CYTOSKELETAL MOTORS

Traffic control: regulation of kinesin motors

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Abstract | Kinesins are a family of molecular motors that use the energy of ATP hydrolysis to move along the surface of, or destabilize, microtubule filaments. Much progress has been made in understanding the mechanics and functions of the kinesin motors that play important parts in cell division, cell motility, intracellular trafficking and ciliary function. How kinesins are regulated in cells to ensure the temporal and spatial fidelity of their microtubule-based activities is less well understood. Recent work has revealed molecular mechanisms that control kinesin autoinhibition and subsequent activation, binding to cargos and microtubule tracks, and localization at specific sites of action.

Ciliopathies
A collection of human diseases that have a common underlying genetic defect in the assembly or function of cilia.

Two large families of molecular motors, kinesins and dyneins, drive transport along microtubule filaments. As molecular motors, these enzymes convert the chemical energy of ATP hydrolysis into mechanical energy and force production. Defects in motor-dependent transport are associated with many diseases, including neurodegeneration, cancer, developmental defects and a group of diseases termed the ciliopathies[1–4].

Genetic and biochemical approaches have identified a large family of kinesin motor proteins. These motors have a common kinesin motor domain that contains nucleotide- and microtubule-binding sites. Evolution has adapted this core motor domain by adding divergent non-motor regions that are important for isoform-specific functions, such as cargo binding, regulation and localization (BOX 1; TABLE 1). The variety of approaches and model systems used to identify new kinesin motors led to independent and confusing names for kinesin family members from different species. In 2004, a standard kinesin nomenclature was adopted based on phylogenic analyses[5]. For clarity, we use this nomenclature here for kinesin families. More recent work, including greater taxon sampling, has identified additional kinesin subfamilies, the distribution among organisms of which is more reflective of shared biology than evolutionary relationships[6].

The kinesin motor domain can be situated at either end or in the middle of the polypeptide chain (BOX 1). In general, kinesins with an amino-terminal motor domain undergo directed motility towards the plus (rapidly growing) end of the microtubule, whereas kinesins containing a carboxy-terminal motor domain move in the opposite direction, towards the minus (slowly growing) end of the microtubule. Kinesin motors with a central motor domain destabilize microtubules rather than move along their surface. However, recent work has added exciting and interesting complexities to these generalizations. For example, some Kinesin-8 and Kinesin-14 motors can both walk along and depolymerize microtubules[7–9]. Furthermore, members of several kinesin families can undergo both ATP-independent one-dimensional diffusion and ATP-dependent directed motility along the microtubule surface[10–17].

How motor proteins are regulated to ensure their activity at the correct place and time is an important biological question. In this Review, we focus on recent work that has revealed regulatory mechanisms that control the activity of kinesin motors. We first discuss studies demonstrating that kinesin motors evolved autoinhibitory mechanisms to ensure that they remain in an inactive state in the absence of cargo. We then focus on transport motors during interphase, and mechanisms that regulate the motor–cargo and motor–microtubule interactions. Finally, we discuss molecular mechanisms that control the localization and activity of kinesin motors during mitosis.

Autoinhibition in the absence of cargo

In the absence of cargo, kinesin activity must be tightly controlled to prevent futile ATP hydrolysis and congestion of microtubule tracks. Recent work has shown that autoinhibition might be a general mechanism for the regulation of kinesin motors. The molecular mechanism of autoinhibition has been best studied for Kinesin-1 motors, but members of the Kinesin-2, Kinesin-3 and Kinesin-7 families are also regulated by autoinhibition (FIG. 1a). As kinesin families evolved by adopting unique non-motor regions for distinct cellular functions, there

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doi:10.1038/nrm2782

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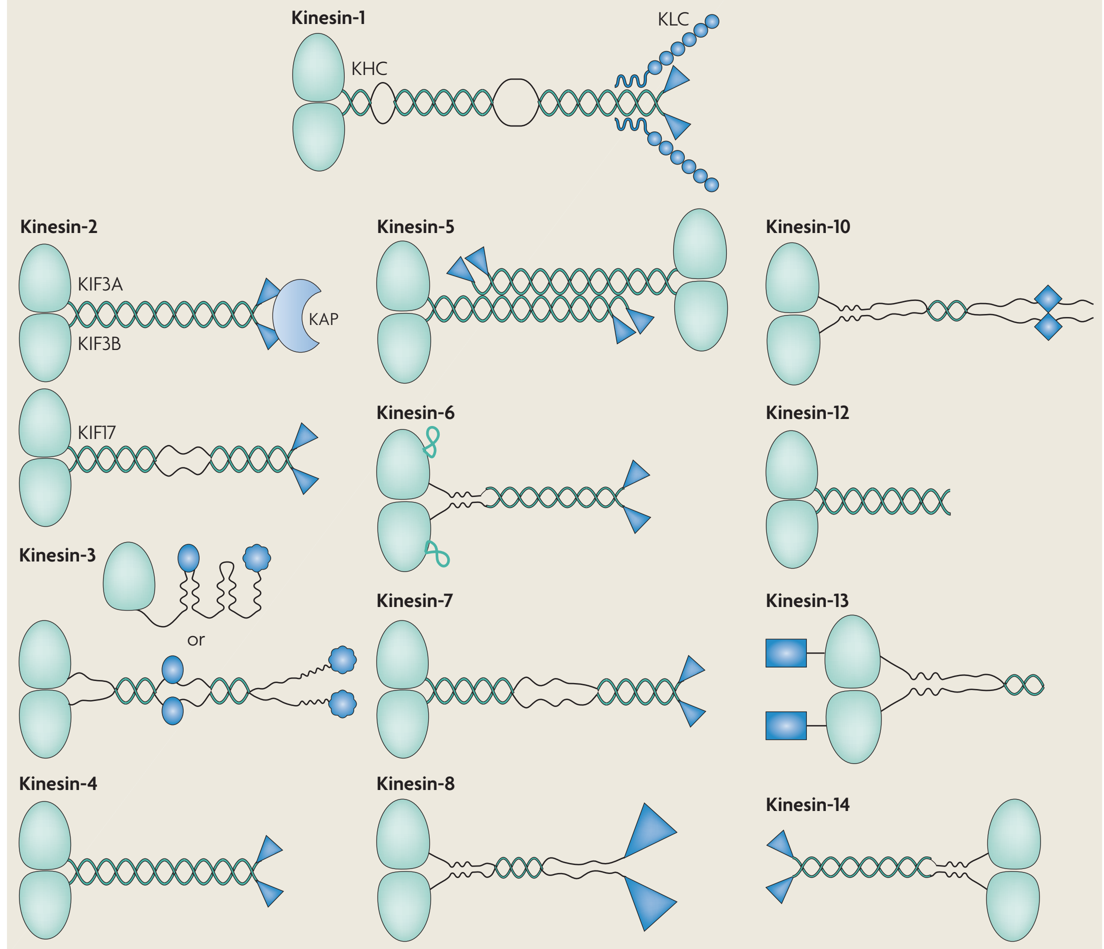
Box 1 | The kinesin superfamily

All members of the kinesin superfamily contain a kinesin motor domain (see the figure; light green). In general, the position of the motor domain in the polypeptide sequence indicates the directional motility of the protein. Kinesins with an amino-terminal motor domain undergo motility to the plus (rapidly growing) end of microtubules, whereas kinesins with a carboxy-terminal motor (Kinesin-14 family) undergo minus end-directed motility. Kinesin motors with a central motor domain (Kinesin-13 family) do not undergo directed motility but instead destabilize microtubules at their plus and minus ends. Some kinesin motors (Kinesin-8 and Kinesin-14 families) can both walk along and destabilize microtubules, and some (Kinesin-5 and Kinesin-14 families) can cross-link and slide adjacent microtubules. Kinesin-6 motors contain a unique loop in their motor domains.

Many kinesins contain coiled-coil segments (see the figure; dark green) for oligomerization. Most kinesin motors exist as homodimers (for example, Kinesin-4, Kinesin-6, Kinesin-7, Kinesin-8, Kinesin-10, Kinesin-12, Kinesin-13 and Kinesin-14 families). Kinesin-1 motors are heterotetramers of two subunits: kinesin heavy chain (KHC) and kinesin light chain (KLC). Kinesin-2 motors can be divided into two subfamilies that are either heterotrimers (for example, KIF3A–KIF3B–kinesin-associated protein (KAP)) or homodimers (for example, KIF17). Kinesin-3 motors can exist as monomers or homodimers, and the Kinesin-5 family consists of homotetrameric motors.

