Erratum

Kinesins at a glance

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There was an error published in *J. Cell Sci*. **123**, 3420-3423.

We misprinted the sentence in the acknowledgements that states the American Heart Association (AHA) as the funding body supporting F. Jon Kull.

The correct sentence is given below:

The authors' research on kinesins is supported by NIH GM046225 and March of Dimes 1-FY07-443 Grants to S.A.E., and AHA Scientist Development Grant 0330345N to F.J.K.

We apologise for this mistake.

Kinesins at a glance

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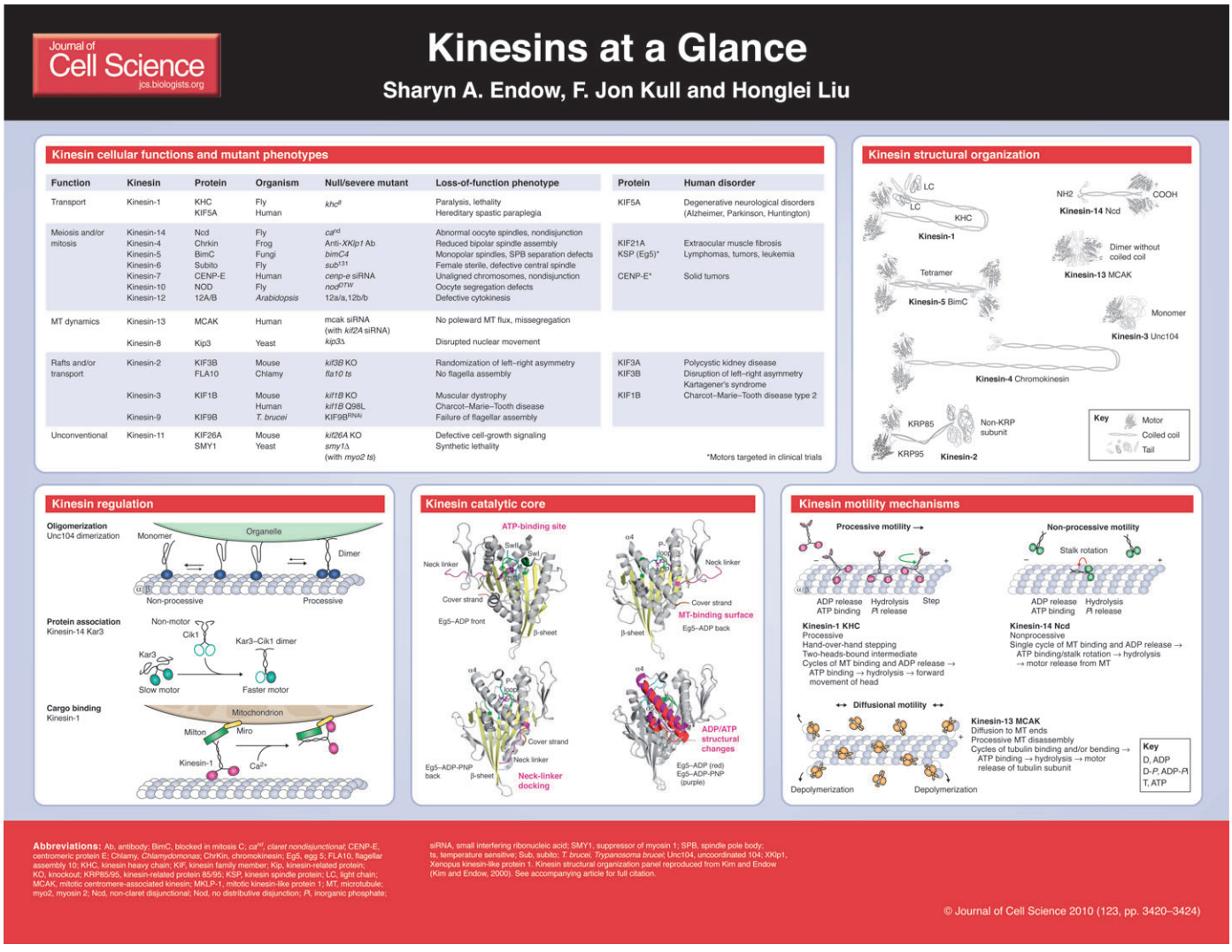
This article is part of a Minifocus on microtubule dynamics. For further reading, please see related articles: 'Microtubule plus-end tracking proteins (+TIPs)' by Anna Akhmanova and Michel O. Steinmetz (*J. Cell Sci.* **123**, 3415-3419), 'Tubulin depolymerization may be an ancient biological motor process' by J. Richard McIntosh et al. (*J. Cell Sci.* **123**, 3425-3434), 'Towards a quantitative understanding of mitotic spindle assembly and mechanics' by Alex Mogilner and Erin Craig (*J. Cell Sci.* **123**, 3435-3445) and 'Post-translational modifications of microtubules' by Dorota Wloga and Jacek Gaertig (*J. Cell Sci.* **123**, pp. 3447-3455).

