Role and regulation of kinesin-8 motors through the cell cycle

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Abstract Members of the kinesin-8 motor family play a central role in controlling microtubule length throughout the eukaryotic cell cycle. Inactivation of kinesin-8 causes defects in cell polarity during interphase and astral and mitotic spindle length, metaphase chromosome alignment, timing of anaphase onset and accuracy of chromosome segregation. Although the biophysical mechanism by which kinesin-8 molecules influence microtubule dynamics has been studied extensively in a variety of species, a consensus view has yet to emerge. One reason for this might be that some members of the kinesin-8 family can associate to other microtubule-associated proteins, cell cycle regulatory proteins and other kinesin family members. In this review we consider how cell cycle specific modification and its association to other regulatory proteins may modulate the function of kinesin-8 to enable it to function as a master regulator of microtubule dynamics.

Keywords Kinesin-8 · Kif18A · Kip3 · Klp5 · Depolymerase · Microtubule length

Introduction

Multiple roles for kinesin-8 motors during the cell cycle

Microtubules perform essential functions throughout the cell cycle, most noticeably for chromosome segregation and cytokinesis during M phase and vesicle trafficking and

maintenance of cell polarity during interphase. Precise regulation of microtubule length is crucial for all of these cellular activities. Although the classical function of kinesin motors is to transport cargo along microtubules, members of the kinesin-8 family have instead emerged as key evolutionarily conserved regulators of microtubule length, in that they can act both as highly processive plus end directed microtubule motors but also as regulators of dynamic instability at the microtubule plus end (+TIP). Despite this, it is not presently clear how kinesin-8 molecules ensure precise microtubule length control at different cellular locations and at different times during the cell cycle.

Members of the kinesin-8 family, which include the human Kif18A, Kif18B, budding yeast Kip3, fission yeast Klp5 and Klp6 and fruit fly Klp67A proteins, share a similar domain architecture with an N-terminal motor domain, neck linker region, coiled-coil domain that mediates dimerization and a C-terminal tail of variable length (West et al. 2001; Unsworth et al. 2008; Peters et al. 2010; Su et al. 2011) (Table 1; Fig. 1). During mitosis many, but not all, of these proteins localise to the plus end of kinetochore microtubules indicative of a conserved mitotic function. Suppressing the expression or deleting these motors leads an increase in mitotic spindle length, a failure of chromosomes to align on the metaphase plate and a protracted delay in the onset of anaphase, due to activation of the spindle assembly checkpoint (Straight et al. 1998; Rischitor et al. 2004; Goshima et al. 2005; Mayr et al. 2007; Stumpff et al. 2008; Wargacki et al. 2010; Jaqaman et al. 2010). During early mitosis, sister kinetochore pairs undergo rapid and co-ordinated oscillations, alternating between moving towards and away from the spindle pole (Skibbens et al. 1993; Rieder and Salmon 1994). Depletion of Kif18A or expression of motor inactive Kif18A mutants lead to an increase in amplitude of these

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Table 1 Cellular function of kinesin-8 motors

Species	Gene	Function	Reference
<i>Ashbya gossypii</i>	KIP3	Suppression of nuclear oscillations Cytoplasmic microtubule length control	Grava and Philippsen (2010)
<i>Aspergillus nidulans</i>	KIPB	Anaphase A length Mitotic spindle alignment	Rischitor et al. (2004)
<i>Drosophila melanogaster</i>	KLP67A	Chromosome congression Spindle length Mitochondrial distribution Central spindle stability and formation Spindle elongation	Savoian et al. (2004) Gandhi et al. (2004); Savoian and Glover (2010) Gandhi et al. (2004) Gatt et al. (2005) Wang et al. (2010)
<i>Homo sapiens</i>	KIF18A	Chromosome congression Chromosome oscillation Microtubule dynamic dampening Overexpression in breast, colorectal and lung cancer Human height association	Mayr et al. (2007) Stumpff et al. (2008); Jaqaman et al. (2010) Du et al. (2010) Zhang et al. (2010); Tooker et al. (2011); Nagahara et al. (2011) Kim et al. (2012)
<i>Mus musculus</i>	KIF18B	Astral microtubule length regulation	Tanenbaum et al. (2011); Stout et al. (2011)
	KIF18A	Male fertility	Liu et al. (2010)
	KIF18B	Mutated in mouse melanoma cells, induces immune response	Castle et al. (2012)
	KIF19A	Ciliary length control Female fertility	Niwa et al. (2012)
<i>Saccharomyces cerevisiae</i>	KIP3	Spindle length	Straight et al. (1998); Woodruff et al. (2010, 2012)
		Kinetochore congression	Wargacki et al. (2010); Su et al. (2011)
		Spindle orientation	Cottingham and Hoyt (1997); DeZwaan et al. (1997)
<i>Schizosaccharomyces pombe</i>	KLP5	Metaphase establishment	West et al. (2002); Garcia et al. (2002)
	KLP6	Meiosis progression	West et al. (2001)
		Spindle assembly checkpoint silencing	Meadows et al. (2011)
		Cytoplasmic microtubule regulation	West et al. (2001)