Kinesins contain unique non-motor domains (see the figure; blue) that confer isoform-specific regulatory and/or functional properties to the different kinesin families (TABLE 1). For recent reviews on kinesin functions and mechanochemistry, see REFS 48,150–156.



must have been pressure to ensure the coevolution of inhibitory mechanisms for regulation of the common motor domain.

Mechanisms of autoinhibition. Early work revealed that purified Kinesin-1 motors can adopt a folded, compact conformation or an extended, almost linear conformation[18]. Further work, including sedimentation assays, single-molecule analysis, biochemical assays and fluorescence resonance energy transfer, has shown that the folded conformation corresponds to the inactive state[19–25]. A folded conformation has also been implicated in the autoinhibition mechanism of the Kinesin-2 family member *Caenorhabditis elegans* osmotic avoidance abnormal protein 3 (OSM-3), the Kinesin-3 family member mouse KIF1A and the Kinesin-7 family member human centromere-associated protein E (CENPE)[16,26–28] (J.W.H. and K.J.V., unpublished observations).

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Table 1 | **Kinesin families and their functions**

Family	Functions	Commonly studied family members
Kinesin-1	Vesicle, organelle and mRNA transport	• KIF5 (Mm), KHC (Dm and Nc) and UNC-116 (Ce)
Kinesin-2	Vesicle, melanosome and intraflagellar transport	• Heterotrimeric subfamily: KIF3 (Mm), KLP64D (Dm), KLP68D (Dm), KRP85 (Ce), KRP95 (Ce), Kin1 (Tt), Kin2 (Tt) and FLA10 (Cr) • Homodimeric subfamily: KIF17 (Hs), OSM-3 (Ce) and Kin5 (Tt)
Kinesin-3	Vesicle transport	• Subfamily: KIF1 (Hs), UNC104 (Dm), UNC-104 (Ce) and Kin3 (Nc) • Subfamily: KIF13 (also known as GAKIN; Hs), KIN73 (also known as KHC73; Dm) and KLP-4 (Ce) • Subfamily: KIF28 (Hs) and KLP-6 (Ce) • Subfamily: KIF16 (Hs) and KLP98A (Dm) • Subfamily: KIF14 (Hs)
Kinesin-4	Chromosome positioning	• KIF4 (Hs), chromokinesin (Gg), KLP3A (Dm) and KLP1 (also known as KIF4; Xl)
Kinesin-5	Spindle pole separation and spindle bipolarity	• KIF11 (also known as Eg5; Hs), KIF11 (Mm), Eg5 (Xl), KLP61F (Dm), BimC (An)BMK-1 (Ce), Cin8 (Sc), Kip1 (Sc) and Cut7 (Sp)
Kinesin-6	Central spindle assembly and cytokinesis	• Subfamily: MKLP2 (also known as KIF20A; Hs), KIF20A (also known as Rab6 kinesin; Mm) and Subito (Dm) • Subfamily: MKLP1 (also known as KIF23; Hs), KIF23 (Mm), CHO1 (Cg), Pavarotti (Dm) and ZEN-4 (Ce)
Kinesin-7	Kinetochore–microtubule attachment and chromosome congression	• KIF10 (also known as CENPE; Hs), KIF10 (Mm) and KIP2 (Sc)
Kinesin-8	Chromosome congression	• Subfamily: KIF18 (Hs) and KLP67A (Dm) • Subfamily: KIF19 (Hs), KLP13 (Ce), KIP3 (Sc), KLP5 (Sp) and KLP6 (Sp)
Kinesin-10	Chromosome positioning	• KIF22 (also known as KID; Hs and Xl) and Nod (Dm)
Kinesin-12	Spindle pole organization	• KIF12 (Mm), KIF15 (Mm), KLP54D (Dm) and KLP2 (also known as KIF15A; Xl)
Kinesin-13	Kinetochore–microtubule error correction and chromosome segregation	• Subfamily: KIF2A (Hs), KIF2B (Hs), MCAK (also known as KIF2C; Hs), MCAK (Cg), KCM1 (also known as KIF2C; Xl), KLP10A (Dm), KLP59C (Dm), KLP59D (Dm) and KLP7 (Ce) • Subfamily: KIF24 (Hs) and Kin1 (Pf)
Kinesin-14	Spindle pole organization and cargo transport	• Subfamily: KIFC1 (also known as HSET; Hs), CHO2 (Cg), NCD (Dm), CTK2 (Xl) and Kar3 (Sc) • Subfamily: KIFC2 (Hs), KIFC3 (Hs), KLP3 (Ce) and a large number of plant-specific isoforms

An, Aspergillus nidulans; Ce, *Caenorhabditis elegans*; Cg, *Cricetulus griseus*; CHO, chinese hamster ovary; Cin8, chromosome instability protein 8; Cr, *Chlamydomonas reinhardtii*; CTK2, carboxy-terminal kinesin 2; Cut7, cell untimely torn protein 7; Dm, *Drosophila melanogaster*; Gg, *Gallus gallus*; Hs, *Homo sapiens*; KCM1, kinesin central motor 1; KHC, kinesin heavy chain; KLP, kinesin-like protein; MCAK, mitotic centromere-associated kinesin; MKLP, mitotic kinesin-like protein; Mm, *Mus musculus*; Nc, *Neurospora crassa*; NCD, non-claret disjunctional; OSM-3, osmotic avoidance abnormal protein 3; Pf, *Plasmodium falciparum*; Sc, *Saccharomyces cerevisiae*; Sp, *Schizosaccharomyces pombe*; Tt, *Tetrahymena thermophila*; Xl, *Xenopus laevis*; ZEN-4, zygotic epidermal enclosure defective protein 4.

The folded conformation had two implications concerning the molecular mechanism of kinesin autoinhibition. First, for kinesin motors that contain coiled-coil segments in their stalk regions, the folded conformation requires one or more hinge segments — areas with a low propensity to form coiled coils (FIG. 1a). This was verified by data showing that removal or mutation of the central hinge in Kinesin-1 or Kinesin-2 motors prevents the folded conformation and produces an active state[22,23,27] (J.W.H. and K.J.V., unpublished observations). Second, the folded conformation enables non-motor regions to come into contact with the motor domain and block microtubule binding and ATPase activities. Indeed, a Kinesin-1 tail peptide can inhibit the ATPase and motility properties of the motor domain when added in *trans*[22,29,30]. Further work identified a conserved sequence motif, QIAKPIRP, in the Kinesin-1 tail, the presence of which is crucial for autoinhibition in both kinesin heavy chain (KHC) homodimers and Kinesin-1 heterotetramers[24,25,31]. A detailed mechanism for Kinesin-1 autoinhibition was provided by recent biochemical and structural studies, which showed that the QIAKPIRP-containing tail domain of Kinesin-1 directly contacts the enzymatically crucial Switch I helix in the motor domain and prevents ADP release from the nucleotide pocket[32,33]. This regulatory mechanism of Kinesin-1 autoinhibition extends the similarities between kinesin motors and small GTPases beyond the previously noted structural and kinetic properties[34]. Both kinesin motors and small G proteins are kept in an inactive, ADP-bound state by the action of nucleotide dissociation inhibitors that prevent release of the diphosphate nucleotide. For Kinesin-1 motors, the nucleotide dissociation inhibitor exists in *cis* with the enzymatic domain, whereas specific guanine dissociation inhibitor proteins regulate individual small G proteins in *trans*.

Autoinhibition of the Kinesin-2 family member human KIF17 and the Kinesin-7 family member human CENPE also involves direct interactions of C-terminal tail domains with their motor domains[28] (J.W.H. and K.J.V., unpublished observations). By contrast, the Kinesin-3 motors mouse KIF1A and mouse KIF13B (also known as GAKIN) use internal segments for autoinhibition of motor activity[16,35,36] (FIG. 1a). For these Kinesin-3 motors, the mechanisms of intramolecular binding and enzymatic inhibition remain to be identified.

