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Aurora B goes the distance

Researchers discover how key mitotic enzyme induces widespread effects.

Wang et al. (1) reveal how the Aurora B kinase can trigger a range of responses during mitosis even though it appears to be located far away from its substrates.

Aurora B spurs formation of the mitotic spindle, ensures that microtubules attach correctly to kinetochores, and orchestrates cytokinesis. Not surprisingly, Aurora B's targets are scattered. It phosphorylates molecules on the inner centromere, on chromatin, on the outer kinetochores, and in the cytoplasm (2). Aurora B can even phosphorylate potential substrates attached to spindle microtubules (3). How the enzyme regulates such far-flung molecules is unclear, since Aurora B is concentrated at the inner centromere until early anaphase. Adding to the mystery, Aurora B can only switch on its targets on the outer kinetochore if it is spatially separated from them (4). Any explanation for Aurora B's mysterious abilities also has to account for two other factors. First, the enzyme is continually detaching from the centromere and then reattaching. And phosphatase enzymes inactivate Aurora B in the cytoplasm.

To determine how all these variables fit together, Wang et al. first asked whether Aurora B has to concentrate at the inner centromere in order to switch itself on. Aurora B clusters at the inner centromere with regulatory partners like borealin and INCENP. In cells without borealin, however, Aurora B stays away from the centromere. Using a biosensor that registers Aurora B phosphorylation, the researchers found that targets at the inner centromere and on chromatin were not phosphorylated in cells lacking borealin. But these targets were phosphorylated when the researchers added a version of INCENP that delivers Aurora B to the inner centromere in the absence of borealin.

The team also studied human cells in which they could spur Aurora B and INCENP to relocate from the inner centromere to a distinct spot on chromatin. In these cells, the biosensor on the chromatin was phosphorylated when borealin was absent. These results suggest that Aurora B molecules cluster at the inner centromere to be activated. Recruitment of Aurora B by INCENP induces this activation, and, once some Aurora B is activated, it turns on additional kinase molecules.

When Aurora B is raring to go, how does it influence its more distant targets? One hypothesis is that the activated enzyme lets go of the inner centromere and diffuses away. To test that possibility, Wang et al. created INCENP molecules that varied in how tightly they attached to the inner centromere. Thus, the researchers could speed or slow the exchange of Aurora B to and from the centromere. Chromatin targets were less likely to be phosphorylated in cells that carried a sticky INCENP that was slow to detach.

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Wang et al. visualized this effect by dosing cells with monastrol, which causes the spindle to become monopolar and the chromosomes to re-arrange into a flower-like pattern. In cells with the sticky INCENP, phosphorylation only spread a short distance from the centromeres along the chromatin. But the researchers detected phosphorylation all over the chromatin if the fast-releasing INCENP was present.

The phosphatases that counteract Aurora B in the cytoplasm also have a role. The researchers hypothesize that they help create a gradient of phosphorylation activity, which might be important for regulating spindle assembly around the chromosomes.

"The results explain how Aurora B phosphorylates substrates at a distance," says senior author Michael Lampson. He notes that this mechanism differs from the typical enzyme–substrate interaction, in which the two parties home in on each other. But many of Aurora B's substrates can't move, so this more-involved procedure might allow Aurora B to reach those targets.

What remains unclear, Lampson says, is how the mechanism leads to regulation of substrates at the kinetochore, where proximity to the centromere seems to be important. The researchers suggest that a phosphorylation gradient extends from the centromere, with kinetochore targets reponding to the reduced enzyme activity farther along the gradient.

Focal Point

PHOTO COURTESY OF LINDA ROBINSON

Enxiu Wang (second from left), Michael Lampson (sixth from left), and Edward Ballister (sixth from right) investigated how Aurora B kinase spreads its influence. Treating cells with monastrol spurred the mitotic spindle to rearrange into a flower shape (right), with the centromeres in the middle. Purple indicates high levels of phosphorylation near the centromeres, and orange indicates lower levels farther away. The gradient along the chromosomes suggests that activated Aurora B diffuses to its targets.

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2. Welburn, J.P., et al. 2010. *Mol. Cell.* 38:383–392.
3. Tseng, B.S., et al. 2010. *Dev. Cell.* 18:903–912.
4. Liu, D., et al. 2009. *Science.* 323:1350–1353.