of KIF1A and KIF1Bβ and the MADD domain interacts with the small molecular GTPase Rab3 on the cargo membrane. DENN/MADD binds to the GTP-bound form of Rab3, a synaptic vesicle protein, while it does not bind to the guanosine-5′-diphosphate (GDP)-bound form of Rab3. Vesicles containing GTP-Rab3 can be transported down the axon, but those containing GDP-Rab3 cannot. Thus, conformational change in this small G protein because of

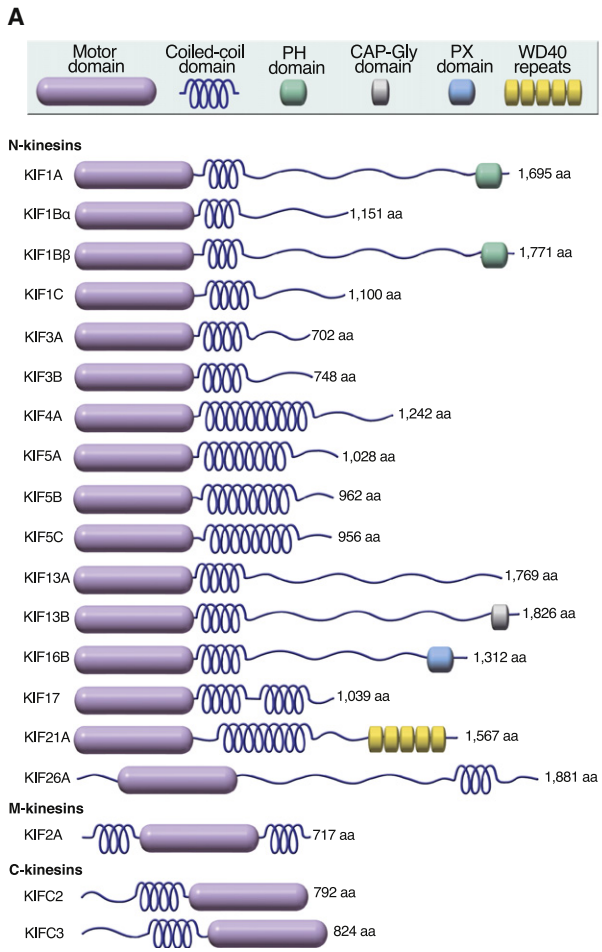

Figure 4. Diversity among KIFs
(A) Structure of KIFs.
(B) Phylogenetic tree of KIFs.

guanosine-5′-triphosphate (GTP) hydrolysis could be a mechanism for cargo unloading. In *Denn/Madd* knockout mice, the number and size of synaptic vesicles are reduced (Tanaka et al., 2001). In the *aex-3 Caenorhabditis elegans* mutant, which lacks the DENN/MADD homolog, Rab3 is mislocalized but synaptotagmin is transported normally (Mahoney et al., 2006). This suggests the existence of another protein involved in synaptotagmin transport.

Liprin-α (SYD-2 in *C. elegans*) is also suggested to function as an adaptor (Shin et al., 2003). Liprin-α regulates the motility of KIF1A (Wagner et al., 2009). KIF1A is able to move processively in the monomeric state (Okada and Hirokawa, 1999; Hirokawa et al., 2009c). However, the formation of clusters of monomers enhances its motility (Okada et al., 2003). It has been suggested that binding of Liprin-α enhances the cluster formation of KIF1A and augments the motility. In *syd-2* mutants, active zone formation was severely affected but the number of synaptic vesicles was not significantly changed (Zhen and Jin, 1999). In *Kif1a*$^{-/-}$ mice and *C. elegans unc-104* mutants, the number of synaptic vesicles was reduced, but no abnormalities in the synaptic plasma membrane were observed (Hall and Hedgecock, 1991; Otsuka et al., 1991; Yonekawa et al., 1998). In contrast, not only reduced synaptic vesicles but also abnormal synaptic bouton formation was reported in *Drosophila imac* mutant flies where a homolog motor of KIF1A or KIF1Bβ is mutated (Pack-Chung et al., 2007). This suggests that multiple levels of regulation exist. Interestingly, not only anterograde axonal transport of synaptic vesicle proteins but also retrograde axonal transport is affected in *imac* mutant flies (Barkus et al., 2008). Consistent with this, it has been suggested that the anterograde and retrograde machinery support each other (Ally et al., 2009). mRNA-containing complexes are also transported anterogradely in some species by kinesin 3 family members. Although KIF1A is a neuron-specific motor, KIF1Bβ is expressed in both neurons and glia. In *Kif1b* zebrafish mutants, *Mbp* mRNA encoding myelin basic protein is mislocalized in the glia. Isoform-specific perturbation of KIF1Bβ has confirmed that KIF1Bβ is essential for proper mRNA transport in glia (Lyons et al., 2009). The precise molecular mechanisms by which KIF1Bβ recognizes this mRNA remain elusive.

KIF1Bα. KIF1Bα transports mitochondria (Nangaku et al., 1994). Interestingly, this motor is derived from the same gene as KIF1Bβ by alternative splicing of mRNA, even though their tail domains are completely distinct from each other. Kinesin binding protein (KBP) has been identified as a KIF1Bα-associated protein (Wozniak et al., 2005). Both KIF1Bα and KBP are localized to mitochondria. However, KIF1Bα is able to bind to mitochondria in the absence of KBP. KBP augments the motility of KIF1Bα in vivo and in vitro by an unknown mechanism. Knockdown of KBP causes mitochondrial aggregation (Wozniak et al., 2005). This may be due to the lowered activity of KIF1Bα in the absence of KBP.

KIF5. KIF5 (kinesin 1 family) forms a complex with kinesin light chains (KLCs) that binds to the tail domains of KIF5s (Brady, 1985; Vale et al., 1985; Hirokawa et al., 1989). Mammals have three *Kif5* genes: *Kif5a*, *Kif5b*, and *Kif5c* (Miki et al., 2001). All three KIF5 isoforms are expressed in neurons, but their expression levels vary among different cell types (Kanai et al., 2000). KIF5A, KIF5B, and KIF5C form homodimers and heterodimers. Thus, they are thought to have similar function, although one study has suggested functional differences between them (DeBoer et al., 2008). By binding to distinct adaptor proteins, KIF5 transports many different cargos, including various vesicles and mitochondria. Among them, the axonal transport of APP has been studied intensively because it may be involved in the

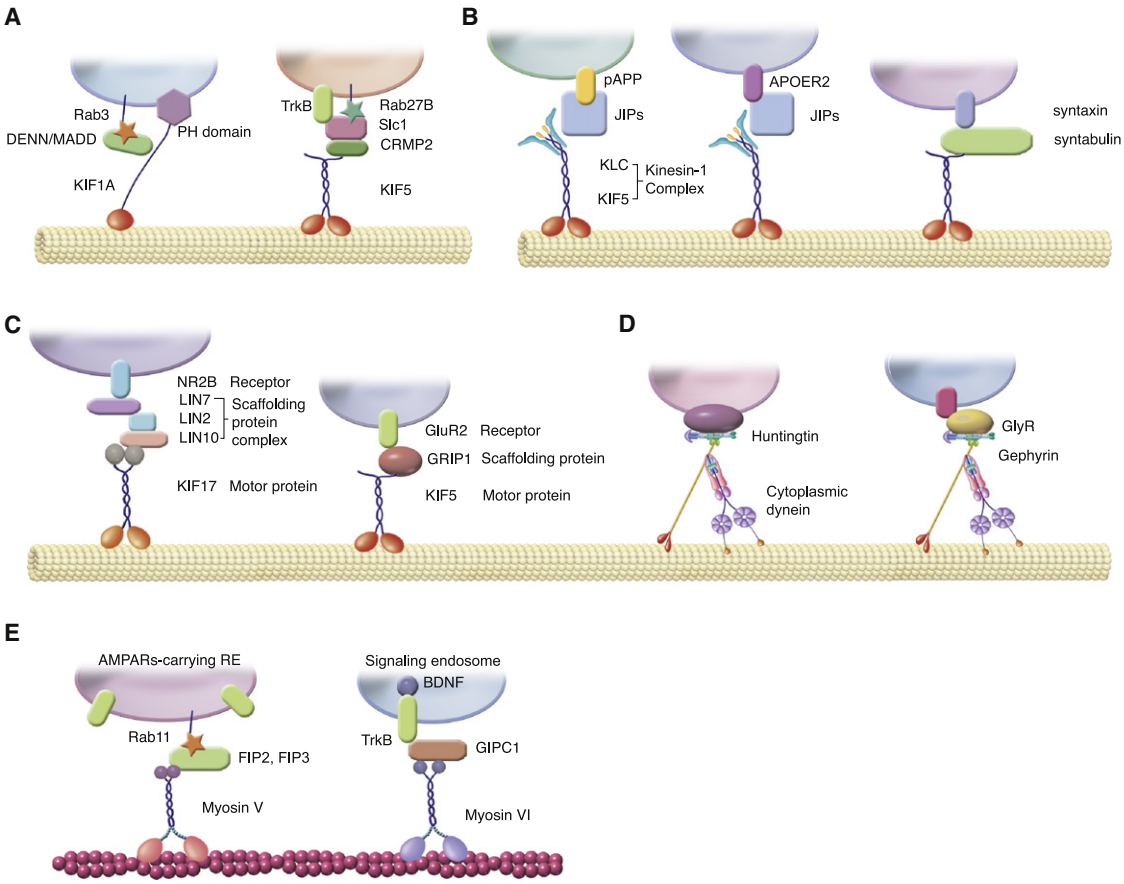

Figure 5. Cargo Recognition Mechanisms

(A) Cargo recognition via Rab GTPases. KIF1A transports Rab3-carrying synaptic vesicle precursors via its PH domain and the DENN/MADD-Rab3 complex. This dual binding ensures precise cargo recognition. KIF5 transports TrkB vesicles via the CRMP2-Slc1 complex. Rab27B and TrkB both bind to Slc1; this also ensures precise association with cargos.

(B) KIF5 transports axonal vesicles via JIPs and syntabulin. JIPs are suggested to associate with KLC and vesicular proteins such as phosphorylated APP (pAPP) and APOER2. Syntabulin directly associates with KIF5 and functions as an adaptor to recognize syntaxin vesicles.

(C) KIFs transport dendrite receptors via scaffolding proteins. KIF17 transports NMDA-type glutamate receptors NR2 by associating with a scaffolding complex consisting of LIN10 (Mint1), LIN2, and LIN7. KIF5 transports the AMPA-type glutamate receptor GluR2 via the scaffolding protein GRIP.

(D) Cargo recognition by cytoplasmic dynein. The dynactin complex binds to huntingtin and retrogradely transports vesicles. Cytoplasmic dynein transports glycine receptors (GlyR) via the scaffolding protein gephyrin; this mechanism is similar to cargo recognition by KIFs.

(E) Myosin V recognizes AMPAR-carrying recycling endosomes (REs) via the Rab11-FIPs complex. Myosin VI retrogradely transports BDNF-TrkB-signaling endosomes via GIPC1.

progression of Alzheimer disease (Bowman et al., 2000; Gunawardena and Goldstein, 2001; Kamal et al., 2001). It is well established that APP is transported by KIF5, but the role of APP in KIF5-dependent axonal transport is controversial. One model has suggested that APP binds directly to KLC and functions as an adaptor between the KIF5 motor and the cargo vesicles (Kamal et al., 2000, 2001). In this model, APP is essential for the axonal transport of tyrosine kinase receptors, β-secretase, and presenilin 1. However, one study has claimed that APP is not required for the axonal transport of tyrosine kinase receptors (Lazarov et al., 2005). This study also showed that β-secretase and presenilin 1 are not cotransported with APP. Other evidence against the model is that APP is cleaved in cell bodies (Muresan et al., 2009). For APP to function as an adaptor between KIF5 and the vesicles, APP should be intact during axonal transport. Alternatively, KIF5 is suggested to recognize APP vesicles via c-Jun NH_2-terminal kinase-interacting protein 1 (JIP1) (Muresan and Muresan, 2005). JIP1 can associate with vesicles directly, or indirectly by interacting with APOER2 or a phosphorylated form of APP (Muresan and Muresan, 2005; Verhey et al., 2001; Figure 5B). The physiological relevance of the JIP proteins will be discussed later.

