Aurora B puts chromosomes in their place

Small molecule inhibitors of Aurora B activity, characterized by Hauf et al. (page 281) and Ditchfield et al. (page 267), reveal that the mammalian kinase and its budding yeast counterpart, Ipl1, have similar functions. Without Aurora B, mistakes in kinetochore–chromosome interactions go uncorrected.

Early evidence of a function for the Aurora family in correcting syntelic attachments, those in which both chromatids are attached to the same spindle pole, was provided by the ip11 mutant. But visualizing spindle–kinetochore attachments in yeast is difficult. The two articles in this issue examine attachments directly, by inhibiting Aurora B in mammalian cells.

The groups used different compounds, but in both cases the Aurora B inhibitors left chromosomes misaligned and compromised the spindle checkpoint, thus causing division failure and endoreduplication. Hauf et al. saw that syntelic attachments were more common in inhibitor-treated cells. They hypothesize that Aurora B senses the lack of tension between syntelic sister chromatids and destabilizes either one or both so that correct attachments can be established. If the checkpoint is activated by unattached kinetochores, its override by Aurora B inhibition may be an indirect result of stable syntelic attachments. Indeed, drugs that destabilize microtubules restored checkpoint function in the presence of the inhibitors, at least in the short term.

Aurora B may also have a more direct effect on the spindle checkpoint through BubR1 or other kinetochore proteins. Low tension between sister chromatids normally leads to recruitment of BubR1 to kinetochores. But BubR1 was absent from kinetochores in the presence of either inhibitor. Ditchfield et al. show that RNA interference of BubR1 caused a chromosome alignment defect resembling that seen in cells treated with their Aurora B inhibitor. It is possible that BubR1 not only monitors kinetochore–microtubule interactions but also regulates them in response to changes in Aurora B activity.

To grow or to shrink...

Looks can be deceiving. According to two articles in this issue, proteins that look like microtubule stabilizing proteins at times do just the opposite, revealing activities that can both build and destroy microtubules.

Originally described as a Xenopus microtubule stabilizing protein, XMAP215 is a defining member of a large family of microtubule-associated proteins. Depletion of XMAP215 or its homologues leads to decreased spindle microtubule length in several systems, including fly, yeast, and worm. On page 349, however, Shirasu-Hiza et al. find that XMAP215 also promotes depolymerization of microtubules stabilized with a nonhydrolyzable GTP analogue (GMPCPP). This destabilizing activity, like its stabilizing activity, is specific to microtubule plus ends. The new work recalls a 10-year-old report demonstrating that XMAP215 has both activities in vitro.

Sirasu-Hiza et al. used EM analysis to reveal a structure that supports a peeling-like mechanism of XMAP215, similar to that of Kif11 kinesin. Previously, the plus ends of microtubules stabilized by GMPCPP have been thought to resemble a “GTP cap,” a structure postulated to exist at the ends of growing microtubules. Here, the authors suggest instead that GMPCPP-stabilized structures may mimic a “paused state”—a hypothetical third state in microtubule dynamics, intermediate between the growing and shrinking states. They propose that XMAP215 destabilizes this paused state and increases either polymerization or depolymerization rates depending on cellular conditions, thus explaining its dual activities.

On page 359, van Breugel et al. find another XMAP215 family member with destabilizing activity—the budding yeast homologue Stu2p. In vitro, Stu2p depolymerized microtubules by binding directly to plus ends, probably hindering tubulin dimer addition and thus increasing catastrophe rates. In contrast to the short spindle microtubules seen previously in stu2p mutants, cytoplasmic microtubules of stu2p interphase cells are longer than those in the wild type. Thus, for both yeast and frog proteins, cellular context, such as cell cycle status or protein localization, may determine their effects on microtubules. It remains to be seen whether destabilizing activity has been overlooked in other family members.