oscillations and a failure to congress to the metaphase plate, indicating that Kif18A aids chromosome bi-orientation by directly controlling kinetochore microtubule dynamics (Stumpff et al. 2008). Importantly, loss of kinesin-8 function in yeast, fruit flies and human cells causes high rates of chromosome mis-segregation during mitosis (West et al. 2002; Garcia et al. 2002; Savoian and Glover 2010; Wargacki et al. 2010).

In human cells the expression of Kif18A and Kif18B mirrors that of Cyclin B1 being low or undetectable in G1 and high at G2/M phase (Mayr et al. 2007; Lee et al. 2010). Although it is not known how Kif18A levels are modulated, it is intriguing that Kif18A interacts with the anaphase promoting complex (APC/C) (Sedgwick et al. 2013), the E3 ubiquitin ligase that is responsible for Cyclin B1 destruction. The importance of properly regulating kinesin-8 function is highlighted by the fact that human Kif18A is overexpressed in colorectal tumours with its overexpression correlating

with lymphatic invasion, lymph node metastasis and venous invasion and, secondly, that knockdown of Kif18A function reduces the proliferation of cancer cell lines (Nagahara et al. 2011). Kif18B, on the other hand, is nuclear during interphase and localizes to astral MTs during early mitosis. Loss of Kif18B causes an increase in the number and length of astral MTs, suggesting Kif18B is an important modulator of astral MT dynamics (Tanenbaum et al. 2011; Stout et al. 2011).

The functions of kinesin-8 molecules are not restricted to mitosis. During interphase fission yeast microtubule bundles, which are nucleated from MTOCs (microtubule organising centres) surrounding a centrally located nucleus, grow towards both cell ends to deposit factors that are required for the maintenance of cell polarity and to maintain the nucleus in the centre of the cell (Martin 2009; Chang and Nurse 1996; Tran et al. 2000, 2001). In the absence of the Klp5 or Klp6 motors some interphase

Fig. 1 Schematic of Kinesin-8 molecules. Human (Kif18A, Kif18B), *S. cerevisiae* (Kip3) and *S. pombe* (Klp5, Klp6) proteins are shown. The motor domains (blue) were defined by BlastP (Altschul et al. 1990) and aligned with Clustal Omega (Sievers et al. 2011). The white ‘slashes’ indicate that the motor domains from Kip3, Klp5 and Klp6 are longer than that for Kif18A and Kif18B. The secondary microtubule binding

domains in the tail regions of Kif18A and Kip3 are shown in *dark hashed blue* (Weaver et al. 2011; Su et al. 2011). The binding sites for type-1-phosphatase (PP1) and EB1 are shown in *orange* and *black*, respectively. *Green lines* indicate *in vivo* protein phosphorylation sites identified by mass spectrometry (www.phosphosite.org; www.phosphogrid.org; Koch et al. 2011). (Color figure online)

microtubules fail to pause at the cell end and continue to grow, resulting in long microtubules that bend around the cell cortex. This results in a defect in cell polarity particularly in elongated cells (West et al. 2001). Similarly loss of Kip3 in budding yeast interferes with productive interaction of cortical microtubules with the bud cell cortex (Gupta et al. 2006), leading to defects in spindle positioning.

Microtubule depolymerase or suppressor of microtubule dynamicity?