Syntabulin has also been identified as an adaptor for vesicle transport mediated by KIF5 (Su et al., 2004; Cai et al., 2007; Figure 5B). Syntaxin is an active zone protein essential for exocytosis of synaptic vesicles. Syntabulin serves as an adaptor for the KIF5 motor, and syntaxin acts as a receptor of presynaptic transport cargos. The syntaxin-syntabulin-KIF5 complex is the motor-adaptor transport machinery critical for assembling presynaptic boutons in developing hippocampal neurons (Cai et al., 2007). It is known that neuronal activity enhances synaptic formation. Syntabulin is suggested to be

Table 1. Motor-Cargo Relationship in Neuronal Cells

Motor Protein	Binding Protein	Cargo or Function	References
KIFs			
KIF1A (C: Unc-104, D: Imac)	DENN/MADD (C: Aex-3)	Synaptic vesicle precursor	Okada et al., 1995b; Niwa et al., 2008
KIF1A (C: Unc-104, D: Imac)	Liprin-α (C: Syd-2)	Synaptic vesicle precursor	Wagner et al., 2009
KIF1Bα	KBP	Mitochondria	Nangaku et al., 1994; Wozniak et al., 2005
KIF1Bβ (C: Unc-104, D: Imac)	DENN/MADD (C: Aex-3)	Synaptic vesicle precursor	Zhao et al., 2001; Niwa et al., 2008
KIF1Bβ	Liprin-α(C:Syd-2)	Synaptic vesicle precursor	Wagner et al., 2009
KIF1Bβ	Not identified	mRNA	Lyons et al., 2009
KIF1C	KBP	Mitochondria?	Wozniak et al., 2005
KIF2A		Vesicles	Noda et al., 1995; Morfini et al., 1997
KIF2A		Microtubule depolymerizer	Homma et al., 2003
KIF3	Fodrin	Plasma membrane precursor	Takeda et al., 2000
KIF3	Not identified	N-cadherin	Teng et al., 2005
KIF3	Not identified	K_v channel	Gu et al., 2006
KIF4	Not identified	Membraneous organelle	Sekine et al., 1994
KIF4	PARP-1	Neuronal survival	Midorikawa et al., 2006
KIF5 (C: Unc-116, D: KHC)	Not identified	mRNA-protein complex	Ohashi et al., 2002; Kanai et al., 2004
KIF5	FMRP	mRNA-protein complex	Dictenberg et al., 2008
KIF5	JIP-1 (D: APLIP1)	Vesicles	Verhey et al., 2001; Muresan and Muresan, 2005
KIF5	JIP-2	Vesicles	Verhey et al., 2001
KIF5	JIP-3 (C: Unc-16, D: Sunday Driver)	Vesicles, mitochondria?	Bowman et al., 2000; Byrd et al., 2001
KIF5	APP	Vesicles	Kamal et al., 2000, 2001
KIF5	Syntabulin	Syntaxin vesicles	Su et al., 2004
KIF5	Syntabulin	Mitochondria	Cai et al., 2005
KIF5	Milton-Miro complex	Mitochondria	Tanaka et al., 1998; Stowers et al., 2002; Guo et al., 2005
KIF5	GRIP	AMPA receptor vesicles	Setou et al., 2002
KIF5	Slp-Rab27B	TrkB vesicles	Arimura et al., 2009
KIF5	HAP1	$GABA_AR$s	Twelvetrees et al., 2010
KIF5	Huntingtin	BDNF vesicles	Colin et al., 2008
KIF5	LIS1-NUDEL complex	DHC1	Yamada et al., 2008
KIF5	mNUDC	Dynactin complex	Yamada et al., 2010
KIF5	Myosin Va	Vesicles	Huang et al., 1999
KIF5	Hsc70	Cargos of slow transport	Terada et al., 2010
KIF13B (GAKIN)	MAGUKs (D: discs large)	MAGUK vesicles	Hanada et al., 2000; Asaba et al., 2003
KIF13B	PIP3BP	PIP3 vesicles	Horiguchi et al., 2006
KIF17	Mint	NR2B vesicles	Setou et al., 2000; Jeyifous et al., 2009
KIF26A	Grb2	Inhibition of GDNF-Ret signaling	Zhou et al., 2009
KIFC2	Not identified	Multivesicular-body-like organelle	Saito et al., 1997
Dyneins			
DHC1	LIS1-NUDEL	Neuronal migration	Sasaki et al., 2000; Niethammer et al., 2000
DHC1	HAP1	BDNF vesicles	Colin et al., 2008
DHC1	Gephyrin	Glycine receptor	Fuhrmann et al., 2002
DHC1		Rab5 endosome	Satoh et al., 2008; Zheng et al., 2008
DHC1	RILP-Rab7	NGF-TrkA signaling endosome	Saxena et al., 2005

Table 1. *Continued*

Motor Protein	Binding Protein	Cargo or Function	References
DHC1	RILP-Rab7?	p75, TrkB	Deinhardt et al., 2006
DHC1	Neurotrophin receptors	Neurotrophin receptors	Yano et al., 2001
DHC1	Bassoon	Active-zone-protein vesicles	Fejtova et al., 2009
Myosins			
Myosin Vb	FIP-Rab11	AMPA receptor (GluRl) vesicles	Lisé et al., 2006
Myosin Va	Not identified	Axonal vesicles	Bridgman, 1999
Myosin Va	Not identified	Secoretory granules	Desnos et al., 2007
Myosin Va	FIP-Rab11	AMPA receptor vesicles	Correia et al., 2008
Myosin Va	NF-L	Neurofilament	Rao et al., 2002; Alami et al., 2009
Myosin Va	Not identified	mRNA-protein complex	Ohashi et al., 2002; Yoshimura et al., 2006
Myosin VI	GIPC1	BDNF-TrkB signaling endosome	Yano et al., 2006
Myosin VI	AP2-SAP97	AMPA receptor vesicles	Osterweil et al., 2005
Myosin X	Neogenin, DCC	Netrin receptors	Zhu et al., 2007
Myosin X	Not identified	Intrafilopodial vesicles?	Sousa et al., 2006

The following abbreviations are used: C, C. elegans; D, D. melanogaster.

essential for the activity-dependent formation of the active zone.

KIF5 also transports TrkB vesicles via CRMP2-Slc1 complex. Rab27B and TrkB both bind to Slc1. Loading and unloading of cargo are regulated by Rab27 and GSK-3β (Arimura et al., 2009).

In addition to KIF1Bα, KIF5 is involved in mitochondrial transport (Tanaka et al., 1998; Kanai et al., 2000). The Milton-Miro complex was identified as an adaptor between KIF5 and the mitochondria (Stowers et al., 2002; Fransson et al., 2003; Guo et al., 2005). The complex is an attractive candidate for the regulation of mitochondrial transport because Miro has two EF hand motifs, which are controlled in a Ca^{2+}-dependent manner. Besides, it has long been known that the localization of mitochondria is controlled by Ca^{2+} signaling (Hollenbeck and Saxton, 2005). Mitochondria are recruited in Ca^{2+}-rich regions in cells. Two mechanisms have been suggested for how the Milton-Miro complex regulates mitochondrial transport. One model has suggested that Ca^{2+} binding to the Miro EF hand turns off KIF5 engagement with microtubules (Wang and Schwarz, 2009; Figure 6C). This binding prevents KIF5 from binding to microtubules. As a result, mitochondria are recruited where Ca^{2+} influx is high. Although this paper suggested that KIF5 binds constitutively to mitochondria even in high Ca^{2+} concentrations, another model has suggested that Ca^{2+} binding to the Miro EF hand detaches KIF5 from mitochondria (MacAskill et al., 2009; Figure 6D). This also resulted in recruitment of mitochondria in elevated Ca^{2+} regions. However, it has not been clarified what conformational changes are required for this dissociation.

KIF5 is responsible for the transport of retrograde motor proteins. Because cytoplasmic dynein (Dync1h1) transports cargos from the axon terminals to the cell bodies, all the components of the dynein-dynactin complex need to be first transported to axon terminals (Hirokawa et al., 1990). LIS1 and NDEL1 are dynein-associated proteins that function in neuronal migration, as described later, and that are also involved in axonal transport of the dynein-dynactin complex. KIF5 directly associates with LIS1, NDEL1, and mNUDC (Yamada et al., 2008, 2010). This association is reported to be required for the anterograde axonal transport of the dynein-dynactin complex.

Not only cargo binding but also modification of the motor domain is a regulatory mechanism for KIF5-dependent axonal transport. c-Jun NH_2-terminal kinase 3 (JNK3) phosphorylates the motor domain of KIF5 and inhibits its association with microtubules (Morfini et al., 2009). Phosphorylated KIF5 cannot bind to microtubules. Interestingly, the pathogenic form of huntingtin, containing an abnormally long polyglutamine (polyQ) repeat, augments JNK3 activity and causes hyperphosphorylation of KIF5. This may be involved in the pathology of Huntington disease and other polyQ diseases.

Switching between Fast and Slow Axonal Transport. There are two kinds of axonal transport: fast transport and slow transport. In axons, vesicles move fast (50–400 mm/day) while soluble proteins move slowly (less than 8 mm/day). The transport of cytoplasmic proteins by slow transport is essential for neuronal homeostasis. KIF5 transports both fast and slow cargos (Terada et al., 2000; Xia et al., 2003; Roy et al., 2008). How can the same motor protein implement both fast and slow axonal transport? A recent study has shown that slow transport depends on the interaction between the DnaJ-like domain in a tetratricopeptide repeat (TPR) of KLC in the KIF5 motor complex and Hsc70, which forms scaffolding between the cytoplasmic proteins and the KIF5 motor complex. This domain can bind to membranous organelles and competitive perturbation of it in squid giant axons disrupted cytoplasmic protein transport and strengthened membranous organelle transport. This indicates that this domain might function as a switch between slow and fast transport involving Hsc70. Transgenic mice overexpressing a dominant negative form of this domain showed delayed slow transport, accelerated fast transport and optic axonopathy (Terada et al., 2010; Figure 6G). These findings provide a basis for the regulatory mechanism of fast and slow transport and its intriguing implication in neuronal dysfunction.