Kinesin was discovered in 1985 – 25 years ago – based on its motility in cytoplasm extruded from the giant axon of the squid (Allen et al., 1982; Brady et al., 1982; Vale et al., 1985). The purified protein, now known as kinesin-1, consisted of two heavy chains with motor activity that were associated with two light chains, which mediate motor binding to vesicles and other cargo. Vesicle movement was distal to the cell body, towards microtubule plus ends, consistent with the proposal that the motor was the basis of fast axonal transport (Allen et al., 1982; Brady et al., 1982).

For several years, kinesin-1 was the only motor protein known that moved on microtubules towards their plus ends, the opposite direction the previously discovered axonemal dyneins move. Strikingly, many kinesin-related proteins were reported in the early 1990s, soon after the first sequence of a gene encoding a kinesin-1 heavy chain, *Drosophila melanogaster Khc*, was deposited into the public databases (Yang et al., 1989). The predicted KHC protein contained a motor domain with ATP- and microtubule-binding sites, an α-helical coiled-coil dimerization domain (also referred to as the stalk), and a tail that can interact with vesicles or organelles through light chains. A large number of kinesin-related proteins were identified in rapid succession by sequence homology to *Drosophila* KHC. They included the first kinesin-14 proteins, which, despite their sequence homology to kinesin-1, were subsequently demonstrated to be minus-end motors. Screens for kinesins, on the basis of conserved protein motifs, revealed a large number of kinesin-related proteins in a given organism – as many as ~50 in human – each containing a highly conserved motor domain that identified the protein as a kinesin family member.

Phylogenetic analysis defined groups within the kinesin family that perform similar cellular functions in different cells or organisms (Kim



(See poster insert)

and Endow, 2000). A standardized system of kinesin nomenclature was introduced in 2004, renaming the groups by number (Lawrence et al., 2004). There are currently 14 groups and many ungrouped or orphan kinesins. Among these, three kinesins – kinesin-1, kinesin-14 and kinesin-13 – highlight the diverse structure and function of the family.

Kinesin diversity

Kinesin-1, the first-discovered kinesin, has been studied extensively. The development of single-molecule assays and the early finding that single kinesin-1 molecules move processively along microtubules (Howard et al., 1989) made it possible to measure the steps and force produced by single motors. Mutant analysis showed that kinesin-1 has an essential role in vesicle transport in neuronal cells (Saxton et al., 1991). Homologs have been found in a wide range of organisms: from yeast, *Caenorhabditis elegans* and *Drosophila*, to the mouse and human.

Two other kinesins – Ncd, a *Drosophila* kinesin-14, and MCAK, a Chinese hamster kinesin-13 – have been widely studied because of their distinct motor properties. Ncd was the first minus-end kinesin motor reported (Walker et al., 1990; McDonald et al., 1990) and has provided crucial information regarding motor directionality and the mechanism of kinesin function. MCAK was identified in an antibody screen for kinesins and shown to be a centromere-associated protein (Wordeman and Mitchison, 1995). Subsequent studies resulted in the provocative finding that the motor is targeted to microtubule ends where it removes tubulin dimers, destabilizing microtubules and regulating microtubule dynamics (Desai et al., 1999; Wordeman, 2010; Ems-McClung and Walczak, 2010).