The activity of Kinesin-1, Kinesin-2 and Kinesin-3 motors is also regulated by a second mechanism of autoinhibition that prevents coordinated stepping of the two motor domains (FIG. 1a). In Kinesin-1 motors, the kinesin light chain (KLC) subunits play a unique part in preventing processive motility by separating the motor domains of the KHC subunits[25]. Because fungal Kinesin-1 motors lack the KLC subunit, the KHC tail probably carries out this inhibitory mechanism by binding to a non-coiled-coil conformation of the KHC neck[37]. Distinct regions in Kinesin-2 and Kinesin-3 motors have also been identified that regulate processive motility and/or motor coordination[16] (J.W.H. and K.J.V., unpublished observations). Perhaps the presence of dual inhibitory mechanisms provides finer control for full inhibition of all kinesin activities, including microtubule binding, nucleotide exchange and hydrolysis, and cargo association.

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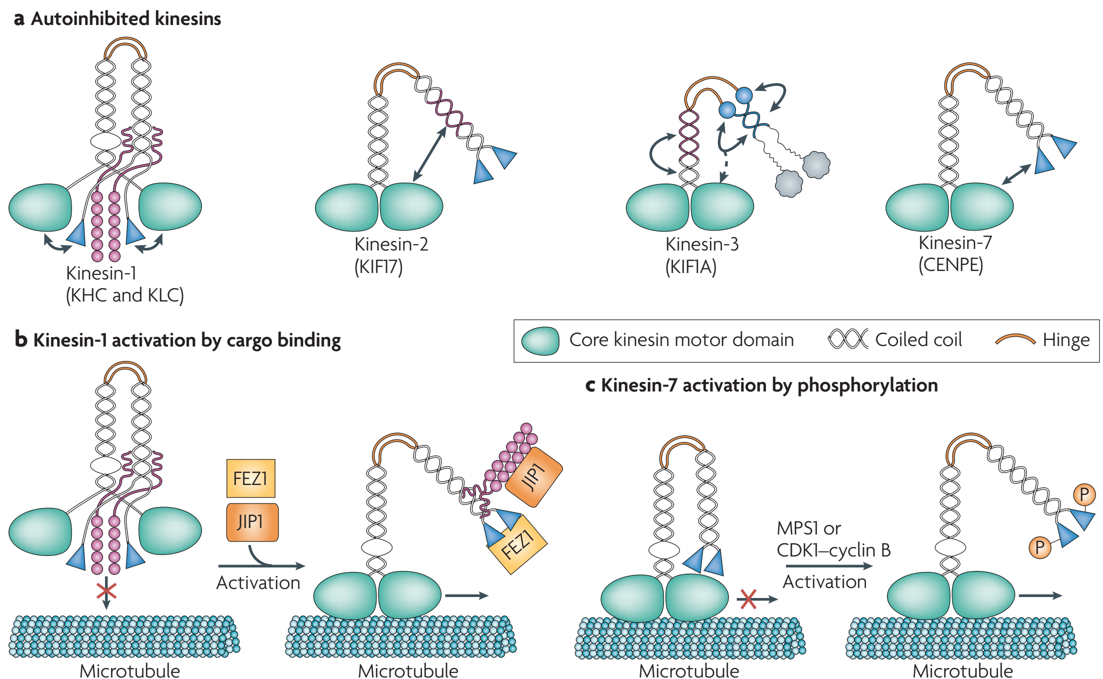

Figure 1 | **Autoinhibitory mechanisms used by kinesin motors. a** | Inactive Kinesin-1 motors (comprising kinesin heavy chain (KHC) and kinesin light chain (KLC) subunits), the Kinesin-2 family member KIF17 and the Kinesin-7 family member centromere-associated protein E (CENPE) assume a folded conformation that enables an inhibitory and direct motor-to-tail interaction. The inactive Kinesin-3 family member KIF1A also adopts a folded conformation, but one that is more compact and globular. Double arrows indicate regions that interact in the folded, inactive conformation and dotted arrows indicate plausible interactions. Dual inhibitory mechanisms control Kinesin-1, Kinesin-2 and Kinesin-3 motors through domains that inhibit microtubule binding (blue) and domains that inhibit processive motility (pink). **b** | Autoinhibition of Kinesin-1 motors can be relieved by the interaction with two binding partners, fasciculation and elongation protein-ζ1 (FEZ1; also known as zygin 1) and Jun N-terminal kinase-interacting protein 1 (JIP1; also known as MAPK8IP1), that release the restraints of microtubule binding and processive motility. **c** | Autoinhibition of the Kinesin-7 family member CENPE can be relieved by phosphorylation of the inhibitory tail domain by the kinases monopolar spindle protein 1 (MPS1; also known as TTK) and cyclin-dependent kinase 1 (CDK1; also known as CDC2)–cyclin B, and results in processive motility on microtubules.

Coiled coil
A structural motif in proteins, often used to control oligomerization, in which two or more coils — α-helical seven amino acid (heptad) repeats — wrap around each other.

Kinesin heavy chain
The catalytic subunit of a Kinesin-1 motor, the domain organization of which consists of a kinesin motor domain, a coiled-coil stalk and a globular tail.

Kinesin light chain
The accessory subunit of a Kinesin-1 motor that contributes to autoinhibition and is important for binding to some cargos.

Release of autoinhibition. The simplest model for motor activation is one in which cargo binding to the tail region relieves autoinhibition and enables microtubule-based motility. Indeed, mimicking cargo by attaching glass beads to the tails of recombinant Kinesin-1 or Kinesin-2 motors results in processive motility along microtubules[22,27]. Cargo binding has recently been shown to result in activation of Kinesin-1 motors in a cellular context. Because Kinesin-1 motors are autoinhibited by two mechanisms, two proteins (fasciculation and elongation protein-ζ1 (FEZ1; also known as zygin 1) and Jun N-terminal kinase (JNK)-interacting protein 1 (JIP1; also known as MAPK8IP1)) are required to bind to the two inhibitory regions of the molecule (the KHC tail and the KLC subunit, respectively) for activation of microtubule-based motility[38] (FIG. 1b). For recombinant KHC-only motors, a single binding partner is sufficient for enzyme activation[33,39].

How autoinhibited Kinesin-3 motors are activated for motility is controversial. Early work showed that the Kinesin-3 family member mouse KIF1A is a monomeric motor[26]. When forced to dimerize, Kinesin-3 motors under went processive motility, leading to the idea that cargo binding activates the processive motility of monomeric Kinesin-3 motors by concentration-driven dimerization on the membrane surface[40,41]. However, recent evidence that mammalian Kinesin-3 motors are dimeric in solution but still autoinhibited[16] indicates that the mechanochemistry and regulation of Kinesin-3 motors may be similar to that of other transport motors. Indeed, other members of the Kinesin-3 family can exist in a dimeric state and/or be activated by binding to a cargo protein[36,42–44].

Cargo binding, however, may not be the full answer to motor activation. Kinesin-1 motors that are present on purified membranes can be inactive while attached to the membrane cargo[45]. And phosphorylation has been shown to play an important part in relieving autoinhibition of two mitotic kinesins, the Kinesin-5 family member KIF11 (also known as Eg5) and the Kinesin-7 family member CENPE. For Kinesin-5 motors, phosphorylation of Thr937 in the inhibitory C-terminal tail by cyclin-dependent kinase 1 (CDK1; also known as CDC2) increases the efficiency of microtubule binding[46]. For Kinesin-7 motors, phosphorylation of the inhibitory C-terminal tail by monopolar spindle protein 1 (MPS1; also known as TTK) and/or CDK1–cyclin B causes the motor to unfold, or to assume a less compact