Table 2. Genetic Abnormalities of Microtubule Motors in Mammalian Nervous System

Class	Role	Gene Symbol in Mouse	Genetic Defects	Human Disease	Phenotype/ Symptoms	Implicated Roles	References
Kinesin-1	Motor	*Kif5a*	Human point mutations	Spastic paraplagia SPG10	Dying-back neuropathy showing progressive weakness and spasticity of the legs	Axonal transport	Reid et al., 2002; Xia et al., 2003
	Motor	*Kif5a*	Knockout mouse, conditional knockout mouse		Loss of large caliber axons and neurofilament accumulation in neuronal cell bodies	Axonal transport of neurofilaments	Xia et al., 2003
	Motor	*Kif5b*	Knockout mouse		Embryonic lethality with perinuclear clustering of lysosomes and mitochondria	Transport of mRNP, mitochondria, lysosomes	Tanaka et al., 1998
	Motor	*Kif5c*	Knockout mouse		Smaller brain size and loss of motor neurons	Axonal transport	Kanai et al., 2000
	Motor subunit	*Klc1*	Knockout mouse		Smaller body size with motor disabilities	Axonal transport	Rahman et al., 1999
	Cargo	*ALS2/alsin*	Human mutations, Knockout mice	Amyotrophic lateral sclerosis (ALS)	Progressive muscle weakness and paralysis by motor neuron degeneration	Activation of Rab5 for endosome dynamics	Devon et al., 2006; Hadano et al., 2006
	Cargo	*APP*	Human mutations, transgenic mouse models	Alzheimer disease	Senile dementia	Precursor of beta-amyloid protein that makes amyloid plaques	Bowman et al., 2000; Gunawardena and Goldstein, 2001; Kamal et al., 2001
	Modulator	*Huntingtin*	PolyQ stretch in human; knockout mouse	Huntington disease	Muscle discordination (chorea) and dementia	Mutant protein blocks axonal transport of BDNF	Gauthier et al., 2004
	Modulator	*Androgen receptor*	PolyQ stretch in human	Kennedy disease (X-linked spinal and bulbar muscular atrophy, SBMA)	Motor neuron degeneration and muscle atrophy	Mutant protein blocks axonal transport	Morfini et al., 2006
	Adaptor	*Jip1*	Knockout mouse; human missense mutation	Diabetes	Viable and fertile, reduced stress-induced apoptosis	Transport of JNK kinases	Whitmarsh et al., 2001
	Adaptor	*Jip2*	*Jip1*/*Jip2* Double knockout mouse		Ataxia by Purkinje cell defects	Modulation of NMDA receptor function	Kennedy et al., 2007
	Adaptor	*Jip3*	Knockout mouse, conditional knockout mouse		Newborn lethality by respiratory failure	Positive regulator of DLK signaling	Kelkar et al., 2003; Iwanaga et al., 2007

Table 2. *Continued*

Class	Role	Gene Symbol in Mouse	Genetic Defects	Human Disease	Phenotype/ Symptoms	Implicated Roles	References
	Modulator	*Hap1*	Knockout mouse, conditional knockout mouse, human polymorphism	Huntington disease	Early postnatal lethality with depressed feeding behavior; nonessential in adults	Regulation of transport direction	Dragatsis et al., 2004
Kinesin-2	Motor	*Kif3a*	Knockout mouse		Embryonic lethality with laterality defects and exencephaly	Transport of plasma membrane precursors and intraflagellar transport (IFT)	Marszalek et al., 1999a; Takeda et al., 1999
	Motor	*Kif3a*	Conditional knockout mouse		Ciliopathies	IFT	Marszalek et al., 2000; Breunig et al., 2010; Jiang and Hui, 2008; Jones et al., 2008; Jenkins et al., 2006
	Motor	*Kif3b*	Knockout mouse		Embryonic lethality with laterality defects and exencephaly	Transport of plasma membrane precursors and IFT	Nonaka et al., 1998
	Motor	*Kif3c*	Knockout mouse		Viable and fertile	Unknown	Yang et al., 2001b
	Motor subunit	*Kap3 (Kifap3)*	Conditional knockout mouse		Fetal brain tumors	Cytoplasmic transport of N-cadherin and β-catenin and IFT	Teng et al., 2005
	Motor	*Kif17*	Overexpression tg mouse		Enhanced spatial learning	Transport of NMDAR-containing vesicles	Wong et al., 2002
Kinesin-3	Motor	*Kif1a*	Knockout mouse		Perinatal lethality by neurological disorder	Transport of synaptic vesicle precursors	Yonekawa et al., 1998
	Motor	*Kif1b*	Knockout mouse, human mutation	Charcot-Marie-Tooth disease type 2A1	Perinatal lethal with respiratory failure (KO); Peripheral neuropathy (heterozygotes)	Transport of synaptic vesicle precursors (KIF1Bβ) and mitochondria (KIF1Bα)	Zhao et al., 2001; Niwa et al., 2008
	Motor	*Kif1b*	Human linkage study, zebrafish mutants	Multiple sclerosis	Altered localization of *mbp* mRNAs	Transport of mRNP in glia	Aulchenko et al., 2008; Lyons et al., 2009
	Motor	*Kif1b*	Human genomics	Cancer	Hemizygous deletion in neuroblastoma	Haploinsufficient tumor suppressor by inducing apoptosis	Munirajan et al., 2008
	Motor	*Kif1c*	Knockout mouse		Viable and fertile	n.a.	Nakajima et al., 2002
Kinesin-4	Transcriptional regulator/Motor	*Kif4a*	Knockout mouse		KO-Reduced rate of neuronal apoptosis	PARP	Midorikawa et al., 2006

(*Continued on next page*)

Table 2. *Continued*

Class	Role	Gene Symbol in Mouse	Genetic Defects	Human Disease	Phenotype/ Symptoms	Implicated Roles	References
	Motor	*Kif21a*	Human mutations, Knockout mice	CFEOM1	Atrophy of extraocular muscles	Unknown	Yamada et al., 2003
	Motor	*Kif21b*	Human linkage study	s/o Multiple sclerosis	Unknown	Dendritic transport	Marszalek et al., 1999b; IMSGC, 2010
Kinesin-7	Motor	*Kif10 (Cenp-e)*	Conditional knockout mouse		Early lethality due to chrosomosomal instability	Mitosis	Putkey et al., 2002
Kinesin-11	Signal modulator	*Kif26a*	Knockout mouse		Megacolon	Negative regulation of Grb2 function	Zhou et al., 2009
	Unknown	*Kif26b*	Knockout mouse		Kidney agenesis	Negative regulation of Myosin II function	Uchiyama et al., 2010
Kinesin-13	Microtubule depolymerizer/ Motor	*Kif2a*	Knockout mouse		Embryonic lethal w/brain defects	Microtubule depolymerizer in axon collaterals	Homma et al., 2003
Kinesin-14A	Motor	*Kifc1*	Knockout mouse		Viable and fertile	n.a.	
Kinesin-14B	Motor	*Kifc2*	Knockout mouse		Viable and fertile	n.a.	Yang et al., 2001a
	Motor	*Kifc3*	Knockout mouse		Viable and fertile	Golgi positioning	Yang et al., 2001c; Xu et al., 2002
Cytoplasmic dynein	Motor	*Dync1h1*	Knockout mouse		Lethal in early embryonic development with altered localization of organelles	Retrograde intracellular transport; mitosis	Harada et al., 1998
	Motor	*Dync1h1*	ENU-induced mouse mutants		Legs at odd angles *(Loa);* Cramping 1 *(Cra1)*	Retrograde axonal transport	Hafezparast et al., 2003
	Motor	*Dync1h2*	Human mutations, mouse mutants	Short-rib polydactyly syndrome	Brain patterning defects, laterality defects, polydactyly	Retrograde IFT	May et al., 2005; Merrill et al., 2009
	Dynactin complex component (Glued)	*Dctn1 ($p150^{Glued}$)*	Human mutation, Mutant tg mouse	Motor neuron disease, ALS	Vocal fold paralysis, facial weakness, distal limb muscle weakness and atrophy	Retrograde transport; mutant protein aggregates	Puls et al., 2003; Lai et al., 2007; Levy et al., 2006
	Dynactin complex component (Dynamitin)	*Dctn2*	Overexpression tg mouse		Late-onset, slowly progressive motor neuron degeneration like ALS	Overexpression disrupts dynein-dynactin complex	LaMonte et al., 2002
	Accessory factor	*Lis1*	Human mutation, mutant mouse	Lissencephally	Smooth cerebral surface; a paucity of gyral and sulcal development	Facilitation of anterograde transport of cytopalsmic dynein	Faulkner et al., 2000; Yamada et al., 2008

n.a. is used as an abbreviation for not applicable.

KIFs and Dendritic Transport

In dendrites, various cargos are conveyed by KIFs, including NMDA receptor vesicles by KIF17, AMPA receptor vesicles by KIF5, GABA receptor vesicles by KIF5, and mRNAs with large protein complexes by KIF5 (Figure 3 and Table 1).

KIF5. In addition to axonal cargos, several dendritic cargos are transported by KIF5. KIF5 associates with GRIP, a scaffolding protein that binds to α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs) and transports them in dendrites (Setou et al., 2002; Figure 5C). Interestingly, the binding of GRIP to AMPARs drives KIF5 into dendrites, although the KIF5 motor domain preferentially moves into axons (Nakata and Hirokawa, 2003). Another dendritic receptor species, GABA receptors, are transported by KIF5 via huntingtin-associated protein 1 (HAP1) (Twelvetrees et al., 2010).

Recent studies have suggested that local protein synthesis is important for neuronal function. KIF5 binds to mRNA-containing complexes in dendrites (Kanai et al., 2004; Ling et al., 2004; Mallardo et al., 2003; Ohashi et al., 2002). How KIF5 recognizes mRNA-containing protein complexes (mRNPs) remains largely unknown. One study has shown that KIF5 binds to a large mRNP complex comprising at least 42 proteins including Purα, Purβ, and hnRNP-U and mRNAs such as *CaMKIIα* mRNA and *Arc* mRNA (Kanai et al., 2004). Another study has presented evidence that FMRP, an RNA-binding protein disrupted in fragile X mental retardation syndrome, binds indirectly to KLC (Dictenberg et al., 2008). Stimulation of metabotropic glutamate receptors (mGluR) augments the association between FMRP and the KIF5 motor protein. Translocation of mRNA such as *CaMKIIα* mRNA and *SAPAP4* mRNA in dendrites and synaptogenesis is affected in neurons containing mutant FMRP that is similar to that in the neurons of fragile X syndrome patients. Thus, disruption of KIF5-dependent mRNA transport may be involved in the pathogenesis of fragile X syndrome.

KIF17. NMDARs are thought to play an important role in synaptic plasticity, learning, and memory. NMDARs are transported selectively to dendrites. KIF17 is a motor protein that transports NR2B (a subunit of NMDARs)-carrying vesicles (Figure 5C). Because KIF17 is dendrite-specific, it guarantees the dendritic localization of NMDARs (Setou et al., 2000; Yuen et al., 2005). KIF17 recognizes NR2B vesicles through the Mint1 (LIN10) scaffold protein complex (Jeyifous et al., 2009; Setou et al., 2000; Figure 5C).

When NR2B vesicles approach the postsynaptic region, KIF17 must release the vesicles (Figure 6A). It has been revealed that CaMKIIα, which is active near the postsynapse, phosphorylates KIF17 (Guillaud et al., 2008). CaMKIIα binds to the tail region of KIF17 and phosphorylates it at Ser1029, which dissociates Mint1 from the KIF17 tail domain and releases the cargos. This study clearly revealed that phosphorylation of KIFs is an important mechanism for cargo unloading, besides the small G protein-dependent unloading mechanism mentioned earlier for KIF1A and KIF1Bβ.

KIFC2. KIFC2 is a C-terminal motor domain KIF that is predominantly localized in the neuronal dendrites in mice (Saito et al., 1997). Uniquely, KIFC2 moves on microtubules toward their minus ends, similar to cytoplasmic dynein (Hanlon et al., 1997; Saito et al., 1997). KIFC2 has been shown to transport multivesicular body-like organelles in dendrites (Saito et al., 1997), but the cargo molecules transported by this motor protein and the physiological relevance of this transport remain to be clarified.

Dynein Superfamily Proteins and Transport in the Axon and Dendrites

Although eukaryotes express many dynein superfamily proteins, most of them are related to flagellar motility and intraflagellar transport (Tanaka et al., 1995; Rosenbaum and Witman, 2002; Kamiya, 2002). Only cytoplasmic dynein heavy chain 1 (Dync1h1) is involved in retrograde transport in the axon and the dendritic shafts. Cytoplasmic dynein moves toward the minus ends of microtubules. Therefore, it conveys cargos retrogradely in the axon and distal dendrites, while in the proximal dendrites it conveys cargos to both the periphery and the cell center because of the mixed polarity of the microtubules. Cytoplasmic dynein transports TrkA and TrkB vesicles (Deinhardt et al., 2006; Ha et al., 2008; Saxena et al., 2005), brain-derived neurotrophic factor (BDNF) vesicles (Gauthier et al., 2004; Colin et al., 2008), the piccolo/bassoon complex (Fejtova et al., 2009), mitochondria (Hollenbeck and Saxton, 2005), and myosin V (Huang et al., 1999) retrogradely in the axon, while in the dendrites the cargos carried by cytoplasmic dynein include glycine receptor vesicles (Fuhrmann et al., 2002; Maas et al., 2006), the LSm-1/mRNPs/CBP80/(pre)mRNA complex (di Penta et al., 2009), and Rab5 and Rab7 endosomes (Satoh et al., 2008; Johansson et al., 2007; Figure 3).

