

Aurora B helps the central spindle measure up

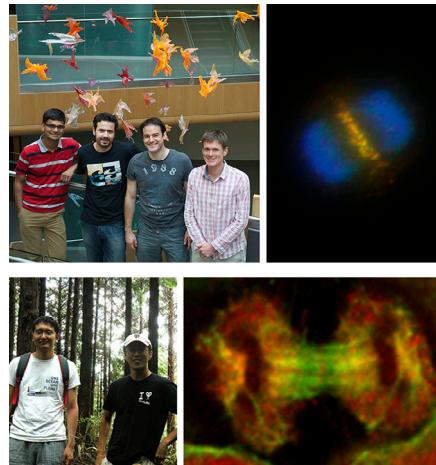
A mitotic kinase controls anaphase spindle length by regulating two kinesin motor proteins.

During anaphase, cells assemble a central spindle between the segregating chromosomes. Microtubule plus ends overlap in the middle of the cell, creating a spindle midzone that recruits factors involved in positioning the cytokinetic actomyosin ring around the cell equator. Regulating the length and organization of central spindle microtubules is therefore critical for ensuring that mitotic cells divide in the right place. Two papers reveal how the mitotic kinase Aurora B controls central spindle formation by regulating two different kinesin motor proteins (1, 2).

Central spindle assembly is controlled in part by the anti-parallel microtubule-bundling protein PRC1 and its binding partner KIF4A, a kinesin motor that suppresses the growth of microtubule plus ends (3). Cyclin-dependent kinase 1 prevents premature central spindle formation by inhibiting PRC1 and other assembly factors in early mitosis. This inhibition is relieved at anaphase onset, but Francis Barr from the University of Oxford, UK, reasoned that there must also be positive signals promoting PRC1 and KIF4A's recruitment to the overlapping microtubules of the spindle midzone. "There are microtubule plus ends all over the cell. What makes those at the central spindle special?" Barr says.

Barr and colleagues, led by Ricardo Nunes Bastos, found that inhibiting Aurora B prevented KIF4A's recruitment to the spindle midzone (1). Aurora B is transported to the anaphase central spindle by the kinesin Mklp2, generating a gradient of kinase activity that radiates outwards from the spindle midzone (4, 5). Eliminating this pool of Aurora B by knocking down Mklp2 blocked KIF4A recruitment, indicating that KIF4A's localization to the central spindle is regulated by local, rather than global, levels of Aurora B activity.

Aurora B phosphorylated KIF4A on a threonine residue in the kinesin's central stalk domain. Phosphorylation promoted KIF4A's localization to the central spindle



by enhancing the kinesin's interaction with PRC1. But Aurora B also stimulated KIF4A's ATPase activity, which could increase the motor protein's ability to move toward the plus ends of microtubules. "The interaction with PRC1 biases KIF4A's recruitment to microtubule overlaps," Barr explains. "It can then move toward the plus ends and shut down microtubule dynamics." Accordingly, phosphorylated KIF4A strongly suppressed the growth of microtubules *in vitro*, whereas cells expressing a nonphosphorylatable version of the kinesin grew longer central spindles than cells expressing wild-type KIF4A. Barr now wants to test his model by examining how Aurora B affects the behavior of single molecules of KIF4A on reconstituted spindles *in vitro*.

KIF4A suppresses the growth of microtubule plus ends, but Gohta Goshima, Ryota Uehara, and colleagues from Nagoya University in Japan discovered that a second kinesin, Kif2a, limits central spindle length by depolymerizing microtubule minus ends (2). During anaphase, Kif2a—a member of the kinesin-13 family of microtubule-depolymerizing motors—was enriched at either end of the central spindle, where the majority of microtubule minus ends are located. Cells lacking Kif2a formed abnormally long and disorganized central spindles.

"The shorter spindles oscillate back and forth."

Two groups of scientists describe how the Aurora B kinase controls the size of anaphase central spindles by regulating two different kinesin motor proteins. (Top row, left to right) Sapan Gandhi, Ricardo Nunes Bastos, Ryan Baron, Francis Barr, and colleagues (not pictured) demonstrate that Aurora B promotes the recruitment and activation of KIF4A (red) at the spindle midzone (green), where it suppresses the growth of microtubule plus ends. Meanwhile, (bottom row) Ryota Uehara (left), Gohta Goshima (right), and colleagues (not pictured) reveal that Aurora B restricts Kif2a (red) to the distal ends of the central spindle, where it depolymerizes the minus ends of microtubules (green). Both kinesins are regulated by the pool of Aurora B that forms a phosphorylation gradient emanating from the spindle midzone.

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Kif2a was also regulated by Aurora B, but, unlike KIF4A, this kinesin's localization to the central spindle was inhibited, rather than promoted, by the mitotic kinase. "If we partially inhibit Aurora B, Kif2a localizes throughout the central spindle and depolymerizes the microtubules so that the central spindle becomes shorter," Goshima explains. "The shorter spindles oscillate back and forth, leading to uneven chromosome distribution. This phenotype is completely rescued by knocking down Kif2a."

Mathematical modeling suggested that the Aurora B phosphorylation gradient—at its strongest in the spindle midzone—can regulate central spindle length by controlling Kif2a's activity. "If the microtubule minus ends are far from the midzone, Kif2a is active enough to depolymerize and shorten the microtubules," Goshima says. "But if the minus ends are closer to the midzone, Aurora B inhibits Kif2a so that depolymerization is reduced."

Although anaphase spindles are disorganized in the absence of Kif2a, cells can realign these spindles in telophase so that they can complete cytokinesis. Goshima now wants to understand how this backup mechanism is coordinated.

1. Nunes Bastos, R., et al. 2013. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201301094>.
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3. Bieling, P., et al. 2010. *Cell.* 142:420–432.
4. Grunberg, U., et al. 2004. *J. Cell Biol.* 166:167–172.
5. Fuller, B.G., et al. 2008. *Nature.* 453:1132–1136.