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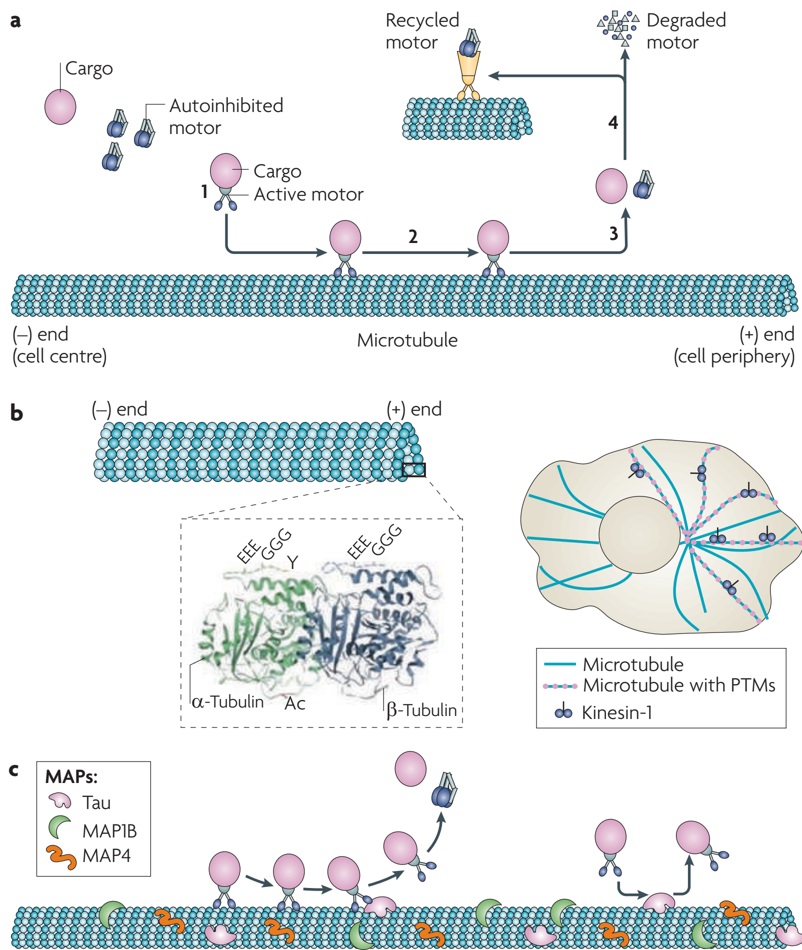

Figure 2 | **Transport cycle of kinesin motors. a** | In the absence of cargo, kinesin motors are autoinhibited (top left). At the point of departure, inactive motors bind to their cargos and become activated for transport (step 1). During transport, motor–cargo complexes must navigate microtubule tracks (step 2; see parts **b** and **c**). At the destination, cargo release (step 3) is presumably coupled to inactivation of the motor. The fate of the motor is not clear (step 4). It might be degraded or recycled for further rounds of transport by a retrograde motor (yellow). **b** | Kinesin-1-driven transport events can be influenced by post-translational modifications (PTMs) of the microtubule tracks. In the left panel, microtubules are polymerized from α-tubulin–β-tubulin heterodimers (Protein Data Bank code 1TUB), which can be altered by PTMs. Polyglutamylation (EEE), polyglycylation (GGG) and detyrosination (Y) occur on the amino-terminal tail or tails (disordered in their structures). Acetylation (Ac) occurs on Lys40 of α-tubulin. In the right panel, Kinesin-1 motors associate preferentially with microtubules marked by PTMs. **c** | Kinesin-1-driven transport can be negatively influenced by the microtubule-associated proteins (MAPs) tau, MAP1B and MAP4. MAPs bind to the outer surface of microtubules and can cause decreased attachment and/or increased detachment of Kinesin-1 motors and/or vesicles.

MAPK family
(Mitogen-activated protein kinase family). A family of Ser/Thr-specific protein kinases that respond to extracellular signals and regulate a range of intracellular events. The MAPK is the third kinase in a cascade and is activated by a MAPK kinase (MAPKK), which is activated by a MAPKK kinase (MAPKKK).

conformation, and increases processive motility along microtubules[28] (FIG. 1c). As MPS1 is a component of CENPE's cargo, the kinetochore, and CDK1–cyclin B is active only during mitosis, coordinated phosphorylation by these two kinases could provide spatial and temporal control over CENPE activation.

In summary, autoinhibition seems to be a general model for preventing erroneous kinesin activity, although further work is required to determine whether this general principle holds for other kinesin families. Based on their unique properties and functions, kinesin motors probably have unique activation mechanisms. So far, cargo binding and phosphorylation events have been shown to relieve autoinhibition. Interestingly, cargo binding can also activate motors by switching their mode of motility. Recent work has shown that binding to a second microtubule (the cargo) switches the motility mode of Kinesin-5 motors from diffusive to processive[47].

Regulation of transport motors

The spatial and temporal regulation of motor-based transport is essential to ensure precise cargo delivery in all cell types. The list of molecules that are known to link specific transport motors to their cargos is rapidly expanding[48]. How transport is regulated is less well understood. A simple model suggests that transport motors can be regulated at several points. Early events include motor–cargo binding, motor activation and microtubule track selection, and late regulatory events include cargo release at the destination and the recycling of motors (FIG. 2a). In this section, we discuss recent work that has shed light on the regulation of motor–cargo and motor–microtubule interactions.

Regulating the motor–cargo interaction. How motor–cargo linkages are regulated at the point of departure (FIG. 2a; step 1) is largely unknown. Recent work has implicated two groups of molecular players — small GTPases of the Rab family and protein kinases — as positively influencing the association of kinesin motors with their cargos[48–52]. Here we focus on exciting work that has begun to shed light on how kinesin motors are released from their cargos once they reach their destination (FIG. 2a; step 3).

Recent work has implicated the MAPK family in negatively regulating the interaction of kinesin motors with their cargo in two experimental systems: axonal transport and intraflagellar transport (IFT) (BOX 2). During axonal transport, one evolutionarily conserved set of cargo proteins of Kinesin-1 motors are the JIP scaffolding proteins that have important roles in the assembly of JNK signalling pathways by binding to the MAPKKK, MAPKK and JNK components of the kinase cascade[53–56]. Work in *Drosophila melanogaster* has shown that activation of the MAPKKK or MAPKK components results in dissociation of the Kinesin-1 motor from the JIP cargo protein[56]. This work indicates that not only are the components of the MAPK signalling pathway cargos of Kinesin-1 motors, but the pathway actively participates in regulation of the Kinesin-1 motor. Activation of JNK in other signalling contexts, particularly in disease states, might also block Kinesin-1-driven transport. For example, neuronal injury that induces local activation of JNK results in a shift from anterograde transport (which is kinesin-dependent) to retrograde transport (which is dynein-dependent)[57]. Whether this is owing to the release of Kinesin-1 motors from vesicles is not clear because other reports have indicated a negative influence of JNK signalling on the ability of Kinesin-1 motors to bind to microtubules[58–60].

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Box 2 | Model systems for studying kinesin-dependent transport

Biochemical and biophysical approaches have been widely used to determine the mechanical properties of kinesin motors. However, to understand kinesin-dependent transport in cells, *in vivo* model systems that incorporate the complexity of cargo–motor complexes and their regulatory mechanisms are invaluable tools.

Axonal transport

Neurons are highly polarized cells that typically have a single long axon to transmit information and multiple shorter dendrites to receive information. The axon is packed with cargos that are being moved towards the nerve terminal (anterograde transport) by kinesin motors and towards the cell body (retrograde transport) by cytoplasmic dynein motors. The motility of fluorescent protein-tagged vesicle proteins and organelles can be studied by live-cell imaging in isolated primary neurons or animals such as *Caenorhabditis elegans* and *Drosophila melanogaster*[157].

Melanophores

Fish and frogs contain melanophore cells that are packed with pigment granules called melanosomes. The cellular distribution of melanosomes is under hormonal control, giving the animals the ability to camouflage. Cells become darker on melanosome dispersion owing to plus end-directed transport by the Kinesin-2 heterotrimer KIF3A–KIF3B–kinesin-associated protein (KAP) followed by transport on actin filaments by myosin V. Conversely, melanosome aggregation makes the cells translucent or grey and is due to minus end-directed transport by cytoplasmic dynein[158].

Lipid droplets

Lipid droplets are energy storage sites and regions of steroid biogenesis. In *D. melanogaster* embryogenesis, lipid droplets undergo developmentally regulated changes in their motility. In phase I there is no net movement. In phase II a kinesin motor accomplishes net plus end transport. In phase III, cytoplasmic dynein mediates net minus end transport[159].

Intraflagellar transport

The biogenesis and maintenance of cilia and flagella depend on intraflagellar transport, in which cargo particles are transported along axonemal microtubules by the Kinesin-2 family members KIF3A–KIF3B–KAP, KIF17 and *C. elegans* osmotic avoidance abnormal protein 3 (OSM-3), and the cytoplasmic dynein motors. Intraflagellar transport was first identified in *Chlamydomonas reinhardtii* and has since been studied in *C. elegans*, *Tetrahymena thermophila* and cultured mammalian cells[160].