How does only one isoform of the dynein motor differentially transport multiple cargos? There are two ways to accomplish this goal. (1) Cytoplasmic dynein 1 consists of a heavy chain, intermediate chains, light intermediate chains, and light chains (Karki and Holzbaur, 1999; Pfister et al., 2006). Because the isoforms of each component have diverged to associate with specific cargo molecules, one cytoplasmic dynein can transport multiple different cargos. For example, dynein intermediate chain 1 (DIC1; Dync1i1), but not DIC2 (Dync1i2), is involved in the transport of TrkB-carrying vesicles (Ha et al., 2008). Dynein LC8 light chain 1 (DLC1; Dynll1) and DLC2 (Dynll2) are directly associated with bassoon, an active zone protein (Fejtova et al., 2009). This association is required for the retrograde transport of active zone proteins and is thought to be involved in synaptic plasticity. Gephyrin, a dendritic scaffolding protein, is a direct binding protein of DLC1 and DLC2 (Fuhrmann et al., 2002; Figure 5D). Similar to GRIP and Mint1 in the KIF-dependent dendritic transport described above, gephyrin functions as an adaptor between the glycine receptor and dynein and is essential for internalization of the glycine receptor (Maas et al., 2006; Figure 5D). A structural study revealed difference between respective cargo binding surfaces of two similar Tctex1 light chains that may result in selective binding of rhodopsin to Tctex1 (Dynlt1) but not to rp3 (Dynlt3) light chains (Wu et al., 2005). (2) Furthermore, cytoplasmic dynein recruits its associated proteins, $p150^{Glued}$ and dynamitin (dynactin complex), to transport cargos (Karki and Holzbaur, 1999; Schroer, 2004). While $p150^{Glued}$ binds to huntingtin-associated protein 1 (HAP1) (Engelender et al., 1997; Colin et al., 2008; Li et al., 1998), huntingtin also binds directly to dynein (Caviston et al., 2007). Interestingly, HAP1 is essential for the bidirectional transport of BDNF

Table 3. Known Genetic Abnormalities of Nonmuscle Myosins

Class	Gene Symbol in Mouse	Genetic Defects	Human Disease	Phenotype/ Symptoms	Implicated Roles	References
Myosin I	*Myo1a*	Human mutations	Autosomal dominant deafness	Sensorineural bilateral hearing loss	Molecular force sensor	Donaudy et al., 2004; Laakso et al., 2008
	Myo1c	Tg mouse of an inhibitor-sensitized mutant		Block of adaptation of hair cells in the inner ear	Stereocilia adaptation; GLUT4 traffic	Holt et al., 2002
Non-muscle Myosin II	*Myh9*	Human mutation, mouse knockout	May-Hegglin anomaly, Fechtner syndrome, Sebastian syndrome	Giant-platelet disorders; deafness; embryonic lethality (KO mice)	Actin network disassembly in crawling cells	Seri et al., 2000; Wilson et al., 2010
	Myh10	Mouse knockout		Fewer and larger myocytes	Growth cone turning and protruding motility of spines; cytokinesis	Takeda et al., 2003
Myosin III	*Myo3a*	Human mutations	Autosomal recessive deafness	Hearing loss	Unknown	Walsh et al., 2002
Myosin V	*Myo5a*	Human mutation, mutant mouse (*dilute lethal*)	Griscelli syndrome; Neuroectodermal melanolysosomal disease	Hypopigmentation and neurological problems	Short distance transport of vesicles	Mercer et al., 1991; Pastural et al., 1997
	Myo5b	Human mutations	Microvillus inclusion disease	Life-threatening watery diarrhea	Recycling endosome motility; AMPAR traffic	Wang et al., 2008
Myosin VI	*Myo6*	Human mutations, mutant mouse (*Snell's waltzer*)	DFNB37	Inherited deafness	Minus-end-directed trafficking for endocytic trafficking; Internalization of TrkB and AMPAR	Avraham et al., 1995; Ahmed et al., 2003; Osterweil et al., 2005; Yano et al., 2006
Myosin VII	*Myo7a*	Human mutation, mutant mouse (*shaker-1*)	Usher syndrome type IB; unsyndromic deafness	Balance problems and deafness; retinopathy (human)	Microtubule organization for morphogenesis of the inner ear sensory cell stereocilia	Gibson et al., 1995; Weil et al., 1995
Myosin IX	*Myo9b*	Human gene variation as a risk factor	Association to celiac disease	Hypersensitivity to gluten	Minus-end-directed motility; actin-based processes in myeloid cells	Wirth et al., 1996
Myosin XIV	*Myh14*	Human mutations	Autosomal dominant deafness	Hearing loss	Unknown	Donaudy et al., 2004
Myosin XV	*Myo15a*	Human mutation, mutant mouse (*shaker-2*)	Autosomal recessive deafness	Deafness with vestibular defects	Targeting of whirlin to the tips of stereocilia	Wang et al., 1998; Belyantseva et al., 2005
Myosin XVIII	*Myo18b*	Human loss of heterozygosity	LOH in lung cancer	Tumor progression	Tumor suppressor	Nishioka et al., 2002

vesicles. Consistent with this, the huntingtin-HAP1 complex associates with the plus end-directed motor KIF5 (Colin et al., 2008). This issue will be discussed later.

Cytoplasmic dynein is associated with endosomes and regulates protein degradation and signal transduction in general. RILP and ORP1L have been identified as dynactin complex-binding proteins (Johansson et al., 2007; Jordens et al., 2001). Both proteins preferentially bind to the GTP-bound form of Rab7 and control the localization of lysosomes (Figure 6E). When neurotrophin binds to its receptors at axon terminals, the neurotrophin receptor complex is endocytosed to form signaling endosomes. Rab7 is involved in the retrograde axonal transport of this signaling endosome (Saxena et al., 2005), conveying the signal to the cell body.

Another dynein cargo, the Rab5-carrying endosome, is involved in dendrite morphogenesis in *Drosophila*. In the *dandelion clock* (*dlic*) *Drosophila* mutant, dendritic branching is increased in the proximal regions and significantly decreased in the distal regions (Satoh et al., 2008). Genetic analysis revealed that the dynein light intermediate chain is mutated in *dlic* flies. Another genetic study demonstrated the involvement of dynein light intermediate chain 2 (*dlic2*) and dynein

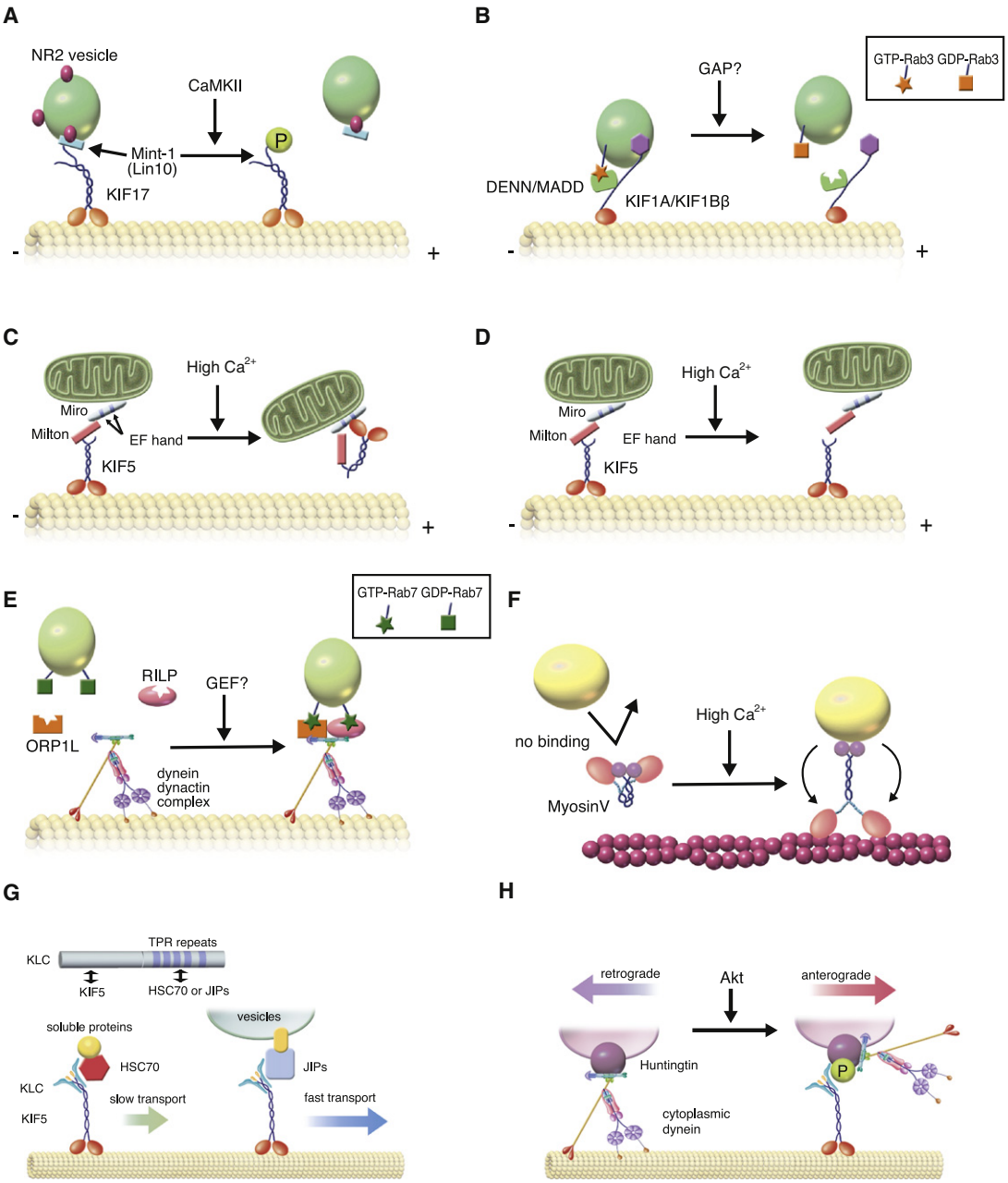

Figure 6. Regulation and Switching of Cargo Transport

(A) KIF17 releases NR2 vesicles when phosphorylated by CaMKII, the activity of which is high around postsynapses.

(B) KIF1A or KIF1Bβ recognizes GTP-Rab3 via DENN/MADD and transports Rab3-carrying synaptic vesicle precursors. Rab3 then cycles to the GDP-bound form, probably through the action of Rab3 GAP at axon terminals, and is released from the motor.

(C) A model showing that high Ca^{2+} modifies the EF hand motifs of Miro and inhibits the motor activity. In this model, KIF5 is constitutively localized on mitochondria.

(D) A model showing that mitochondria are released from KIF5 by Ca^{2+}.

(E) A Rab7 GEF converts Rab7 to its GTP-bound state. GTP-bound Rab7 binds to the dynactin complex via two Rab7 effector proteins, RILP and ORP1L.

(F) Upon stimulation by Ca^{2+}, the tail inhibition of myosin V is released. The activated myosin V is able to bind to cargo vesicles.

(G) HSC70 and JIPs competitively associate with the TRP repeats of KLC. Slow transport cargos are recognized via HSC70, whereas fast axonal cargos are recognized via JIPs.

(H) Both cytoplasmic dynein and KIF5 associate with BDNF vesicles via huntingtin. Dynein retrogradely transports BDNF vesicles. Upon phosphorylation by AKT, KIF5 associates with the phosphorylated form of huntingtin and mediates anterograde transport.

intermediate chain (*dic*) in this process and in uniform microtubule orientation in axons (Zheng et al., 2008). It has not been clarified whether this mechanism is evolutionarily conserved in mammals.