Kinesin structural organization and regulation

All kinesins contain a motor domain – the head – usually attached to a stalk and tail, but the position of the head varies – it is at the N-terminus of kinesin-1, C-terminus of kinesin-14 and centrally located in kinesin-13 (Kim and Endow, 2000). Crystal structures revealed invariant folds in divergent kinesins, indicating that the head is highly conserved (Kull et al., 1996; Sablin et al., 1996).

The coiled-coil stalk mediates protein dimerization, although some kinesins, e.g. kinesin-13, lack a stalk but nonetheless exist as dimers. The kinesin-1 stalk contains a flexible region – the hinge – permitting the tail to fold back onto the head, inhibiting motor binding to microtubules (Hackney and Stock, 2000). The stalk also coordinates the kinesin-1 heads, resulting in processive movement along microtubules. Kinesin-5, a homotetrameric motor, contains a stalk formed by interactions between the coiled coils of two anti-parallel dimers (Tao et al., 2006); the motor can bind by its heads to different microtubules to crosslink and slide microtubules in mitosis.

Other kinesins dimerize dynamically by coiled-coil stalk formation, thereby regulating motor activity. *C. elegans* kinesin-3 Unc104 exists as a monomer, but, remarkably, forms dimers with velocities much faster than kinesin-1 (Tomishige et al., 2002). The monomer neck – the region of the stalk adjacent to the head – can inhibit dimerizaton by folding back onto itself (Al-Bassam et al., 2003). Unc104 binds to lipid membranes and can dimerize when clustered in rafts (Klopfenstein et al., 2002).

Some kinesins associate with different proteins through a coiled-coil stalk. For example, two different kinesin proteins dimerize and associate with a non-motor protein to form hetereotrimeric kinesin-2 (Cole et al., 1993); budding yeast kinesin-14 Kar3, however, can dimerize either with itself or with two non-motor proteins, Vik1 and Cik1 (Manning et al., 1999; Barrett et al., 2000). Dimerization with Cik1 alters Kar3 structurally and converts it into a faster motor (Chu et al., 2005). Strikingly, the Vik1 C-terminal globular domain contains a fold similar to the kinesin catalytic core, although it lacks an ATP-binding cleft (Allingham et al., 2007).

The tail binds to cellular cargo and is important for transport, but has been less well studied than the head and stalk. Kinesin-1 binding to vesicles and organelles can occur through light chains that exist in different isoforms and arise by alternative splicing (Cyr et al., 1991), although adaptor or scaffold proteins have now been identified that bind kinesins to cargo (Hirokawa et al., 2009). For example, the adaptor protein Milton mediates kinesin-1 binding to mitochondria, which is inhibited by Ca^{2+}. Further molecules are being discovered that facilitate kinesin-1 binding to endosomes, vesicles and organelles (Hirokawa et al., 2009). Other kinesins, such as kinesin-14 Ncd, bind to microtubules by their tails, as well as their heads. This could crosslink and slide microtubules, explaining Ncd function in oocyte spindle assembly (Hallen and Endow, 2009).

Structural features, including protein dimerization, thus have an important role in regulating kinesin activity. However, the defining characteristic of the kinesin motors – the ability to hydrolyze ATP and produce force – is a property of the catalytic core.

Kinesin catalytic core

The kinesin motor domain consists of an eight-stranded β-sheet with three α-helices on each side, a design conserved in the myosins (Kull et al., 1996; Sablin et al., 1996). The nucleotide-binding cleft on one side of the central β-sheet contains a highly conserved GQTGSGKT motif that forms the P-loop. The microtubule-binding site on the opposite side includes the structural elements L11-α4-L12-α5, which interact with tubulin and undergo movement between the ADP and ATP states. The motor contains highly conserved switch I (SSRSH) and II (DLAGSE) motifs, which change in conformation during the ATP hydrolysis cycle, similar to their counterparts in G-proteins (Rice et al., 1999; Yun et al., 2001; Hirose et al., 2006). Switch I and II form a salt-bridge that, in myosin, closes the nucleotide-binding cleft, enabling the motor to hydrolyze ATP (Geeves and Holmes, 1999). The closed conformation has now been seen in a crystal structure of frog kinesin-5 Eg5 bound to AMP-PNP (a nonhydrolyzable ATP analog) (Parke et al., 2010).