Evidence that a MAPK pathway also regulates dissociation of motor–cargo linkages (FIG. 2a; step 3) during IFT comes from work in several organisms. A screen for mutants defective in IFT in the ciliated endings of *C. elegans* chemosensory neurons identified the dye filling defective gene *dyf-5*. DYF-5 is a predicted Ser/Thr protein kinase that shows extensive homology to eukaryotic MAPKs of the MAK subfamily, as well as to the *Chlamydomonas reinhardtii* long flagella protein LF4 and the *Leishmania mexicana* MPK9 protein. *dyf-5*, *LF4* and *MPK9* loss-of-function mutants all have elongated cilia or flagella, which suggests that these kinases regulate the termination of IFT events, perhaps by facilitating the dissociation of Kinesin-2–cargo complexes[61–63]. Consistent with this hypothesis, the heterotrimeric Kinesin-2 IFT motor accumulates at the distal end of the cilium in *dyf-5* mutants rather than displaying its normal restriction to the ciliary middle segment[63]. Taken together, these studies from diverse organisms and experimental systems suggest a general principle in which MAPK signalling regulates kinesin-driven transport by facilitating the proper spatial and temporal dissociation of motors and their cargos.

Intraflagellar transport
The system for bidirectional movement of ciliary components along the ciliary axoneme by Kinesin-2 and cytoplasmic dynein motors.

Other signalling pathways probably also have important roles in regulating kinesin–cargo interactions in specific cellular contexts. Recent work in mammalian neurons has shown that Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) plays an important part in regulating the dissociation of the homodimeric Kinesin-2 motor KIF17 from its neuronal cargo, *N*-methyl-D-aspartate receptor (NMDAR)-containing vesicles, on reaching their destination (FIG. 2a; step 3). Neuronal excitation leads to Ca^{2+} entry and activation of CaMKII, which then phosphorylates the C-terminal cargo-binding tail domain of KIF17, causing dissociation of KIF17 from its vesicular cargo. Release of the motor–cargo linkage provides additional NMDARs at the postsynaptic density for synaptic development and remodelling[64]. CaMKII also affects neuronal survival by causing dissociation of the Kinesin-4 motor KIF4 from its binding partner poly(ADP-ribose) polymerase 1 (PARP1), thereby freeing PARP1 to enter the nucleus and participate in DNA repair and transcriptional regulation[65]. Finally, the protein kinase glycogen synthase kinase 3β (GSK3β) can directly phosphorylate the KLC subunit of a Kinesin-1 motor and decrease its association with membrane-bound organelles[66].

Together, the recent work demonstrating a role for signalling pathways in regulating the interaction of kinesin motors with their cargos opens up many new and exciting experimental possibilities. Interestingly, elements of the signalling pathways involved in motor regulation can be cargos of the motor or can be independently localized at the destination. Future work will probably yield many more examples of the crosstalk between signalling and trafficking pathways and may provide mechanisms for the coordination of transport events in distinct compartments and in cell polarization.

Regulating the motor–microtubule interaction. Once bound to cargo and activated for transport, the ability of kinesin motors to interact with their microtubule tracks can be influenced by the state of the tracks themselves (FIG. 2a; step 2). Kinesin-1 motors seem to be particularly sensitive to the state of the microtubule track. This was first shown in neurons, where constitutively active Kinesin-1 motors undergo selective translocation to the axonal compartment in response to microtubule cues in the axon initial segment[67,68]. Even in unpolarized cells such as fibroblasts, Kinesin-1 motors distinguish microtubule populations and preferentially associate with stable microtubules marked by specific post-translational modifications of tubulin subunits[69,70] (FIG. 2b). Recent work has indicated that post-translational modifications can differentially regulate Kinesin-1 activity. Acetylation of α-tubulin has a general positive role in influencing Kinesin-1 motors transport events, whereas detyrosination of α-tubulin has a more specific role in directing Kinesin-1 transport to specific cellular destinations[71–75]. Interestingly, although kinesin families share a highly conserved motor domain, they differ in their response to post-translational modifications and microtubule heterogeneity. Unlike Kinesin-1 motors, motors in the Kinesin-2 and Kinesin-3 families do not show a preference for acetylated or detyrosinated microtubules in fibroblasts[69]. Instead, Kinesin-3-driven transport of presynaptic vesicles can be influenced by polyglutamylation of tubulin subunits[76]. Together, this work suggests that the heterogeneity of post-translational modifications can provide a 'tubulin code' for directing

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events along the microtubule polymer, analogous to the 'histone code' that spatially regulates transcriptional events along chromatin[77].

By contrast, non-motor microtubule-associated proteins (MAPs) negatively influence the ability of kinesin motors to interact with their microtubule tracks (FIG. 2c), probably owing to their localization on the surface of the microtubule. Much effort has focused on the role of the MAP tau in regulating motor-driven transport events in neurons, as overexpression of tau interferes with anterograde transport[78–80]. Work *in vitro* has shown that short isoforms and/or the filamentous form of tau is crucial for inhibition of kinesin transport[81,82] and that tau can decrease the rate of attachment of single kinesin motors to microtubules[83], cause detachment of single moving motors[84] and decrease the travel distance and stalling force of multiple motors present on a bead[81]. Together, this work shows that tau can block Kinesin-1 motility, but whether these effects relate to the normal and/or pathophysiological functions of tau remains to be clarified. In addition, it may be too soon to make broad generalizations about the inhibitory effects of MAPs on kinesin motors as recent work in *D. melanogaster* has shown that the MAP Ensconsin stimulates the microtubule-binding and motor activity of Kinesin-1 motors[85].

Regulatory events that abolish the motor–microtubule interaction can be used to position cargos at specific locales. For example, in axons local signals act through increased Ca^{2+} levels to arrest mitochondria in areas that require an energy supply and Ca^{2+} buffering. The anterograde transport and distribution of mitochondria is driven by the KHC subunit of Kinesin-1 motors, which associates with the mitochondrial membrane protein mitochondrial Rho-GTPase (Miro), most likely through the adaptor proteins *D. melanogaster* Milton 1 (or the mammalian homologue trafficking kinesin-binding protein 1 (TRAK1; also known as OIP106)) and *D. melanogaster* Milton 2 (or the mammalian homologue TRAK2; also known as GRIF1)[86–89]. Miro contains two Ca^{2+}-binding EF hands that are crucial for Ca^{2+}-dependent control of mitochondrial movement in cultured hippocampal neurons[90–92]. Recent reports have now provided two different models of how Ca^{2+} relays a stop signal to a Kinesin-1 motor. Wang and Schwarz have shown that Ca^{2+} binding to the EF hands of Miro enables Miro to interact directly with the Kinesin-1 motor domain and thereby interfere with the motor–microtubule interaction[91]. By contrast, MacAskill *et al.* have shown that increased Ca^{2+} levels result in the dissociation of a Kinesin-1 motor from the mitochondrial surface[90]. Whether these two models represent differences between vertebrates and invertebrates or differences in experimental protocols needs to be established. It is interesting to note that plants contain an unusual minus end-directed kinesin motor, the Kinesin-14 kinesin-like calmodulin-binding protein (KCBP), the microtubule binding of which is regulated by the Ca^{2+}-binding protein calmodulin[93]. Binding of Ca^{2+}-activated calmodulin to a regulatory helix at the C-terminus of the KCBP motor domain blocks the microtubule binding site of KCBP[94]. Thus, local Ca^{2+} concentrations may have a similar role in the localization of KCBP cargo delivery.

EF hand
A structural domain in proteins that binds to Ca^{2+} ions.

In summary, the work discussed in this section shows that the regulation of the motor–microtubule interaction involves more than a simple prevention of microtubule association in the autoinhibited state. Rather, this work opens up exciting avenues of further research to investigate how activated motors can 'read' the microtubule surface and respond to post-translational modifications and MAP marks in various experimental settings. Furthermore, we are beginning to understand how localized signalling and other inputs can affect motor conformation to directly regulate the motor–microtubule association and kinesin-dependent transport events.

Regulation of mitotic motors

Kinesin motors that act during mitosis are involved in the formation, organization, stabilization and function of the mitotic spindle (FIG. 3). They also work directly in chromosome alignment and segregation. Here, we focus on recent work aimed at understanding how the activity of mitotic motors is controlled spatially and temporally. At a global level, regulation of mitotic motors involves the control of protein level and activation by cell cycle regulators such as kinases and GTPases. At a local level, many mitotic motors carry out their functions at specific spindle locales. Understanding the mechanisms that control motor localization is therefore important for understanding the regulation of motor activity. However, it is important to note that localization of a kinesin motor within the spindle does not necessarily indicate that the motor is active at that locale. Future work should therefore separate regulation of motor localization from regulation of motor activity.