Myosin Superfamily Proteins and Transport in the Synaptic Regions

Actin filaments are enriched beneath the plasma membrane, especially at the pre- and postsynaptic regions in neurons (Figures 1D–1F). Among the myosin superfamily proteins, myosin Va, myosin Vb, and myosin VI are primarily involved in transport in the synaptic regions. Myosin I and myosin VII function in the morphogenesis of the stereocilia in sensory hair cells in the inner ear, while myosin II plays important roles in migrating neurons and growth cones (Vallee et al., 2009). Myosin II is also involved in dynamic organization of actin bundles in the postsynaptic spines and is related to synaptic plasticity through control of spine shape (Ryu et al., 2006).

Myosin II. Myosin II is a founding member of myosin superfamily and mainly works for contraction of actin networks in muscle and nonmuscle cells. In this regards myosin II plays important roles in migrating neurons and their growth cones (Vallee et al., 2009). Myosin II and F-actin dynamics drive the coordinated movement of the centrosome and soma during CNS glial-guided neuronal migration (Solecki et al., 2009). Myosin II is detected in the postsynaptic dendrites of mature brain (Miyazaki et al., 2000; Cheng et al., 2006) and modulating the development of dendritic spines (Ryu et al., 2006). A recent study showed that myosin II is necessary for the emergence of specialized actin structures that stabilize an early phase of long-term potentiation (LTP) and suggested that myosin II regulates plasticity by imparting mechanical forces onto the spine actin cytoskeleton in response to synaptic stimulation (Rex et al., 2010).

In addition, myosin II is localized in the presynaptic terminals and is involved in transmitter release by facilitating delivery of synaptic vesicles to active zones or their subsequent exocytosis (Mochida et al., 1994; Polo-Parada et al., 2005).

Myosin V. Myosin Va is localized to the postsynaptic density and vesicle fractions in the brain. Mutations in myosin Va are associated with Griscelli syndrome, which is characterized by severe neurological symptoms such as seizures and mental retardation (Pastural et al., 1997). *Myo5a*$^{-/-}$ mice, called *dilute lethal*, also exhibit severe neuronal phenotypes (Mercer et al., 1991). It has been suggested that myosin Va is involved in neuronal function and cognition. Indeed, several studies have shown that myosin Va is required for transport in axons and dendrites. In axons, myosin Va transports endoplasmic reticulum vesicles (Tabb et al., 1998). Axonal transport of vesicles over long distances is generally dependent on microtubule motors. Because myosin Va is directly associated with KIF5, it may function in microtubule-dependent transport (Bridgman, 1999; Huang et al., 1999). It may also function in short-distance transport in the presynaptic terminal after the cargos are unloaded from the microtubule-KIF system (Figures 3 and 5D).

Myosin Va is associated with mRNP complexes (Ohashi et al., 2002). In hippocampal neurons, overexpression of the cargo-binding domain of myosin Va dominant-negatively inhibited the transport of mRNP complexes into dendritic spines (Yoshimura et al., 2006).

For some KIFs and myosins, it has been established that the tail domain is able to associate with the motor domain within the same molecule and inhibit the motor activity (Hackney and Stock, 2000; Li et al., 2008). Thus, the motor protein is inactivated when cargos are not bound to it. This mechanism is called tail inhibition. Tail inhibition of myosin V is regulated by Ca^{2+} (Krementsov et al., 2004; Figure 6F). Because calcium flux is high in spines during long-term potentiation (LTP), myosin Va is activated by LTP in hippocampal neurons (Correia et al., 2008). Activated myosin Va transports GluR1, one of the AMPARs in spines. In contrast, one study showed that synaptic function and plasticity at CA3-CA1 hippocampal synapses are preserved in the *dilute lethal* mice (Schnell and Nicoll, 2001). Other myosins may have redundant functions. Myosin Vb, which is highly homologous to myosin Va, transports AMPAR-carrying recycling endosomes (Lisé et al., 2006). LTP-dependent Ca^{2+} influx also activates myosin Vb (Wang et al., 2008). Activated myosin Vb triggers local exocytosis from recycling endosomes carrying AMPARs in dendritic spines. This exocytosis augments the levels of surface AMPARs and the sizes of the spines, leading to LTP.

Myosin VI. Myosin VI is a unique myosin superfamily protein as only this family member moves toward the minus end of actin filaments (Wells et al., 1999). In *Myo6*$^{-/-}$ mice, known as *Snell's waltzer*, there are significantly fewer synapses and the dendritic spines of hippocampal neurons are shorter (Avraham et al., 1995). Because myosin VI is a retrograde motor, it may be involved in internalization and retrograde transport of cargos. Myosin VI forms a complex with AP2 and SAP97 and regulates the stimulation-dependent internalization of AMPARs (Osterweil et al., 2005). Furthermore, myosin VI is required for the internalization of TrkB associated with BDNF, essential for the BDNF-TrkB signaling-dependent facilitation of LTP (Yano et al., 2006; Figure 5E). GIPC1 is a linker between myosin VI and TrkB. To transport BDNF-TrkB endosomes, myosin VI needs to bind to the GIPC1 adaptor protein (Figure 5E).

Myosin X. Myosin X is reported to be a molecular motor involved in intrafilopodial transport (Berg and Cheney, 2002) and mainly works during neuronal development (Figure 3). In neurons, filopodia extend from the growth cones and are required for axon elongation. Myosin X vesicle movement has been observed in growth cone filopodia (Sousa et al., 2006). Netrin receptors, essential for axon guidance, have been identified as cargos of myosin X (Zhu et al., 2007).

Regulation of the Direction of Transport toward the Axon versus the Dendrites

Neuronal polarity is fundamental for brain wiring. KIFs are involved in the generation of this neuronal polarity. Interestingly, the KIF5 motor domain preferentially localizes to axonal tips rather than dendrites (Nakata and Hirokawa, 2003). The KIF5 motor domain specifically recognizes axonal microtubules, which somehow relates to microtubule dynamics. When neurons are treated with a low concentration of paclitaxel, axonal microtubules lose these characteristics, and the KIF5 motor domain localizes in both the axon and the dendrites (Nakata and Hirokawa, 2003). Consistent with this finding, the KIF5 motor domain accumulated in nascent axons during neuronal maturation (Jacobson et al., 2006). What molecular structure does the

KIF5 motor domain recognize? Several posttranslational modifications of tubulin are suggested to augment the affinity of KIF5 for microtubules. For example, KIF5 preferentially associates with acetylated tubulin in Cos-7 cells (Reed et al., 2006). Another study suggests that tubulin tyrosination steers KIF5 to axons (Konishi and Setou, 2009). However, a previous study has shown that the distribution of neither acetylated nor tyrosinated tubulins is biased toward axons (Dotti and Banker, 1991). Consistent with this, recent papers have shown that known tubulin modifications are not critical for the KIF5 motor domain to selectively localize to axons (Hammond et al., 2010; Muresan et al., 2009; Verhey and Hammond, 2009). It thus remains an interesting question how the KIF5 motor domain discriminates axons from dendrites. The minus end-directed motor dynein is involved in cell-body-to-dendrite sorting of cargos (Kapitein et al., 2010). The mixed polarity of microtubules in dendrites is suggested to guide dynein into dendrites. The dendrite-specific KIF17 also sorts cargos into dendrites (Setou et al., 2000).

From another point of view, it has been proposed that in cell-body-to-axon sorting, the initial segment of the axon has an ankyrin G- and F-actin-containing filter that functions as a diffusion barrier (Song et al., 2009). This selective axon initial segment-filtering has been proposed to contribute to preferential trafficking and segregation of cellular components in polarized neurons (Song et al., 2009).

KIF13B (GAKIN) was identified also as a KIF that mediates transport of the protein discs large (Nakagawa et al., 1997; Asaba et al., 2003; Hanada et al., 2000). KIF13B was reported recently to be involved in neuronal polarization. During axonal specification, PIP_3 accumulates at one neurite tip. PIP_3 recruits Akt and specifies one neurite to become an axon. KIF13B directly binds to PIP_3-binding protein and transports PIP_3-carrying vesicles (Horiguchi et al., 2006). Par1b is a kinase that is required for generation of polarity. Par1b-dependent phosphorylation of KIF13B is reported to inhibit the function of KIF13B (Yoshimura et al., 2010). The in vivo function of KIF13B remains to be clarified.

Finally, suppression of retrograde transport in axons could also be involved in polarized transport of presynaptic components in axons (Ou et al., 2010). In *C. elegans* mutants of cyclin-dependent kinase genes, retrograde traffic of synaptic vesicle precursors in axons is augmented and their dendritic missorting occurs. However, molecular details of the possible phosphorylation-mediated regulation of cytoplasmic dynein are opened to future studies.

Physiological Relevance of Intracellular Transport: Genetic Models, Mutations, and Human Diseases

Recent advances in molecular genetics in mice and humans have revealed that molecular motor-mediated axonal transport is relevant to neurogenesis and various neurological disorders. As we have seen in this review, molecular motors transport housekeeping molecules and signaling molecules and sometimes even have nonmotor functions in the regulation of signal transduction cascades. The delivery of healthy mitochondria, trophic factor receptors and neurotransmitters, cytoskeletal proteins, membrane lipids, and mRNP complexes to the nerve terminals is indispensable for proper neuronal function. In addition, molecular motors can participate in signaling themselves: by transporting signaling molecules or their associated factors from one location to another within a neuron they can modulate cellular behaviors such as fate decisions toward survival or apoptosis. In this way, molecular motors can be regarded as a new type of modifier of signal transduction molecules, not by changing their posttranslational modifications but merely by changing their locations. In the next section, we explore the genetic evidence for the physiological relevance of molecular motors in development, neuronal function, and disease (Tables 2 and 3).

Genetic Models Relevant to the Role of Molecular Motors in Axonal and Dendritic Transport

Molecular motors are essential for synapse generation and maintaining synaptic transmission. The importance of molecular motors at synapses has been revealed by both reverse and forward genetic studies in animal models and in human pedigrees carrying inherited diseases.

KIF1A and KIF1Bβ. A major role of the KIF1A and KIF1Bβ kinesin 3 motors is to transport synaptic vesicle precursors (Niwa et al., 2008; Okada et al., 1995b; Zhao et al., 2001). These two motors share high similarity and both bind to DENN/MADD, which is a new effector of Rab3 GTPase that tethers the motor to the synaptic vesicle precursor membrane only when it is in a GTP-bound form (Niwa et al., 2008). Knockout mice for the *Kif1a* or *Kif1b* genes are similarly lethal during the perinatal period, because of severe neurological disorders (Yonekawa et al., 1998; Zhao et al., 2001; Figure 7A). *Kif1b* knockout pups do not start breathing because of defects in the respiratory centers in the brain stem (Zhao et al., 2001). The number and density of synaptic vesicles were decreased in the presynaptic area (Figure 7A). In addition to defects in synaptic vesicle transport, $Kif1a^{-/-}$ mice and $Kif1b^{-/-}$ mice exhibited neuronal cell death (Yonekawa et al., 1998; Zhao et al., 2001). This phenotype is also observed in the zebrafish *Kif1b* mutant (Lyons et al., 2009). Generally, synaptic vesicle defects are not considered to be involved in neuronal survival. The axonal transport machineries underlying synaptic formation and neuronal survival may be different in vertebrates, flies and worms. It is also possible that KIF1A and KIF1Bβ can transport other cargos besides synaptic vesicle precursors. This will be the subject of future research.

Haploinsufficiency in the *Kif1b* gene revealed a late-onset neuropathy. One-year-old animals exhibited significant deficits in behavioral tests including the rotarod (Figure 7B) and showed a staggering gait (Figure 7C). Although the amplitude of the muscular potential was decreased, motor nerve conduction velocity was preserved. Because this excludes the presence of major demyelination phenotype, the failure was considered to be mainly of an axonal origin. The identification of a functional mutation in the motor domain in a family with Charcot-Marie-Tooth disease Type 2A1 (CMT2A1) neuropathy suggested that KIF1B is involved in normal neuronal function in humans (Zhao et al., 2001).