The motor domain is structurally conserved among the kinesin proteins; differences in motility and cellular function are largely due to regions outside the catalytic core. Motor directionality is determined by the region adjacent to the motor core, the kinesin-1 neck linker or Ncd neck (Endow, 1999). The kinesin-1 neck linker connects the head to the stalk (Kozielski et al., 1997) and has been proposed to dock onto the motor core in the ATP state and undock after hydrolysis, producing force to drive motor movement along microtubules (Rice et al., 1999). Although neck linker docking has been observed in crystal structures, its role in generating force has been controversial because it occurs with a small free energy change (Rice et al., 2003). Recently, the 'cover strand', a structural element at the N-terminus of the motor, has been proposed to dock onto the catalytic domain together with the neck linker to drive kinesin-1 steps along microtubules (Hwang et al., 2008). This hypothesis is supported by mutant analysis showing that the cover strand is essential for kinesin-1 motility (Khalil et al., 2008).

Ncd and other kinesin-14 motors lack a neck linker; instead, the heads attach directly to the stalk and interact extensively with the end of the stalk – the neck – stabilizing the motor in the microtubule-unbound conformation. Mutating a conserved neck residue that interacts with the head causes Ncd to move in either direction on microtubules. Thus, the neck determines directionality, presumably by interacting with the head to position the stalk for a stroke by the motor (Endow and Higuchi, 2000). Rotation of the stalk, observed in a crystal structure, is thought to represent the Ncd power stroke (Yun et al., 2003). Although Ncd lacks a neck linker,

C-terminal residues that are analogous to the kinesin-1 cover strand dock onto the catalytic core in a conformation resembling the neck linker (Heuston et al., 2010). These residues are similar to the *Arabidopsis* kinesin-14 KCBP C-terminus which docks onto the motor, regulating motor binding to microtubules (Vinogradova et al., 2004).

Kinesin-13 lacks both a neck linker and coiled-coil stalk, but contains a neck adjacent to the conserved motor domain (Ovechkina et al., 2002). Neck mutations reduce the microtubule depolymerase activity of MCAK, but can be rescued by replacing the neck with positively charged residues. This has led to a model in which weak electrostatic charges between the neck and the microtubule permit motor diffusion along microtubules. This model was revised recently owing to new data, which show that the microtubule on-rate is greatly affected by MCAK neck mutants; the requirement for a positively charged neck is now attributed to catalysis of the motor association with microtubules by the neck (Cooper et al., 2009), enabling the motor to catalytically remove tubulin dimers from microtubule ends (Hunter et al., 2003). Binding by the motor to tubulin subunits is crucial for kinesin-13 microtubule depolymerase activity; the role of ATP binding and hydrolysis might be to release bound subunits (Wagenbach et al., 2008). Thus, the kinesin-13 neck might promote interactions of the motor with microtubules, and tubulin release following nucleotide hydrolysis. Although the catalytic core underlies the ability of the kinesins to hydrolyze ATP and produce force, the way they move and use force varies with different motors.

Kinesin motility

Kinesin-1 is a highly processive motor protein that takes more than hundred steps each time a single motor binds to a microtubule (Howard et al., 1989; Block et al., 1990; Hackney, 1995). Each step is 8 nm (Svoboda et al., 1993), the distance between kinesin binding sites along a microtubule protofilament, and is tightly coupled to ATP hydrolysis – the motor takes one step for each ATP it hydrolyzes (Schnitzer and Block, 1997; Coy et al., 1999) – and produces 6–8 pN of force per step (Svoboda and Block, 1994). Kinesin-1 walks along microtubules by an alternating head or 'hand-over-hand' mechanism (Kaseda et al., 2003; Higuchi et al., 2004; Yildiz et al., 2004), which results in long excursions towards the microtubule plus end.