To understand how kinesin-8 molecules regulate microtubule length we first need to review the properties of microtubules that underlie their dynamic instability. Microtubules are formed of α - and β -tubulin heterodimers which form linear proto-filaments which associate together to form a hollow cylinder (Mandelkow and Mandelkow 1994). Microtubules exhibit polarity with the β -tubulin at the ‘plus’ end and α -tubulin at the ‘minus’ end. *In vivo* microtubule growth and shrinkage occurs primarily from the plus end. Importantly, microtubules undergo periods of growth before stochastically switching (microtubule catastrophe) to periods of shrinkage followed by return to periods of growth (microtubule rescue). GTP-bound α,β -tubulin dimers are added to the growing plus tip of a microtubule. Once bound the GTP bound to β -tubulin undergoes hydrolysis following a lag period (Nogales et al. 1998). For this reason the growing plus tip is said to have a “GTP-cap” whereas the

rest of the lattice is composed of GDP- β -tubulin. GTP hydrolysis induces a conformational change in the α,β -tubulin dimer that imposes stress on the microtubule. Once the GTP-cap is removed the GDP-bound α,β -tubulin dimers adopt a bent conformation that causes proto-filaments to peel away from the microtubule, which destabilizes the microtubule plus-end and initiates shrinkage (Mitchison and Kirschner 1984; Wang and Nogales 2005). Catastrophe and rescue frequencies, together with growth and shrinkage rates, are the four parameters commonly used to describe microtubule dynamics (Desai and Mitchison 1997).

Much of our current understanding of kinesin-8 action relies on biophysical analysis of the budding yeast Kip3 and human Kif18A proteins. Initial studies indicated that Kip3 and, to a lesser extent Kif18A, can accelerate the depolymerisation of GMPCPP (guanylyl-(α,β)-methylene-diphosphonate) stabilised porcine and bovine microtubules, indicative of intrinsic microtubule depolymerase activity (Hyman et al. 1992; Gupta et al. 2006; Varga et al. 2006; Mayr et al. 2007). However, subsequent studies showed that Kif18A does not possess intrinsic depolymerase activity but instead prevents both the growth and shrinkage of microtubules from the plus tip of dynamic microtubules (Du et al. 2010). Crystallographic studies also argue against a role for Kif18A as a microtubule depolymerase. The loop 2 region in the motor domain of kinesin-13, a well-established microtubule depolymerase, is thought to stabilise the curved conformation of tubulin and contains a crucial KVD motif which is necessary for the depolymerase activity (Ogawa

et al. 2004; Shipley et al. 2004; Tan et al. 2008; Asenjo et al. 2013). Kif18A also contains an extended loop 2 region but this lacks the critical KVD residues, arguing it performs a different function (Peters et al. 2010). Although Kip3 does not depolymerise taxol-stabilised GMPCPP microtubules in vitro, the end residence time of individual Kip3 molecules at the plus end inversely correlates with Kip3 concentration. This has led to the proposal that Kip3 depolymerises microtubules in a cooperative manner, in that incoming Kip3 motors “bump-off” previously bound Kip3 at the plus end, with the bumped off motors removing tubulin heterodimers. Unfortunately, the effect of Kip3 on dynamic microtubules is rather more complex, since microtubules that had been growing for a longer period of time are more likely to undergo catastrophe (Gardner et al. 2011). Nevertheless, addition of Kip3 causes dynamic microtubules to undergo catastrophe at shorter lengths, indicating that Kip3 also destabilises dynamic microtubules in vitro (Gardner et al. 2011).

Wagging the tail: motor processivity and microtubule length control

Kinesin-8 motors are amongst the most processive of the kinesin superfamily. Kip3 has been reported to take up to 1,500 steps before dissociating (Varga et al. 2006). Recently, the processivity of both Kip3 and Kif18A motors has been found to be dependent on a second microtubule-binding region in the non-catalytic C-terminal tail regions of both proteins (Stumpff et al. 2011; Su et al. 2011; Mayr et al. 2011; Weaver et al. 2011). Deletion or mutation of

these domains prevents the accumulation and reduces the dwell time of Kif18A and Kip3 at microtubule plus ends in vitro and in vivo. Moreover, Kif18A and Kip3 motors that lack this domain are unable to control microtubule length or support Kif18A or Kip3 function in vivo (Stumpff et al. 2011; Su et al. 2011; Weaver et al. 2011). In addition to aiding motor processivity the tail of Kip3 has been proposed to be able to stabilise microtubules. Kip3 mutants, in which the tail is replaced by a leucine zipper, have higher shrinkage rates and decreased rescue rates than wild type Kip3 (Su et al. 2011). These observations have lead researchers to propose a model by which kinesin-8 motors act as ‘microtubule rulers’ (Varga et al. 2009). In this model kinesin-8 molecules bind on the microtubule lattice and move processively towards the microtubule plus end where they accumulate. The processive movement requires both the motor activity and the C-terminal microtubule binding domain. As longer microtubules provide more binding sites for kinesin-8 motors, the accumulation of motors at the plus end is dependent on microtubule length, but so is the propensity to undergo microtubule catastrophe, via co-operative action of motors at the plus end (Varga et al. 2006, 2009; Gardner et al. 2011). Consistently, the rate of Kip3-induced microtubule depolymerisation linearly correlates with Kip3 flux to the plus end (Varga et al. 2009). As the microtubule shrinks kinesin-8 molecules are lost. On shorter microtubules, which accumulate a lower concentration of motor at the plus tip, the microtubule stabilising effects of the C-terminal tail out-compete the destabilising activity of the motor resulting in microtubule rescue (Su et al. 2011) (Fig. 2).