Human and zebrafish studies have suggested an additional role for KIF1B in myelination. A Thr-to-Pro mutation of the *Kif1b* gene was identified in a zebrafish mutant called *st43* that showed altered localization of *mbp* mRNAs in the myelinating oligodendrocyte process, which was reproduced by a KIF1Bβ-specific antisense morpholino injection and chimera analyses (Lyons et al., 2009). Accordingly, the authors

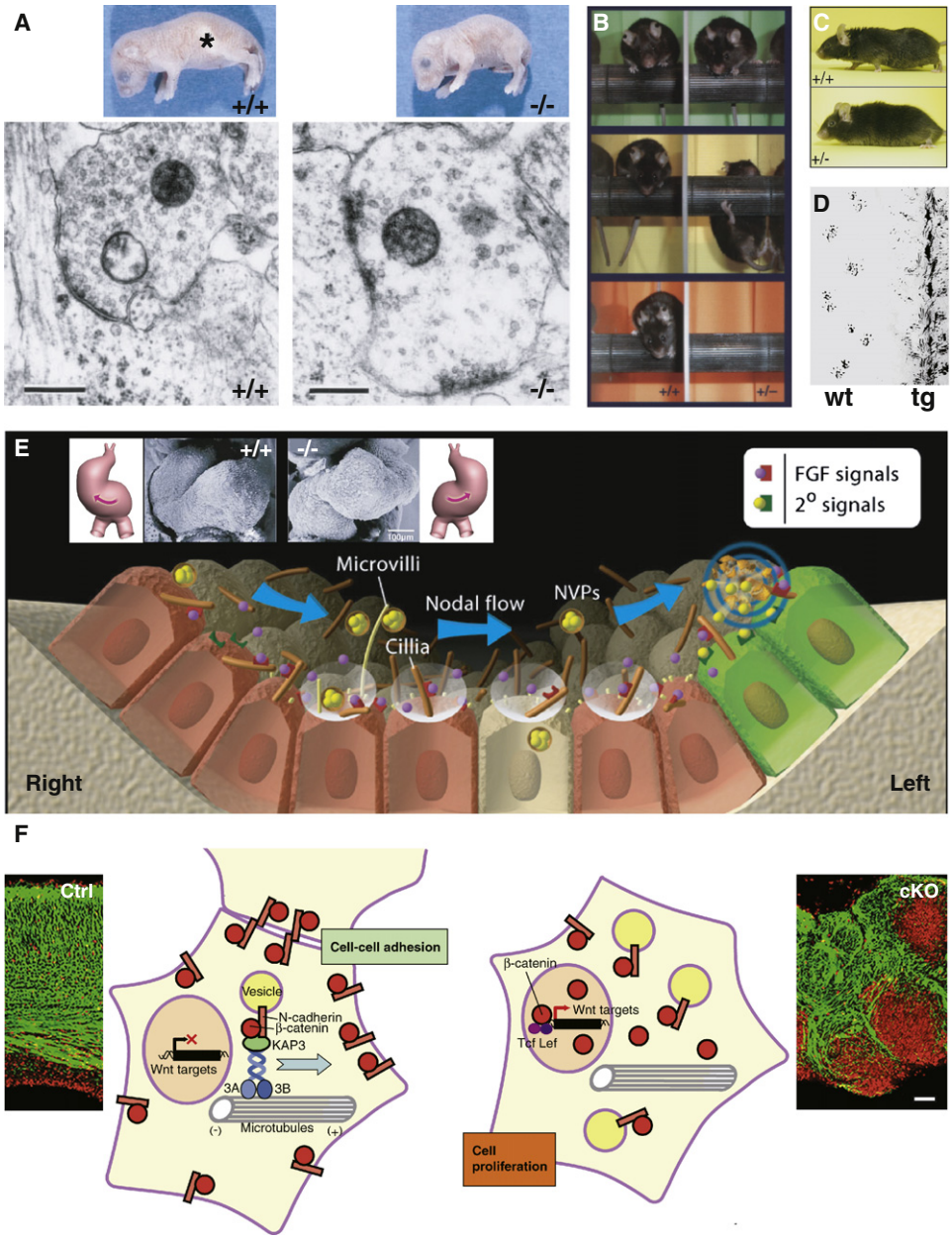

Figure 7. Genetic Models of Molecular Motors in Axonal and Dendritic Transport

(A) General appearance (upper) and synapse ultrastructure (lower) of *Kif1a*$^{+/+}$ and *Kif1a*$^{-/-}$ mice. Note that the knockout mice die without suckling (asterisk). Reproduced with permission from Yonekawa et al. (1998).

(B and C) Rotarod test (B) and general appearance (C) of *Kif1b*$^{+/+}$ and *Kif1b*$^{+/-}$ mice. Haploinsufficiency of this motor results in peripheral neuropathy. Reproduced with permission from the cover of Cell, *105(5)* and Zhao et al. (2001), respectively.

(D) Decreased stride length and gait abnormalities in dynamitin-overexpressing mice compared with wild-types. Reproduced with permission from LaMonte et al. (2002).

(E) Mechanism of left-right determination. As a result of ciliary rotation, there is a leftward flow of the extraembryonic fluids on the ventral surface of the node, a primordial structure of the notochord in midgestation. Fibroblast growth factor signaling facilitates secretion of extracellular particles called nodal vesicular particles (NVPs). These particles are transported toward the left side and may evoke Ca^{2+} signaling specifically on that side. (Insets) The randomization of heart looping that is observed in *Kif3b*$^{-/-}$ mice that lack nodal cilia. Reproduced with permission from Hirokawa et al. (2006) and Hirokawa et al. (2009a).

(F) The KIF3 motor as a tumor suppressor. According to the KIF3 motor, N-cadherin and β-catenin are transported toward the plasma membrane to facilitate cell-cell adhesion and negatively regulate Wnt signaling. Disruption of this function by conditional knockout (cKO; the right-hand side) of the *Kap3* gene resulted in brain tumor formation. Green, neurons; red, neural progenitors. Reproduced with permission from Teng et al. (2005).

suggested that KIF1Bβ is required for axonal outgrowth autonomously in neurons and for *mbp* mRNA localization autonomously in glia. In humans, a genome-wide association study identified the rs10492972[C] single nucleotide polymorphism (SNP) variant in the *KIF1B* gene as a new locus associated with multiple sclerosis with a high probability ($p = 2.5 \times 10^{-10}$) (Aulchenko et al., 2008). However, this remains controversial because the above mentioned mouse knockouts did not reveal an apparent demyelination phenotype and because another study by the International Multiple Sclerosis Genetics Consortium (IMSGC) did not replicate this association (Booth et al., 2010). Instead, in another genome-wide association study, the Consortium claimed an association of multiple sclerosis with the *KIF21B* locus, which encodes a kinesin 4 family motor (IMSGC, 2010). Polymorphisms in *KIF1B* have also been identified in cancers, suggesting that this gene can function as a tumor suppressor (Munirajan et al., 2008; Schlisio et al., 2008; Yeh et al., 2008). Because multiple sclerosis and cancer involve multiple cell-nonautonomous steps, including the immune system, further study of the roles of KIFs in their pathogenesis using genetic animal models is required.

KIF17. The kinesin 2 motor KIF17 transports vesicles containing NMDARs to dendrites (Setou et al., 2000). Transgenic mice overexpressing KIF17 demonstrated greatly enhanced spatial and working memory (Wong et al., 2002). Interestingly, the phosphorylation level of the transcription factor CREB and the transcription and translation of NR2B were significantly upregulated by KIF17 overexpression. This suggests that KIF17-mediated dendritic transport facilitates a positive feedback loop of NR2B signals in a subset of neurons specifically involved in learning and memory.

Cytoplasmic Dynein. Cytoplasmic dynein is a major motor for retrograde axonal transport that varies its function by associating with different subsets of subunits (Susalka and Pfister, 2000). The simple knockout mice for the cytoplasmic dynein heavy chain 1 gene (*Dync1h1*) are embryonic lethal with cytoplasmic dispersion of the Golgi and endosome-lysosome system (Harada et al., 1998). The dynein/dynactin complex is associated with Golgi membranes by βIII-spectrin (Holleran et al., 2001; Muresan et al., 2001) or ZW10 (Vallee et al., 2006). It binds to late-endosome and lysosome membranes via the Rab7 effector protein RILP (Cantalupo et al., 2001). In addition, activated Rab6 recruits dynein to post-Golgi vesicles via bicaudal-D proteins (Matanis et al., 2002). Allelic point mutations of the cytoplasmic dynein heavy chain 1 were identified in the *Loa* and *Cra1* mouse strains, causing late-onset motor neuron degeneration in heterozygotes and neuronal apoptosis in homozygotes (Hafezparast et al., 2003). In addition, disruption of the dynein-dynactin complex by overexpressing dynamitin in transgenic mice caused late-onset motor neuron degeneration similar to human amyotrophic lateral sclerosis (ALS), causing phenotypes such as a staggering gait (LaMonte et al., 2002; Figure 7D). One possible mechanism for this neurodegeneration is impaired retrograde transport of activated neurotrophin receptors by direct association of the dynein light chain Tctex1 (Dynlt1) with Trk neurotrophin receptors (Heerssen et al., 2004; Yano et al., 2001). Dynein also plays a role in the transport of nerve injury signals, phosphorylated Erk (Perlson et al., 2005), and phosphorylated JNK (Cavalli et al., 2005) and in the clearance of misfolded proteins by autophagy (Ravikumar et al., 2005). Impairment of these functions would also contribute to a worsening neurological status. Unexpectedly, *Loa* mutation rescues the phenotype of another ALS mouse model, superoxide dismutase 1 (SOD1) transgenic mice (Kieran et al., 2005). This was partially explained by a proteomics study revealing that the SOD1 mutation augments retrograde transport of stress factors (P-JNK, caspase-8, $p75^{NTR}$ cleavage fragment) and simultaneously impairs retrograde transport of survival factors (P-Trk and P-Erk1/2) (Perlson et al., 2009).

Cytoplasmic dynein is also directly involved in brain development. Lissencephaly is a rare human brain malformation that results in the absence of brain folds and grooves. The responsible gene, *LIS1*, is required for correct cell migration, cell division, and nuclear positioning mediated by dynein (Reiner et al., 1993; Faulkner et al., 2000). NDEL1 has been identified as a LIS1- and cytoplasmic dynein-binding protein using a yeast two-hybrid assay (Niethammer et al., 2000; Sasaki et al., 2000). When cytoplasmic dynein binds to the LIS1-NDEL1 complex, cytoplasmic dynein functions as a motor for neuronal migration during brain development (Sasaki et al., 2005). Cdk5/p35, a kinase complex required for neuronal migration, phosphorylates NDEL1 and regulates neuronal migration. Loss of LIS1 or NDEL1 impairs the positioning of the nuclei of migrating neurons (Shu et al., 2004), consistent with the symptoms of lissencephaly (Lam et al., 2010; Liang et al., 2004; Sasaki et al., 2000; Shu et al., 2004; Yamada et al., 2008).

Regulation of Axonal Transport by Kinesin 1, Its Binding Proteins, and Associated Diseases

The kinesin 1 motors KIF5A, B, and C have multiple roles in neurons. In particular, primary or secondary axonal transport defects can result in neuronal degeneration in several neurological diseases (Chevalier-Larsen and Holzbaur, 2006; De Vos et al., 2008; Roy et al., 2005). Here, we will explore the roles of the KIF5 motors and then specifically discuss the pathogenesis of Alzheimer and Huntington diseases as examples.