Regulation of protein levels. For proteins that function during the mitotic phase of the cell cycle, an obvious mechanism of regulation is to control their synthesis and degradation such that they are present only during M phase. Indeed, oscillation of protein levels during the cell cycle has been shown for several motors, including the Kinesin-6 family members mitotic kinesin-like protein 1 (MKLP1; also known as KIF23) and KIF20A (also known as Rab6 kinesin and MKLP2), the Kinesin-7 family members CENPE and *Saccharomyces cerevisiae* Kip2, the Kinesin-8 family member KIF18A, the Kinesin-10 family member KIF22 (also known as KID) and the Kinesin-13 family member mitotic centromere-associated kinesin (MCAK; also known as KIF2C)[9,95–102]. Selective ubiquitylation and degradation of proteins at key points in mitosis is crucial for entry into the next phase, and Kinesin-7, Kinesin-10 and Kinesin-13 motors have been shown to be selectively degraded in anaphase[95,96,101,103]. Changes in protein levels can also be due to increased synthesis, as increased transcription of Kinesin-6 motors at the G1–S transition contributes to their maximal expression in M phase[97,102].

Nuclear or cytoplasmic sequestration. Another mechanism of regulation is to sequester motors away from microtubules or their cargo until the appropriate time in the cell cycle (FIG. 4a). The Kinesin-6 family members MKLP1 and *D. melanogaster* Pavarotti, the Kinesin-8 family member

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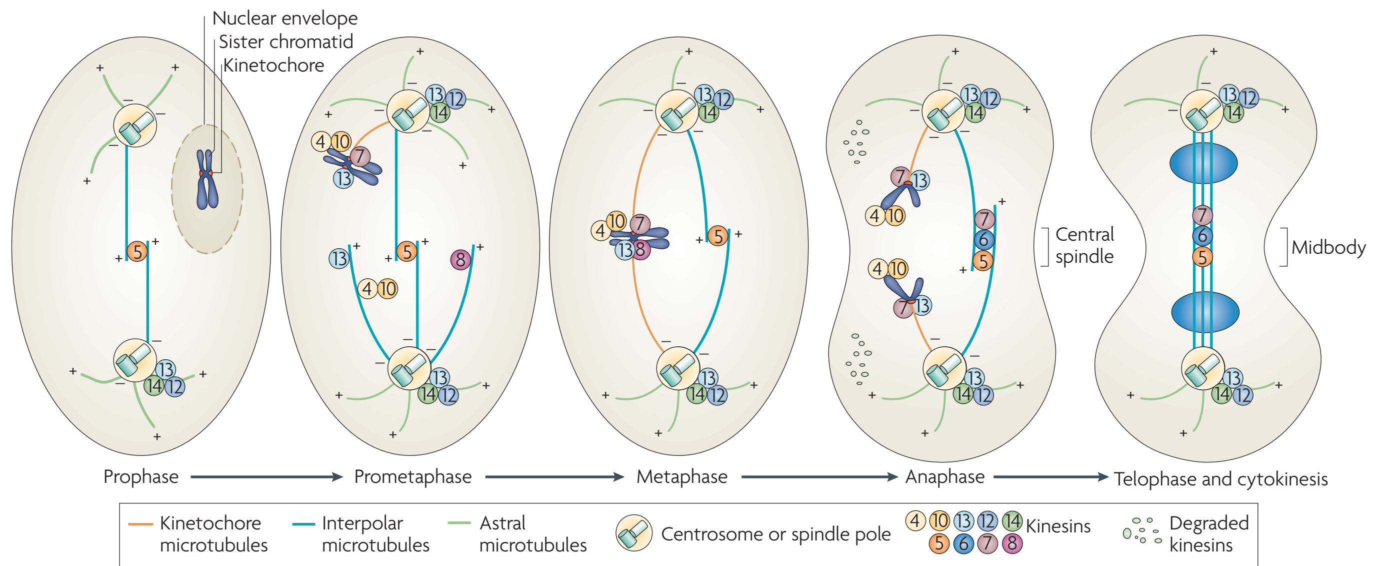

Figure 3 | **Kinesin motor localization during mitosis in mammalian cells.** During prophase, chromosomes condense and the duplicated centrosomes (composed of centrioles and other components) are separated to form the bipolar spindle, probably by Kinesin-5 motors. Kinesin-12, Kinesin-13 and Kinesin-14 motors localize to the spindle poles, where they function in spindle assembly and organization. Nuclear envelope breakdown marks the transition to prometaphase. During prometaphase through to metaphase, Kinesin-5 motors drive spindle pole separation and spindle bipolarity by sliding antiparallel microtubules that extend from the two spindle poles. Localization of Kinesin-7 and Kinesin-13 motors to the kinetochores and of Kinesin-4 and Kinesin-10 motors to the chromosome arms facilitates microtubule capture and chromosomal congression to the metaphase plate. Kinesin-8 motors also congregate at the kinetochore during metaphase to facilitate congression and limit chromosomal oscillations. During anaphase, sister chromatid separation and movement towards the spindle poles are facilitated by the Kinesin-7 and Kinesin-13 motors that are localized at the kinetochore and the Kinesin-13 motors at the spindle poles. As the chromosomes segregate, motors and other kinetochore components are left behind at the central spindle, the formation of which is driven by Kinesin-6 motors. During telophase, these Kinesin-6 motors continue to localize to the midbody and are involved in cytokinesis.

D. melanogaster KLP67A and the Kinesin-14 family member *D. melanogaster* non-claret disjunctional (NCD) are restricted to the nucleus during interphase, probably owing to interactions with the nuclear import proteins importin-α and importin-β[104–106]. Nuclear sequestration prevents inappropriate motor depolymerization or cross-linking activities on cytoplasmic microtubules. The Kinesin-7 motor CENPE, however, is sequestered in the cytoplasm until nuclear envelope breakdown and then localizes to its chromosomal cargo at the kinetochores[107].

Because yeast undergoes a closed mitosis, whereby the nuclear envelope is maintained throughout the process, the components required must undergo nuclear import. In *Schizosaccharomyces pombe*, the nuclear import and export of the Kinesin-8 heterodimer Klp5–Klp6 is controlled to ensure localization to cytoplasmic microtubules in interphase and to the nuclear mitotic spindle during mitosis, although the molecular mechanisms remain to be elucidated[108].

Activation by the small GTPase Ran. A third mechanism of regulation for kinesin motors during mitosis involves the small GTPase Ran, which was first discovered to regulate nucleocytoplasmic shuttling during interphase and is now known to have a crucial role in the formation and organization of the microtubule spindle during mitosis. A high level of active GTP-bound Ran is maintained in the nucleus during interphase and at the chromosomes during mitosis owing to the presence of the chromosome-bound guanine nucleotide exchange factor (GEF) regulator of chromosome condensation 1 (RCC1). Ran-GTP at the chromosomes is thought to release spindle assembly factors that are kept in an inactive state by association with importin-α and importin-β (see REF. 109 for a recent review). The identification of these spindle assembly factors is an important goal, and several kinesins have been shown to function in this manner. During interphase, interaction of importin-α and importin-β with the Kinesin-10 family member KIF22 and the Kinesin-14 family member *X. laevis* C-terminal kinesin 2 (XCTK2) prevents their microtubule-binding and cross-linking activities, respectively. On nuclear envelope breakdown, the high local concentration of Ran–GTP at chromosomes causes the dissociation of importin–kinesin complexes and thereby positively spatiotemporally regulates the activity of Kinesin-10 and Kinesin-14 motors during spindle function[106,110–112] (FIG. 4b).

Recruitment to specific spindle locales in yeast. A fourth mechanism for regulating kinesin motors during mitosis is to control their localization to, and function at, specific sites in the spindle. Recent work on the Kinesin-14 motor Kar3 in *S. cerevisiae* has provided an example of the recruitment of a motor to specific spindle locales

Guanine nucleotide exchange factor
A protein that facilitates the exchange of GDP for GTP in the nucleotide-binding pocket of a G protein.