Fig. 2 Model of microtubule length control by Kinesin-8. 1 Kinesin-8 either binds directly to the lateral surface of the microtubule and uses its motor activity to reach the plus tip or, alternatively, binds directly to the plus tip. 2 The concentration of Kinesin-8 molecules at the plus tip increases with increasingly microtubule length. 3 At a

critical concentration, incoming kinesin-8 molecules bump off tip associated motors in combination with tubulin dimers and so causes microtubule catastrophe. 4 As the microtubule shrinks the tail region of Kinesin-8 stabilises microtubule tips and so causes microtubule rescue. Figure adapted from (Su et al. 2011, 2012)

Klp5–Klp6: an exception to the rule?

At present it is not clear whether the mechanism of microtubule length control, derived from *in vitro* studies of the budding yeast Kip3 and human Kif18A motors, is applicable to all cell cycle roles of kinesin-8 or to all members of the kinesin-8 family. Fission yeast contains two proteins of the kinesin-8 family, Klp5 and Klp6, which form a complex (Garcia et al. 2002) that binds to and regulates microtubules at all locations through the cell cycle (West et al. 2001). Notably, however, full length heterodimeric Klp5–Klp6 are not processive motors *in vitro* (Grissom et al. 2009; Erent et al. 2012). This may be because, when expressed in either bacteria or baculovirus, the Klp5–Klp6 complex lacks either essential modifications or addition as-yet-unidentified component(s) that are important for motor processivity *in vivo*. Moreover, in *in vitro* motility assays, Klp5–Klp6 heterodimers slide microtubules more slowly than the growth rate of microtubule plus ends *in vivo* (Erent et al. 2012). As it stands these properties are incompatible with a model by which Klp5–Klp6 controls the frequency of microtubule catastrophe dependent solely as a function of microtubule length. One possibility is that the rate of Klp5–Klp6 movement on the lattice is set just below the maximum rate of microtubule tip growth so that Klp5–Klp6 motors only accumulate at the plus tips of paused microtubules. This is consistent with the observations that both the pausing of microtubule growth, microtubule catastrophe, and the accumulation of Klp5–Klp6 at the plus tips of interphase microtubules is more prevalent when microtubule tips near the cell end cortex, irrespective of microtubule length (Tischer et al. 2009). Indeed it has been suggested that compressive forces, imposed by physical interaction of the growing microtubule tips with the cell end, may cause microtubules to pause by physically inhibiting new tubulin dimer incorporation into the microtubule tip (Tischer et al. 2009). Although such a model is difficult to disprove it does not explain why microtubules in cells lacking the Tea1 cell polarity factor fail to pause at cell ends (Mata and Nurse 1997). An alternative, albeit untested, hypothesis is that the action of Klp5–Klp6 in accelerating catastrophe at cell ends is dependent, directly or indirectly, on productive interaction of the microtubule plus tip bound Tea2–Tip1–Tea1 complex with the cell end cortex.

The kinesin-8 interactome: collaborators and modulators

Increasing evidence suggests that kinesin-8 motors do not work in isolation but in collaboration with other MAPs and motor proteins to control microtubule mechanics. Some prominent examples are listed below.