KIF5s. Mice deficient for the *Kif5b* gene die during early embryonic development because of impaired transport of multiple essential organelles, including mitochondria and lysosomes (Tanaka et al., 1998). *Kif5c* knockout mice are viable and fertile, but their brain sizes were smaller than those of controls, with accompanying loss of neurons in the brain motor nuclei (Kanai et al., 2000). Because KIF5A, 5B, or 5C was similarly able to rescue the mitochondrial phenotype of *Kif5b*-deficient extraembryonic cells, their functions were considered partially redundant. A mutation in *KIF5A* is responsible for human hereditary spastic paraplegia, which causes a dying-back neuropathy characterized by progressive weakness and spasticity of the legs (Reid et al., 2002; Xia et al., 2003). Mutant mouse models revealed loss of large caliber axons and neurofilament accumulation in neuronal cell bodies.

JIPs. JIPs were identified as binding partners of KLC (Verhey et al., 2001). JIP1 and JIP2 share similarity with each other but JIP3 is distinct. In a *Drosophila* JIP1 mutant, *aplip1*, anterograde and retrograde axonal transport of vesicles is reduced (Horiuchi et al., 2007). Interestingly, retrograde, but not anterograde, axonal transport of mitochondria is reduced in the *aplip1* mutant.

In *Drosophila* and *C. elegans* JIP3 mutants, known as *sunday driver* (*syd*) and *unc16*, respectively, axonal transport of KIF5 cargos is affected (Bowman et al., 2000; Byrd et al., 2001). Because JIPs are scaffolding proteins for the JNKs, several studies have shown that cargo association and dissociation is regulated by JNK signaling. For example, JIP3 is required for the phosphorylation of APP (Muresan and Muresan, 2005). Only the phosphorylated form of APP can associate with JIP1. *C. elegans* JNK mutants also exhibit axonal transport defects, suggesting that JNK signaling supports axonal transport (Byrd et al., 2001). In mammals, however, JIPs are not required for axonal transport. Mislocalization of cargos is not observed in *Jip1*$^{-/-}$ mice nor *Jip1*$^{-/-}$/*Jip2*$^{-/-}$ mice (Whitmarsh et al., 2001; Kennedy et al., 2007). *Jip3* mutant mice have brain malformations, but it has not been clarified whether this phenotype is related to KIF5 function. The roles of JIPs in mammals may be different from those in worms and flies. It is also possible that all JIPs (JIP1–4) function redundantly as adaptors between KIF5 and vesicles in mammals, although their amino acid structure is variable. Further in vivo analyses with knockout mice would help to clarify this issue.

Alzheimer Disease. The brains of Alzheimer disease patients contain neurofibrillary tangles containing (1) paired helical filaments with hyperphosphorylated microtubule-associated protein tau and (2) amyloid plaques, which are degenerating neurites surrounding a core of amyloid-β peptide, derived from serial proteolysis of APP by β and γ-secretases. Familial Alzheimer disease-linked presenilin 1 variant transgenic mice demonstrate impaired anterograde fast axonal transport of APP and Trk receptors in the sciatic nerves and increased phosphorylation of tau and neurofilaments in the spinal cord (Lazarov et al., 2007). Application of amyloid-β inhibits mitochondrial trafficking (Rui et al., 2006). Thus, the KIF5-mediated transport of APP is likely to be deeply involved in the pathogenesis of this disease (Stokin et al., 2005; Terada et al., 2010). In addition, a mouse model of Down syndrome shows increased App expression, disrupted nerve growth factor transport, and caused cholinergic neuron degeneration (Salehi et al., 2006).

Huntington Disease. Huntington disease and Kennedy disease are familial neuronal disorders caused by expanded polyQ stretches within the huntingtin protein and androgen receptor proteins, respectively. Overexpression of mutant proteins in mammalian neurons disrupted the axonal transport of BDNF (Gauthier et al., 2004). The effect of huntingtin on the regulation of axonal transport has been claimed to be indirect or direct by different groups. The polyQ-androgen receptor leads to JNK-mediated phosphorylation of KIF5, which reduces motor activity (Morfini et al., 2006). On the other hand, the huntingtin-HAP40 complex is a new Rab5 effector that regulates early endosome motility and is upregulated in Huntington disease (Pal et al., 2006). Regulation of the intracellular trafficking of HAP1 is critical for TrkA protein levels and neurite outgrowth (Rong et al., 2006). HAP1 is reported to bind to KLC (McGuire et al., 2006) and huntingtin also facilitates dynein/dynactin-mediated vesicle transport (Caviston et al., 2007). Delivery of $GABA_A$ receptors to synapses is also mediated by the HAP1-KIF5 complex and is disrupted by mutant huntingtin (Twelvetrees et al., 2010).

Phosphorylation of wild-type huntingtin is crucial in controlling the direction of vesicle transport in neurons. When phosphorylated, huntingtin recruits KIF5 to the dynactin complex on vesicles and microtubules and promotes anterograde transport of BDNF. Conversely, when huntingtin is not phosphorylated, KIF5 detaches, and the vesicles are more likely to undergo retrograde transport (Colin et al., 2008; Figure 6H). Thus, this protein complex is suggested to be a molecular switch to change the direction of axonal transport.

The Roles of Kinesin 2 in Ciliogenesis and Brain Development

Kinesin 2 motors act in both cilia and cytoplasm. The heterotrimeric KIF3 complex (KIF3A/KIF3B/KAP3) bimodally functions in intraflagellar transport (IFT) of ciliary components (Rosenbaum and Witman, 2002) and in axonal or intracellular transport of plasma membrane precursors (Takeda et al., 2000) and the N-cadherin/β-catenin complex (Teng et al., 2005).

KIF3 and KIF17 as IFT Motors. Knockout mice for the *Kif3a* or *Kif3b* genes exhibit randomized left-right determination of the body axis (Figure 7E). Approximately half of knockout mouse embryos develop an abnormal heart loop (Marszalek et al., 1999a; Nonaka et al., 1998; Takeda et al., 1999; Figure 7E, insets). The molecular mechanisms of this striking body axis formation were approached microscopically by observing the ventral node of mouse embryos, which is a ciliated organ transiently exposed on the surface of the ventral midline (Nonaka et al., 1998; Hirokawa et al., 2009a). Scanning electron microscopy revealed the absence of ciliogenesis, consistent with KIF3 being an essential IFT motor. Interestingly, the cilia were clockwise-rotating on an axis tilted to the posterior, which could generate a leftward flow of extraembryonic fluid according to the shear stress of the embryonic surface (Okada et al., 2005). This flow appeared to concentrate essential signaling molecules on extracellular particles toward the left side to break the bilateral symmetry of the embryos (Tanaka et al., 2005). This nodal flow hypothesis could be an evolutionarily conserved mechanism for left-right determination (Figure 7E).

This role of the KIF3 motor in generating fluid flow via ciliogenesis is also essential for brain development (Breunig et al., 2010). Neurons and neural progenitor cells contain primary cilia, which are essential for hedgehog signaling during development and carcinogenesis (Jiang and Hui, 2008). IFT in cilia plays essential roles in the sensory cells of the inner ear (Jones et al., 2008), olfactory epithelium (Jenkins et al., 2006), and photoreceptors of the retina (Marszalek et al., 2000). Cilia of the ependymal cells generate flow of cerebrospinal fluids. A lack of this flow results in hydrocephalus (Mirzadeh et al., 2010). This flow guides the migration of neural progenitor cells from the subventricular zone to the olfactory bulb (Sawamoto et al., 2006) and is also essential for spontaneous generation of planar cell polarity of the ependymal cell themselves (Breunig et al., 2010).

Another kinesin 2 motor, KIF17, has been predicted from a *C. elegans* study to function in IFT. Dominant negative KIF17 affected ciliary trafficking of the olfactory cyclic-nucleotide gated (CNG) channel but not cilia length in the *osm-3 C. elegans* mutant (Ou et al., 2005; Jenkins et al., 2006).

KIF3 as an Intracellular Transport Motor. In addition to its role in IFT, the KIF3 motor also serves in cytoplasmic transport (Takeda

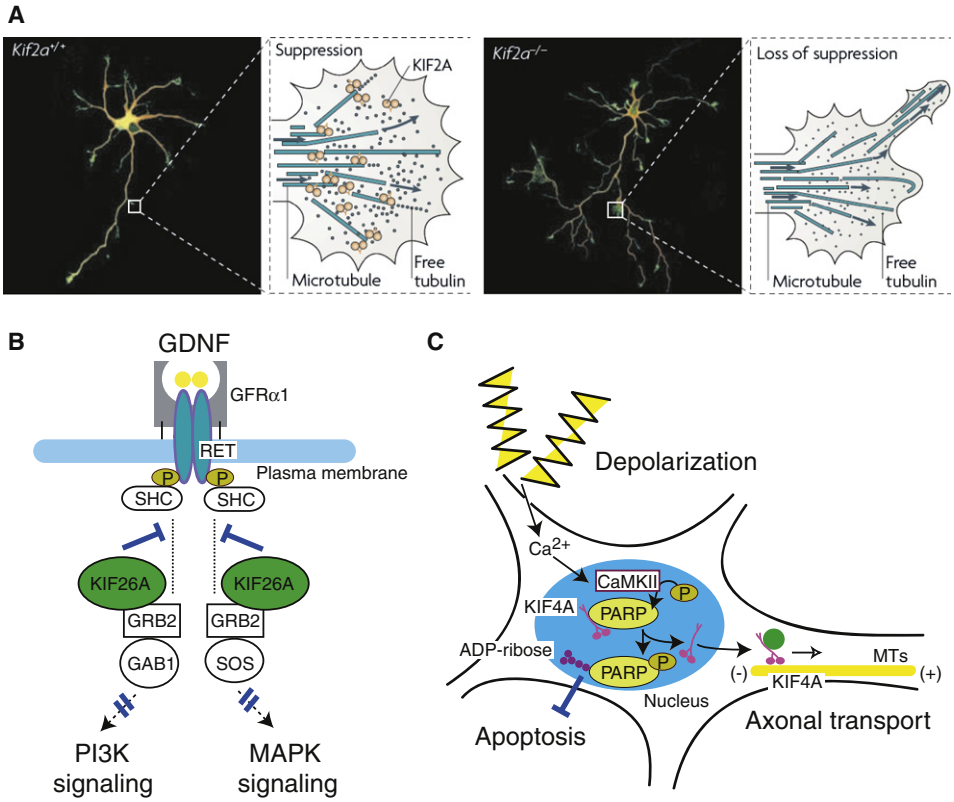

Figure 8. Molecular Motors in Brain Wiring and Neuronal Development

(A) KIF2A and suppression of axonal collateral formation. KIF2A depolymerizes microtubules. *Kif2a*$^{-/-}$ neurons (lower column) failed to suppress unnecessary branches because of impaired microtubule depolymerization activity. Reproduced with permission from Hirokawa et al. (2009b).

(B) KIF26A and megacolon. KIF26A negatively regulates GDNF-RET signaling by inhibiting SHC-Grb2 interaction in enteric neurons. Knockout animals develop megacolon because of malformations in the enteric nervous system.

(C) KIF4A and activity-dependent neuronal survival. KIF4A binds to nonphosphorylated PARP in the nucleus and negatively regulates it. Activity-dependent phosphorylation of PARP by CaMKII releases KIF4A from PARP and induces automodification of PARP that suppresses apoptosis of the neuron.

et al., 2000). Conditional gene targeting in mice of a nonmotor subunit of the KIF3 complex, *Kap3*, results in disorganization of the proliferative zone of the neuroepithelium and transforms these cells into tumors (Teng et al., 2005; Figure 7F). In the knockout cells, N-cadherin and β-catenin failed to be transported to the plasma membrane and abnormally accumulated in the cytoplasm and nucleus. Accordingly, they enhanced canonical Wnt signaling in the nucleus to facilitate cell proliferation and reduce cell-cell adhesion by N-cadherin. Thus, KIF3 seems to exclude oncoproteins from the perinuclear region (Figure 7F). On the other hand, the human SNP rs1541160 on the *KIFAP3 (KAP3)* promoter, which reduces gene expression, was found to confer a survival advantage in sporadic ALS patients (Landers et al., 2009). Its molecular mechanism is open to future study.