Kinesin-14 Ncd, by contrast, is a non-processive motor that binds to a microtubule, hydrolyzes a single ATP and then detaches (Endow and Higuchi, 2000; deCastro et al., 2000). Single-molecule laser-trap assays show displacements during the microtubule-attached phase, either upon initial binding and ADP release or upon ATP binding. As noted above, the Ncd power stroke is thought to occur when the stalk of the motor rotates towards the microtubule minus end. The stalk-rotated conformation would then represent the post-power stroke state and the previous structures, the pre-power stroke state (Yun et al., 2003). Multiple Ncd motors probably act in arrays in vivo, crosslinking and sliding microtubules by alternately binding and hydrolyzing ATP, and releasing from the microtubule (Howard, 2001).

MCAK and other kinesin-13 motors differ even more in their motility from kinesin-1. These motors do not move directionally on microtubules – instead, they bind to microtubules and diffuse to the plus or minus end where they catalytically remove tubulin subunits from the ends (Hunter et al., 2003). The mechanism of disassembly is thought to involve bending of tubulin subunits (Moores et al., 2002). Budding yeast kinesin-8 Kip3 is a plus-end-directed motor that also disassembles microtubules, although it does so in a length-dependent manner (Gupta et al., 2006; Varga et al., 2006). Long microtubules are disassembled faster than shorter ones by a proposed cooperative dissociation mechanism (Varga et al., 2009) that could explain the catastrophes promoted by Kip3 in yeast cells (Gupta et al., 2006). The divergent motility mechanisms of the kinesins underlie their diverse cellular functions.

Kinesin cellular functions

Vesicle and organelle transport

Kinesin-1 is essential for transporting vesicles to the presynaptic region of axons to mediate synaptic transmission. Mutants cause paralysis, lethality and vesicle jams (Saxton et al., 1991; Hurd and Saxton, 1996), and degenerative neurological disorders (Reid et al., 2002). Kinesin-1 binds to mitochondria, as noted above, as well as to lysosomes, receptor and adaptor proteins, and signaling-pathway-interacting proteins, indicating that it can transport diverse cargos and spatially regulate signal transduction (Verhey and Rapoport, 2001). Interactions with disease-associated proteins have implicated kinesin-1 in Alzheimer, Huntington and Parkinson disease (Gerdes and Katsanis, 2005).

Kinesin-2 hetereotrimeric motors are involved in intraflagellar transport needed for formation and maintenance of flagella and cilia, which are essential to many human cells (Rosenbaum and Witman, 2002; Scholey, 2008). Remarkably, deletion of mouse kinesin-2 KIF3B causes defects of the heart and other organs due to the failure to establish normal bilateral asymmetry during development, which is caused by the absence of nodal cilia in embryos (Nonaka et al., 1998). Other kinesin-2 motors might also transport precursors for cilia assembly – *C. elegans osm-3* mutants are defective in chemosensation because they cannot form normal ciliated chemosensory neurons.

Mitosis and meiosis

Kinesins have essential roles in cell division by assembling spindles, separating centrosomes and attaching chromosomes to spindles. The motors have been proposed to produce tension on kinetochore fibers, disassemble kinetochores, and drive poleward chromosome movement in anaphase by depolymerizing microtubules. Kinesin mutants can cause female sterility, cell cycle arrest or cell death, providing further evidence for their requirement in meiosis and mitosis.

Kinesin-14 Ncd is required for the assembly of anastral oocyte spindles in *Drosophila*, presumably by sliding and crosslinking microtubules to form bipolar spindles (Sköld et al., 2005). The kinesin-5 proteins BimC and Eg5 (KSP in humans), and kinesin-6 MKLP1 are thought to generate sliding forces in midzones of mitotic spindle. Microtubule sliding depends on the ability of the motors to diffuse along microtubules, while remaining attached to other microtubules. For example, Ncd binds tightly to microtubules by its tail (Hallen et al., 2008) and could slide by its head along other microtubules, whereas the four-headed kinesin-5 Eg5 can bind microtubules and slide along antiparallel microtubules by different heads to expand the arrays (Kapitein et al., 2005).