EB1 binding

Kip3 and Kif18A are processive plus end directed motors that can accumulate with growing plus tips in the absence of other proteins. By contrast plus end accumulation of Kif18B to the tips of astral microtubules relies on its ability to bind EB1, an evolutionary conserved +TIP protein that tracks microtubule plus tips by recognising the GTP cap, and potentially GDP.Pi tubulin subunits (Carrier et al. 1989; Maurer et al. 2011; Kumar and Wittmann 2012; Zanic et al. 2009). Many EB1 binding proteins contain a conserved T/S-X-IP motif (Honnappa et al. 2009) (where x is any amino acid (Jiang et al. 2012) with a preference for lysine and arginine (Buey et al. 2012)) that is essential for their ability to bind EB1 and track the tips of growing microtubules. Association of EB1 is conferred by the presence of several variants of this motif in the Kif18B tail domain (Tanenbaum et al. 2011; Stout et al. 2011). Deletion of Kif18B leads to longer astral microtubules in a manner that is dependent on its ability to bind EB1 (Tanenbaum et al. 2011; Stout et al. 2011). Since binding of EB1 to microtubule is not dependent on microtubule length, it is reasonable to suggest that Kif18B may not trigger depolymerisation of astral microtubules as a function of astral microtubule length, but rather as a consequence of interaction with the cortex. Association of EB1 to other members of the kinesin-8 family, including Kif18A, has not been reported.

Association to other motor proteins

Association of Kif18B to the plus tips of astral microtubule microtubules relies not only on EB1, but also on MCAK, a member of the kinesin-13 family, which is a non-motile microtubule depolymerase and an EB1-binding protein (Lee et al. 2008; Honnappa et al. 2009). MCAK mutants that fail to bind EB1 lead to a diminished level of Kif18B at the plus tip of astral microtubules. For these reasons it is thought that a multi-protein complex containing the Kif18B, MCAK and EB1 proteins controls astral microtubule length (Tanenbaum et al. 2011). Kif18B is thought primarily to aid the transport of the complex to the plus tip of growing astral microtubule, whereas the associated MCAK kinesin is thought to be responsible for astral microtubule depolymerisation (Tanenbaum et al. 2011). It is not presently clear whether Kif18B has intrinsic depolymerase or microtubule growth suppressing activity as no *in vitro* analysis of Kif18B motors has yet been reported. Nevertheless, this suggests caution should be applied when attributing effects on microtubule dynamics of motor depletion directly to that motor activity. The collaboration between Kif18B with MCAK is not unique. It has been

reported that Kif18A co-immunoprecipitates with CENP-E (kinesin-7), a mitotic kinesin that also localises to the kinetochore during mitosis (Huang et al. 2009). Depletion of Kif18A not only leads to a decrease in CENP-E staining at the kinetochore, but also to a decrease in CENP-E stability. In principle, therefore, some phenotypes associated with knockdown of Kif18A function could be due to a reduction of CENPE at the kinetochore. One should note, however, that the effect of suppressing Kif18A function in human cells, in terms of mitotic spindle length and chromosome dynamics, mirrors closely that seen both in budding yeast cells deleted for KIP3 and in fission yeast cells lacking the Klp5 and Klp6 proteins (Garcia et al. 2002; Wargacki et al. 2010). As both fission yeast and budding yeast lack members of the kinesin-7 and kinesin-13 families, co-operation with other motor proteins may not be a universal feature of all kinesin-8 molecules.

Transport of Stu2 (XMAP215/ch-TOG)

Some evidence suggest that kinesin-8 can transport other regulators of microtubule stability. In budding yeast microtubules are required to capture and retrieve kinetochores during the establishment of chromosome bi-orientation. After association to the lateral surface of microtubules the kinetochore is moved towards the spindle pole by one of two mechanisms. In the first, disassembly of the microtubule tip promotes end-on pulling of the kinetochore at the microtubule tip, a process that is dependent on the kinetochore associated Dam1/DASH complex. In the second, the kinetochore is moved polewards along the lateral surface of the microtubule by the action of the Kar3 motor (Tanaka et al. 2007; Franco et al. 2007). This latter mechanism requires microtubule rescue by Kip3-dependent transport of the Stu2 (XMAP215/ch-TOG), a known microtubule polymerase, to prevent microtubule disassembly and thereby detachment of the microtubule from the kinetochore during retrieval (Gandhi et al. 2011). The mechanism by which Stu2 associates to Kip3 is, however, unknown.