Relevance of Molecular Motors in Brain Wiring and the Development of the CNS and PNS

The nervous system mainly develops from the neural tube and neural crest cells that arise from neuroectoderm on the dorsal side of the embryo. Generally, the neural progenitors for the CNS are located innermost in the neural tube, where they asymmetrically divide and produce neural cell populations that undergo differentiation. These postmitotic neurons migrate toward the cortex of the neural tube and form the cortical layers. Recent results from gene targeting have revealed that molecular motors and their associated proteins are responsible for many essential steps of this neurogenesis cascade. Their roles are quite divergent and many more will probably be revealed in future studies.

KIF2A. The motor domains of the kinesin 13 family including KIF2A and KIF2C have a special function to depolymerize microtubules by hydrolyzing ATP. Knockout mice for the *Kif2a* gene are perinatally lethal, without sucking milk (Homma et al., 2003). Their brains showed multiple abnormalities including ventricle enlargement, laminar defects, and disorganization of nerve nuclei. *Kif2a*$^{-/-}$ neurons exhibited migratory defects both in vivo and in vitro and abnormally elongated collateral branches of axons (Figure 8A). This suggests that KIF2A contributes to brain wiring through suppressing unnecessary elongation of the collateral branches by microtubule depolymerization in growth cones.

KIF26A and KIF26B. The motor domain of the kinesin 11 family, including KIF26A/B, has significantly diverged and lost the microtubule-activated ATPase activity and the microtubule-dependent motility. Knockout mice for the *Kif26a* gene exhibited severe megacolon because of hyperplasia of enteric neurons and defects in myenteric neurite outgrowth, especially

in the distal colon (Zhou et al., 2009; Figure 8B). *Kif26a*$^{-/-}$ enteric neurons are hypersensitive to glial cell-derived neurotrophic factor (GDNF)-Ret signaling because the KIF26A tail domain directly binds to Grb2 to negatively regulate the formation of the SHC-Grb2, Ret-SOS, and Ret-Gab1 adaptor complexes. Thus, KIF26A plays a significant role as a suppressor of the GDNF-Ret-signaling system and as a controller of development of the enteric nervous system. *Kif26b*$^{-/-}$ mice also exhibited agenesis of the kidney because of impaired ureteric bud invasion into the metanephric mesenchyme and reduced expression of GDNF (Uchiyama et al., 2010).

KIF4A. During brain development, activity-dependent neuronal survival is programmed to eliminate unnecessary neurons. The kinesin 4 motor KIF4A is expressed predominantly in juvenile neurons and is localized both in the nucleus and cytoplasm (Sekine et al., 1994). Unexpectedly, the survival rate of neurons lacking KIF4A was higher than that of control neurons (Midorikawa et al., 2006; Figure 8C). The C-terminal domain of KIF4A could bind to and suppress the activity of the poly(ADP-ribose) polymerase 1 (PARP1) enzyme, which maintains cell homeostasis by repairing DNA and serving as a transcriptional regulator. When neurons are stimulated by membrane depolarization, CaMKII-mediated calcium signaling phosphorylates PARP1 and induces dissociation of KIF4A from PARP1. This activates PARP1 and the neuron escapes apoptosis. The dissociated KIF4A leaves the nucleus and functions as a transport motor. Thus, KIF4A has dual functions: one as a key regulator of activity-dependent neuronal survival and the other as a motor to transport cargos in the cytoplasm. Because KIF17b also participates in transcriptional regulation through interacting with a transcriptional coactivator in male germ cells (Macho et al., 2002), KIFs may occasionally act as transcription factors in the nucleus.

Myosin Superfamily Proteins. So far, fewer genetic models have been established for myosin superfamily proteins than for microtubule motors (Table 3). Many nonmuscle myosin mutations have been linked to inner ear functions, with mutation resulting in hearing loss and/or vestibular defects (*Myo1a*, *Myo1c*, *Myh9*, *Myo3a*, *Myo6*, *Myo7a*, *Myh14*, and *Myo15a)*. For the *Myo7a* gene, the *shaker-1* mouse has been established as a good model for Usher syndrome type IB (Gibson et al., 1995; Weil et al., 1995). The *Snell's waltzer* mouse is a good model for *Myo6* mutation in inherited deafness (DFNB37 in humans), and also suggests *Myo6*'s role in the internalization of TrkB and AMPARs in the nervous system (Avraham et al., 1995; Ahmed et al., 2003; Osterweil et al., 2005; Yano et al., 2006). Myosin V is suggested to function in the short-distance transport of vesicles including in AMPAR trafficking. *Myo5a* is responsible for the *dilute lethal* mutation of the mouse and Griscelli syndrome of humans, causing hypopigmentation and neurological problems (Mercer et al., 1991; Pastural et al., 1997).

Concluding Remarks

Among the three superfamilies of molecular motor proteins, KIFs, cytoplasmic dynein, and myosins play significant roles in intracellular transport in neurons and control neuronal function, morphogenesis, and survival. KIFs and cytoplasmic dynein function in the axon and dendrites, while myosins function mainly in the presynaptic and postsynaptic regions (spines).

In terms of KIF cargos, axon synaptic vesicle precursors (KIF1A and KIF1Bβ), mitochondria (KIF1Bα and KIF5s), APP-containing vesicles (KIF5), TrkB vesicles (KIF5), GABA receptor vesicles (KIF5), N-cadherin vesicles (KIF3), plasma membrane precursors (KIF3), and PIP_3 vesicles (KIF13B) are anterogradely transported. On the other hand, dendritic cargos include the NMDAR vesicles (KIF17), AMPAR vesicles (KIF5), Kv channel vesicles (KIF3), and mRNAs within large protein complexes (KIF5). KIFs recognize and bind their cargos in most cases through scaffold proteins or adaptor protein complexes, whereas in some cases KIFs bind directly to the membrane proteins.

As for the regulatory mechanisms of cargo binding, phosphorylation of KIFs to dissociate adaptor proteins (KIF17; Mint1) and GTP hydrolysis of small G protein to dissociate small G protein from the adaptor protein and KIFs (Rab3; DENN/MADD; KIF1A and KIF1Bβ) are typical mechanisms. A third mechanism involving Ca^{2+} signaling through Milton and Miro has been identified for control of the loading and unloading and transport of mitochondria by KIF5. Specific proteins that regulate motor activity have also been identified, such as KBP for KIF1Bα, SYD2 for UNC104/KIF1A, and JNK3 and huntingtin for KIF5.

Cytoplasmic dynein (Dync1h1) transports cargos retrogradely in the axon. The cargos include TrkA, TrkB, BDNF, and piccolo/bassoon-containing vesicles. In dendrites, cytoplasmic dynein conveys cargos involving glycine receptor vesicles, mRNAs within protein complexes, and Rab5 endosomes. Compared with the divergence of KIFs, and because there is only one species of dynein heavy chain involved in transport in dendrites and the axon, dynein regulates cargo binding through light chains, the light intermediate chain, and the dynactin complex. In this case, the cargos bind to the dynein complex either directly or through adaptor proteins such as gephyrin (glycine receptor), NDEL1/NDE1/LIS1, and HAP1. Nonetheless, in some cases dynein directly binds cargoes such as huntingtin. Regulation of the binding is controlled via phosphorylation (dynein/dynactin/phospho-huntingtin/KIF5) and GTP hydrolysis of the small G protein Rab (dynein/dynactin/RILP/ORP1L/Rab7/lysosome). LIS1 and NDEL1 regulate dynein activity in a Cdk5-dependent manner.

Among the myosin superfamily proteins, myosin Va, myosin Vb, myosin VI, and myosin X are involved in transport in neurons. The AMPAR GluR1 (myosin Va), the TLS mRNP complex (myosin Va), and AMPAR recycling endosomes (myosin Vb) are conveyed toward postsynaptic membranes in the spines, while myosin VI transports AMPAR-containing endosomes retrogradely in the spines. Myosin Va may also function in the presynaptic terminals after certain cargos are unloaded from the microtubule-KIF system. Myosins also use adaptor proteins and small G-proteins for recognition and binding of the cargos. Myosin X is involved in transport in filopodia in the growth cone. Myosin II plays important roles in migrating neurons and growth cones. In addition, it is involved in the dynamic organization of actin bundles in the postsynaptic spines and is related to synaptic plasticity through control of spine shape.

A mechanism for the regulation of bidirectional transport in axons has been revealed involving recruitment of KIF5 by phosphorylation of huntingtin with the dynactin/dynein cargo

complex (anterograde transport) and dissociation of KIF5 from the huntingtin/dynactin/dynein cargo complex for retrograde transport. On the other hand, anterograde transport of the dynein complex by KIF5 is mediated by LIS1, which suppresses dynein activity. In addition, NDEL1 releases the blocking effect of LIS1 on dynein for retrograde transport. These mechanisms need to be clarified in more detail.

The switching mechanism between fast transport of membranous organelles and slow transport of cytoplasmic proteins by KIF5 has been shown to be controlled by Hsp70. If Hsp70 binds to KLC, cytoplasmic proteins can bind to KIF5 through Hsp70; thus they can be transported by KIF5 (slow transport).

For certain molecular motors, the mechanisms of cargo recognition, loading, and unloading have been revealed, but there are a number of KIFs and myosins whose cargos have not yet been characterized. This is also the case for cytoplasmic dynein. Furthermore, their mechanisms of cargo recognition, loading, and unloading have not yet been identified. The clarification of these mechanisms will lead to a deeper understanding of neuronal function. In other words, there are still many important molecules, such as channels, receptors, and scaffold proteins, whose dynamics are totally unknown. More specifically regarding the regulation of molecular motors, the identified kinases are very limited, such as protein kinase A and JNK3 for the KIF5s, and CaMKII for KIF17. Furthermore, regulation of the nucleotide-bound state of small G proteins is controlled by GTPase-activating proteins (GAPs) and GDP-GTP exchange factors (GEFs), many of which are unknown. Future work is needed to identify the kinases and G-proteins related to molecular motors, what signals activate their GAPs and GEFs, and what signals control the association and dissociation of molecular motors and their cargos.

The mechanisms of directional transport are fundamental for the understanding not only of the morphogenesis of polarized neuronal structures and brain wiring but also of neuronal function. A key finding was that the KIF5 motor domain recognizes a difference in microtubule dynamics in the axon versus the dendrites. It would be interesting to establish the basis for this phenomenon. In addition, because directional transport requires the orchestration of several different processes, the related mechanisms, such as selective stabilization, need to be addressed. Other questions for the future include how the motor regulates delivery of the different cargos that can be loaded onto the same motor, such as KIF5 and cytoplasmic dynein; how neurons control the transport of similar cargos by multiple distinct motors; and how bidirectional transport is regulated by crosstalk among the KIFs, cytoplasmic dynein, and myosins.

The molecular genetics of the molecular motors has uncovered not only the fundamental roles of each motor in neuronal and brain function but has also revealed functions in unexpected physiological processes, including brain wiring, activity-dependent neuronal survival, higher brain function, the determination of left-right asymmetry, suppression of tumorigenesis, and development of the enteric nervous system. Furthermore, it has become increasingly evident that molecular motors are deeply related to the pathogenesis of neuronal diseases such as Alzheimer disease, Huntington disease, and neuropathies. In the near future, molecular genetics will deepen our understanding of neuronal and brain function and, at the same time, is likely to reveal more surprising roles of molecular motors.

In summary, molecular motor research is one of the new frontiers of neuroscience, which encompasses molecular and cellular neuroscience, system neuroscience, behavioral neuroscience, and human neuronal pathology. Although certain questions have been answered, a number of problems remain and new questions have arisen. Using a wide variety of approaches in molecular cell biology, new imaging techniques, electrophysiology, biophysics, molecular genetics, structural biology, and molecular motor research will contribute to the further development of neuroscience in many directions.

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