Kinesin-7 CENP-E is a kinetochore motor that is essential for chromosome interactions with the spindle. Other kinesin motors, including Nod and kinesin-4 chromokinesin, bind to chromosomes along their length and could position chromosomes during different stages of meiosis or mitosis. Kinesin-13 is also a kinetochore motor but disassembles microtubules, as discussed below.

Microtubule dynamics

Kinesin-13 depolymerizes microtubules and regulates microtubule dynamics, which is crucial for cell function, especially during division. Kinesin-13 MCAK localizes to kinetochores, spindle poles and microtubule plus ends, and could contribute to chromosome dynamics, poleward microtubule flux and spindle positioning during mitosis (Wordeman, 2010). MCAK is also involved in spindle bipolarity, together with kinesin-13 Kif2a (Ganem and Compton, 2004), and has been proposed to regulate spindle length by modulating dynamic

instability at microtubule plus ends (Ohi et al., 2007). *Drosophila* kinesin-13 KLP10A destabilizes microtubules at mitotic spindle poles of early embryos (Rogers et al., 2004) but stabilizes, rather than destabilizes, microtubules in oocyte spindles and anchors the spindles to the cortex (Zou et al., 2008). These apparently contradictory functions could be caused by motor modifications after oocyte activation.

Budding yeast kinesin-8 Kip3 also disassembles microtubules, but at their plus ends (Gupta et al., 2006), and does so in a length-dependent manner (Varga et al., 2006). But how it works in the spindle is increasingly unclear. Kip3 positions spindles (Cottingham and Hoyt, 1997) and regulates their length (Straight et al., 1998), possibly through effects on interpolar microtubules (Gardner et al., 2008). The overall effect of the motor is to suppress, rather than enhance microtubule dynamics by promoting both catastrophes and rescues, slowing disassembly (Gupta et al., 2006). Mammalian kinesin-8 Kif18A is also reported to suppress chromosome movements (Stumpff et al., 2008). However, conflicting evidence has been reported that Kif18A destabilizes microtubules in vitro and in live cells (Mayr et al., 2007). Further studies are needed to resolve these disparate observations.

Interestingly, kinesin-14 Kar3 depolymerizes microtubules at their minus ends in vitro, which could contribute to its function in moving nuclei together during karyogamy (Endow et al., 1994). Other kinesins, such as kinesin-14 Ncd, affect microtubule dynamics by stabilizing rather than destabilizing spindle microtubules (Endow and Komma, 1997; Goshima et al., 2005).

The diverse cellular functions of the kinesins extend our understanding of complex processes, such as vesicle trafficking, mitosis and meiosis, and cytoskeletal dynamics. They also offer attractive targets for intervention against cellular dysfunction (Wacker and Kapoor, 2010).

Perspectives

Although aspects of the mechanisms by which the kinesin motors produce force and move along microtubules, or disassemble the filaments, are now apparent, how the motors generate force is still not fully understood. Basic features, including the nucleotide state in which force is produced, are still not established. Crystal structures of missing nucleotide states will be a clear advance. The anticipated findings will provide information regarding the cellular mechanisms by which the motors produce force in the cytoskeleton. In addition to structural elements that regulate motor protein function, interacting proteins probably also have important roles – as already found for MCAK (Ems-McClung and Walczak, 2010). Further discoveries are likely to include inhibitors and enhancers of motor activity, and modifications that regulate motor function during development. Given the essential roles of kinesin motors in basic cellular processes, these advances are likely to have substantial impact on human health and disease, including cancer.

We apologize to the many researchers whose work it was not possible to cite because of space limitations. Further information about the kinesins, including links to the DNA, protein and literature databases, can be found at the Kinesin Home Page at http://www.cellbio.duke.edu/kinesin/. The authors research on kinesins is supported by NIH GM046225 and March of Dimes 1-FY07-443 Grants to S.A.E. and A.H.A. and a Scientist Development Grant 0330345N to F.J.K. Deposited in PMC for release after 12 months.

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