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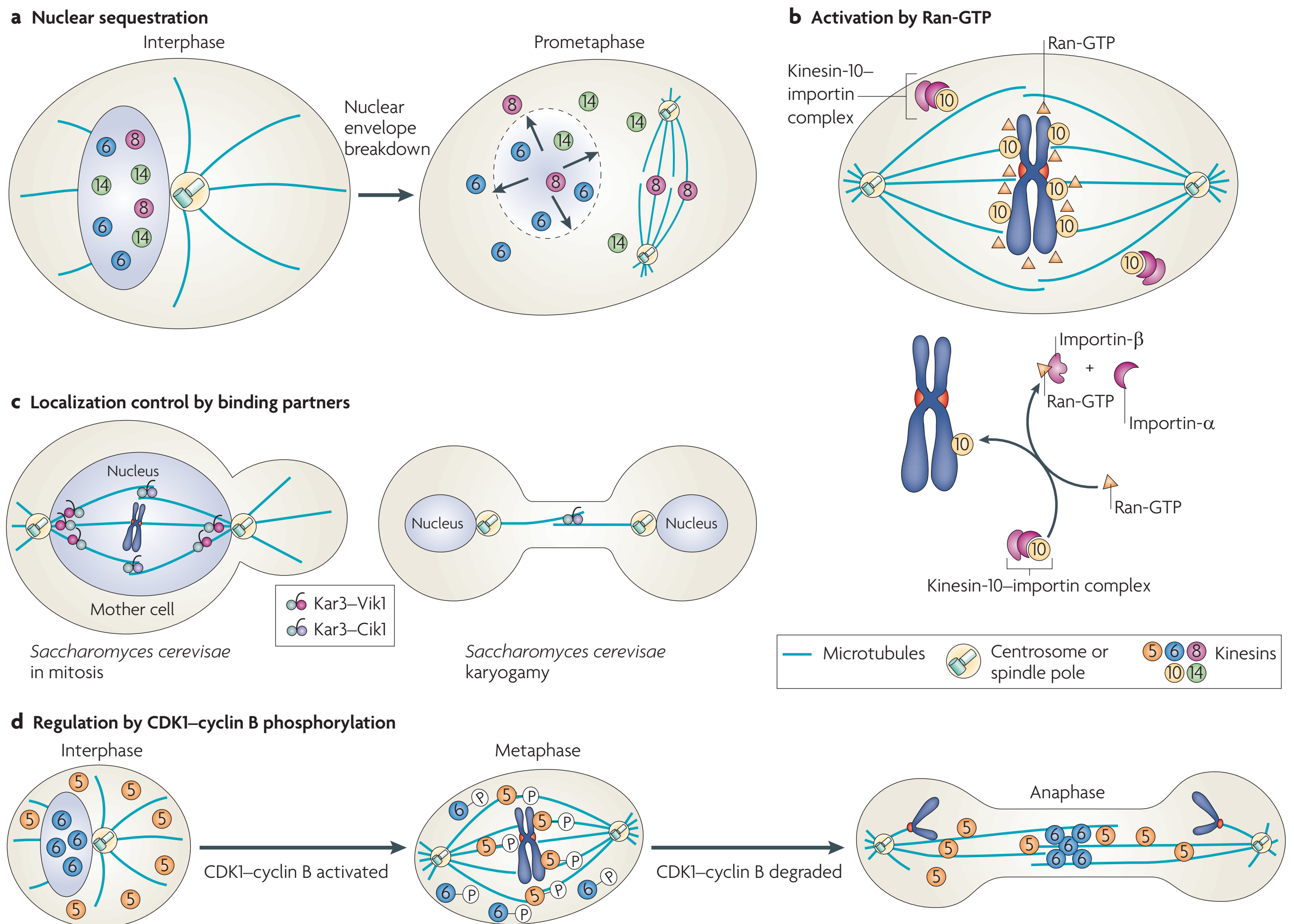

Figure 4 | **Mechanisms of mitotic motor regulation. a** | Nuclear sequestration. During interphase, Kinesin-6, Kinesin-8 and Kinesin-14 motors are sequestered in the nucleus so that cytoplasmic microtubules are protected from their depolymerizing or cross-linking activities. As cells enter mitosis, nuclear envelope breakdown frees these motors to carry out their necessary functions on microtubules in the mitotic spindle. **b** | Activation by Ran-GTP. Kinesin-10 (and Kinesin-14, not shown) motors are kept globally inactive by their association with importin-α and importin-β proteins. During mitosis, the high concentration of Ran-GTP generated around chromosomes releases motor–importin complexes, resulting in a localized activation of Kinesin-10 (and Kinesin-14) motors at the mitotic spindle. **c** | Localization control by binding partners. In *Saccharomyces cerevisiae*, the Kinesin-14 motor Kar3 forms a heterodimer complex with either vegetative interaction with KAR3 protein 1 (Vik1) or chromosome instability and karyogamy protein 1 (Cik1). During mitosis, Vik1 targets Kar3 to spindle poles, whereas Cik1 targets Kar3 to the overlap zone of the spindle. During karyogamy, a s horter isoform of Cik1 targets Kar3 to the plus ends of cytoplasmic microtubules for fusion of the two haploid nuclei. **d** | Regulation by CDK1–cyclin B phosphorylation. In interphase cells, cytoplasmic Kinesin-5 motors are inactive and Kinesin-6 motors are sequestered in the nucleus. On nuclear envelope breakdown and activation of CDK1–cyclin B during early stages of mitosis, CDK1–cyclin B phosphorylation of a Kinesin-5 motor targets it to overlap microtubules for bipolar spindle formation. At the same time, CDK1–cyclin B phosphorylation of a Kinesin-6 motor inhibits its activity, thereby preventing premature central spindle formation. Once CDK1–cyclin B is degraded at the onset of anaphase, Kinesin-6 motors are dephosphorylated and localize to the central spindle, where they participate in cytokinesis.

in order to carry out distinct functions. Kar3 forms a heterodimer with either chromosome instability and karyogamy protein 1 (Cik1) or vegetative interaction with KAR3 protein 1 (Vik1), noncatalytic accessory polypeptides that regulate the localization and function of Kar3 during the mitotic phase of vegetative growth and nuclear fusion during karyogamy[113]. During mitosis, a longer isoform of Cik1 targets Kar3 to the central spindle to cross-link and stabilize overlapping antiparallel microtubules, whereas Vik1 targets Kar3 to the spindle poles to cross-link parallel microtubule ends for organization of the bipolar spindle[114–117] (FIG. 4c). During karyogamy, a shorter isoform of the Cik1 subunit is expressed that lacks a nuclear localization signal and targets Kar3 to the plus ends of cytoplasmic microtubules, where minus end force generation is coupled to microtubule depolymerization activity[117,118] (FIG. 4c). Thus, it seems that association with different accessory polypeptides can bias this Kinesin-14 motor towards specific subcellular locales and influence cross-linking or depolymerase activity.

Karyogamy
The process during mating in which two haploid nuclei come together and fuse to form a diploid nucleus.

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Recruitment to specific spindle locales in animals. In animal cells, binding to specific partner proteins can also serve to localize kinesin motors to specific spindle locales. In addition, motor localization can be regulated by kinases that control cell cycle progression, including cyclin-dependent kinases (CDKs), Aurora kinases and Polo-like kinases (PLKs).

The first step in spindle assembly (FIG. 3; prophase) requires members of the Kinesin-5 family that cross-link and slide adjacent microtubules, resulting in the formation of a bipolar spindle. Association of Kinesin-5 motors with microtubules is enhanced by phosphorylation by the CDK1–cyclin B kinase complex[46,104,119–121] (FIG. 4d). Kinesin-5 motors are probably also regulated by other kinases that drive mitotic progression[46,122–124]. For example, in *C. elegans*, Aurora B phosphorylation of Kinesin-5 motors has been suggested to regulate their localization to spindles[123]. In mammalian cells, the NIMA kinase NEK6 phosphorylates a subset of Kinesin-5 motors that are localized at spindle poles and regulates the activity of motors at this site[124]. Spindle assembly in *X. laevis* extracts also requires the Kinesin-12 family member KLP2 (also known as KIF15A), a plus end-directed motor required for centrosome separation. Localization to spindle poles requires interactions of the C-terminal tail domain of KLP2 with at least two accessory factors, targeting protein for KLP2 (TPX2) and the dynein–dynactin complex[125–127].