Association to type-1-phosphatase (PP1)

Fission yeast cells lacking Klp5 or Klp6 display resistance to microtubule depolymerising agents, abnormally long spindle microtubules, defective chromosomes congression, a delay in anaphase onset and higher rates of chromosome mis-segregation (West et al. 2001, 2002; Garcia et al. 2002). Importantly, cells expressing a motor defective Klp5–Klp6 complex display all of these phenotypes, indicating that motor activity is important for kinesin-8 function. However it has been shown recently that the non-motor tail domains

of Klp5 and Klp6 bind to type 1 phosphatase (PP1) and that this pool of PP1 helps to regulate both mitotic microtubule mechanics and efficiently silence the spindle checkpoint (Meadows et al. 2011). Specifically, fission yeast cells expressing Klp5 and Klp6 mutants that are unable to bind PP1 are highly sensitive to microtubule depolymerising agents and are profoundly deficient in chromosome bi-orientation, but have normal metaphase spindle length. This suggests the mitotic kinesin-8-PP1 complex contains activities that both stabilise and destabilise microtubules. Importantly, PP1-binding motifs exist in the same tail region of many other members of the kinesin-8 family, including H.s. Kif18A, which interacts with the catalytic subunit of PP1- α by two-hybrid analysis (Colland et al. 2004), but are absent in others, such as Kif18B. In principle the pool of PP1 that is associated to kinesin-8 may dephosphorylate targets at the microtubule-kinetochore interface to stabilise these interactions, once chromosome bi-orientation is achieved. An alternative possibility is that PP1 may dephosphorylate the Klp5 and/or Klp6 motors themselves. Indeed, many phosphorylation sites have been mapped on the Klp5, Kif18A and Kif18B proteins (<http://www.phosphosite.org/>; Koch et al. 2011), although the role of these phosphorylation sites, the identity of the kinases that phosphorylate them and the phosphatases that dephosphorylate them have not been examined. At present it is not clear whether Klp5 and Klp6, like Kip3 and Kif18A, contain a secondary microtubule-binding domain in their non-catalytic C-terminal tails. Nevertheless, modulation of the phosphorylation of such a domain would be an attractive mechanism by which mitotic kinases and phosphatases could regulate the activity of kinesin-8 and thus kinetochore microtubule dynamics.

Co-operation with Ase1 (PRC1/MAP65)

Many, but not all, members of the Kinesin-8 family re-localise from the plus end of kinetochore microtubules to the spindle midzone during anaphase B (DeZwaan et al. 1997; West et al. 2002; Stumpff et al. 2008). *A priori* it might seem counter-intuitive that a motor protein that either acts as a microtubule depolymerase or that suppresses microtubule growth should locate to anti-parallel microtubules during early anaphase, as these microtubules are increasing in length and being slid apart to aid the process of spindle elongation. Only when spindle elongation has been completed would one expect kinesin-8 to aid disassembly of the mitotic spindle. A recent study from Su et al. provides a potential explanation for this conundrum (Su et al. 2013). Using micro-patterning techniques, these researchers generated a spindle-like structure in vitro from two fixed microtubule seeds attached to glass slides. They show that

addition of Kip3 to these microtubules lead to an increase in the buckling of anti-parallel bundles, indicative of a sliding activity, an effect that is dramatically enhanced by addition of Ase1 (also known as PRC1/MAP65), a protein that binds to and bundles anti-parallel microtubules at the spindle midzone (Pellman et al. 1995; Mollinari et al. 2002). Notably, a mutant Kip3 in which its C-terminal tail is replaced by a leucine zipper is able to destabilise microtubules in vitro but lacks sliding activity. Conversely, replacing the neck region with a leucine zipper leads to a mutant Kip3 protein that is able to slide anti-parallel microtubules but that is not able to destabilise microtubules. Thus Kip3 has both the ability to destabilise microtubules and to slide anti-parallel microtubules apart, the latter activity being stimulated by the presence of Ase1 (PRC1/MAP65). Su and colleagues suggest that during early mitosis the sliding and destabilising activities of Kip3 are balanced whereas, during spindle disassembly, the destabilising activity is prominent. The co-operation between Ase1/PRC1/MAP65 and other kinesin motors is well established. For example PRC1 interacts with kinesin-4 at the central spindle and this complex controls both spindle formation and length (Kurasawa et al. 2004; Bieling et al. 2010; Hu et al. 2011). However, further studies will be necessary to determine whether co-operation between Ase1/PRC1/MAP65 and kinesin-8 molecules is a conserved feature of the spindle midzone function in other species.

Perspective

In summary mounting evidence suggests that the properties and/or activity of kinesin-8 motors may vary during the cell cycle, in response to post-translational modifications and/or association to other proteins, to enable the motor complex to accurately modulate microtubule length and dynamics at different cell cycle times and at different cellular locations.

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