Once a bipolar spindle is assembled, spindle microtubules and associated motors function to attach chromosomes to both spindle poles and align them at the metaphase plate (FIG. 3; metaphase). At least five kinesin families have been shown to function at this stage: Kinesin-4, Kinesin-7, Kinesin-8, Kinesin-10 and Kinesin-13. Localization of the Kinesin-7 motor CENPE to kinetochores is crucial for microtubule capture, mitotic checkpoint signalling and chromosome congression, and regulation of CENPE has therefore been an important area of research. Localization of CENPE to the outer kinetochore is facilitated by the interaction with kinetochore proteins of the NDC80 complex[128], sumoylation of CENPE and associated proteins[129], and interaction with septins, a conserved family of polymerizing GTPases[130]. In addition, the interaction of kinetochore-localized CENPE with spindle microtubules can be influenced by prenylation of the C-terminus of CENPE[131,132].

Proper attachment and alignment of chromosomes at the metaphase plate also requires the depolymerase activity of the Kinesin-13 motors KIF2A and MCAK. MCAK functions downstream of the protein kinase Aurora B, a component of the chromosomal passenger complex[133,134], to correct improper chromosome–microtubule attachments. Thus, it is important to decipher the mechanisms by which Aurora B regulates the localization and activity of MCAK. Using *in vitro* assays and mass spectrometry, several groups identified residues on MCAK that are phosphorylated by Aurora B[135–137]. Unexpectedly, Aurora B phosphorylation of MCAK had no effect on localization of MCAK to the inner centromere but did inhibit its microtubule depolymerization activity[135–137]. It therefore seems that Aurora B phosphorylation facilitates the loading of inactive Kinesin-13 motors at the inner centromere, thereby positioning a depolymerase for rapid release of improper microtubule attachments. Several lines of evidence support this model. First, phosphorylation of MCAK seems to shift its localization in the centromeric region[136]. Second, the ratio of hypophosphorylated to phosphorylated Ser196 of *X. laevis* MCAK is higher at sites of merotelic than amphitelic centromeres[138]. Finally, using *X. laevis* extracts and site-specific mutants of MCAK, it has been shown that phosphorylation of Thr95 promotes MCAK localization to chromosome arms during G2 phase, phosphorylation of Ser196 reduces binding of MCAK to chromosome arms on entering mitosis, and phosphorylation of Ser110 and dephosphorylation of Thr95 targets MCAK to centromeres[139]. Thus, a precise generation of phospho-variants of MCAK is important for the spatial and temporal regulation of MCAK localization and function. Activation of Kinesin-13 motors also involves inner centromere KINI stimulator (ICIS), a microtubule-associated protein in mitotic extracts that stimulates Kinesin-13 depolymerase activities[140,141]. In addition, a recent study has shown that the Kinesin-13 motor KIF2A is regulated by opposing phosphorylation events, in which Aurora A negatively regulates and PLK1 positively regulates its depolymerase activity[142].

Late phases of mitosis require the formation of the central spindle for positioning of the contractile ring and completion of cytokinesis (FIG. 3; anaphase and telophase). Although motors involved in assembly of the bipolar spindle and chromosome alignment localize to the central spindle, they are not required for assembly of the central spindle. Rather, members of the Kinesin-6 family bind to and cross-link overlapping antiparallel microtubules for central spindle formation in early anaphase. Prior to this, Kinesin-6 motors are kept inactive by the mitotic kinase CDK1–cyclin B complex (FIG. 4d). Phosphorylation by CDK1–cyclin B reduces the activity of Kinesin-6 motors and their affinity for microtubules and prevents premature association of Kinesin-6 motors with the chromosomal passenger complex and the central spindle[104,141,143]. At anaphase, degradation of CDK1–cyclin B and activation of Aurora B and PLK1 kinases results in the localization of Kinesin-6 motors to the central spindle[144–149]. It will be important to determine how kinases that function in late stages of mitosis regulate the Kinesin-6 motors that are involved in central spindle formation. The mechanisms are likely to be complex as multiple mechanisms contribute to the regulation of kinesin motors to ensure that genome segregation during mitosis is coordinated with cellular separation during cytokinesis.

Conclusions and future directions

Genetic and molecular biology approaches have led to the identification of kinesin motor families that have important roles in a range of cellular processes. Biochemical and biophysical approaches have shown that evolution has adapted the core catalytic domain of kinesins for different enzymatic reactions on microtubule polymers, including motility along the surface

Centrosome
A microtubule organizing centre that contains centrioles and the pericentriolar material that nucleates microtubule polymerization. It duplicates during S phase to create the spindle poles for mitosis.

Metaphase plate
The plane at mid-spindle, perpendicular to the spindle microtubules, where the chromosomes are positioned during metaphase.

Kinetochore
A multiprotein complex that assembles on the centromeric region of chromosomes and attaches to spindle microtubules. The inner kinetochore contains proteins that are tightly and persistently associated with centromeric DNA, whereas the outer kinetochore contains dynamic protein components that interact with microtubules during mitosis.

Mitotic checkpoint
A control mechanism in metaphase that ensures that all chromosomes are properly attached to both spindle poles before the cell can proceed into anaphase.

Chromosome congression
The process by which chromosomes attach to spindle microtubules and align or 'congress' to the metaphase plate. It requires both microtubule dynamics and kinesin motor activities.

Prenylation
A post-translational modification of a protein by the attachment of prenyl moieties (geranyl, farnesyl or geranylgeranyl groups) to a C-terminal Cys residue.

Chromosomal passenger complex
A multiprotein complex that localizes to the kinetochore until early anaphase, when it switches to the central spindle. It consists of the Aurora B kinase, inner centromere protein, survivin and Borealin (also known as Dasra and CDCA8).

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Merotelic
Pertains to an incorrect spindle attachment in which a single kinetochore is attached to microtubules from both spindle poles.

Amphitelic
Pertains to a proper spindle attachment in which each sister kinetochore is attached to the microtubules from its nearest facing spindle pole.

and depolymerization of microtubule tracks. Thus, the groundwork has been laid for understanding how regulation of kinesin activity provides the spatial and temporal accuracy of motor-driven events during cell division, cell motility, intracellular transport and ciliary assembly and function.

Common themes that have emerged from studies on kinesin regulation include the autoinhibitory mechanisms that prevent unnecessary ATP hydrolysis and congestion of microtubule tracks. For transport motors, the idea is emerging that heterogeneity of and/or obstacles on the microtubule track can regulate kinesin motors. Further work is needed to understand the mechanisms by which the microtubule surface influences kinesin activity and kinesin-mediated transport events in cells, as well as whether microtubule diversity affects mitotic motors. Genetic and proteomic approaches have provided examples of how signalling pathways regulate transport events in cells. Many more intersections between signalling and trafficking are likely to be discovered in the coming years. Other areas of motor regulation that will probably be the focus of future research include spatial and temporal control of cargo loading and unloading in distinct cellular locales, how the activities of multiple motors present on the same cargo are coordinated and the coupling of transport to other cellular events such as signalling, protein synthesis and cell remodelling.

Signalling molecules are crucial for the spatial and temporal regulation of the cell cycle, and recent years have begun to reveal specific phosphorylation events that regulate the kinesin motors involved in the assembly and function of the mitotic spindle. Important goals are to identify the crucial phosphorylation sites and to decipher how the phosphorylation events relate to kinesin motor localization and activity. Another important mechanism that governs mitotic motors is the regulation by Ran GTPase. We are clearly only at the beginning of elucidating the spindle assembly factors, including kinesin motors, that function downstream of Ran–GTP.

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Acknowledgements

We are grateful to D. Cai, J. Howard, C. Walczak and S. Gilbert for helpful discussions.

DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
dyf-5
Protein Data Bank: http://www.rcsb.org
1TUB
UniProtKB: http://www.uniprot.org
CaMKII | CDK1 | CENPE | Cik1 | FEZ1 | GSK3β | JIP1 | Kar3 | KIF1A | KIF11 | KIF13B | KIF17 | KIF18A | KIF20A | KIF22 | Kip2 | KLP2 | Klp5 | Klp6 | KLP67A | LF4 | Miro | MKLP1 | MPK9 | MPS1 | NCD | NEK6 | OSM-3 | PARP1 | Pavarotti | Ran | RCC1 | TRAK1 | TRAK2 | Vik1 | XCTK2

FURTHER INFORMATION

Kristen J. Verhey's homepage: http://www.med.umich.edu/cdb/people/kjverhey.html

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