How microtubules let go of their attachments during cell division

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Whitehead Institute researchers have determined a key part of how cells regulate the chromosome/microtubule interface, which is central to proper chromosomal distribution during cell division.

"This is the surveillance machinery that makes sure that the chromosomes are divided correctly between cells," says Whitehead Member Iain Cheeseman.

The findings are published in this week's issue of *Molecular Cell*.

During cell division, the cell's DNA is consolidated into X-shaped chromosome pairs that align along the middle of the cell. Where the arms of the X cross, each chromosome has two kinetochores--protein complexes that facilitate microtubule attachment to the chromosome. As cell division progresses, these microtubules pull the right or left half of each chromosome towards the spindle poles to separate them to opposite ends of the cell.

Problems can frequently arise during this process. As a microtubule extends from a spindle pole, it may attach incorrectly to a kinetochore. When this happens, the cell needs a way to detect the mistake, detach the problematic microtubule, and reattach it correctly. If the issue is not addressed and cell division proceeds, the chromosomes typically fail to divide evenly, resulting in cells with the wrong number of chromosomes. This aberrant distribution of chromosomes can lead to cancer or premature cell death.

To correct attachment problems, cells rely on a system of phosphorylation - the addition of a phosphate group to certain proteins - to control whether or not microtubules stay bound to the kinetochore.

According to the *Molecular Cell* paper, the enzyme Aurora B resides within the inner kinetochore and adds phosphates to a key player in the kinetochore, called the KMN network, that attaches to the microtubule.

Aurora B's ability to phosphorylate a molecule wanes the farther that molecule is from the enzyme. In the case of a microtubule properly attached to the kinetochore, the microtubule's increased tension on the KMN network pulls the network taut and farther away from Aurora B, thereby reducing Aurora B's ability to phosphorylate the KMN network. If the microtubule is not correctly attached, the KMN network is not pulled away from Aurora B. The decreased distance lets Aurora B keep the KMN network phosphorylated, which destabilizes the microtubule's attachment to the kinetochore and allows the microtubule to detach and try again.

The KMN network is composed of several subunits arranged at different distances from Aurora B. Each subunit can be individually phosphorylated by Aurora B, which allows the attachment/detachment system to be controlled much like a dimmer rather than an on-off switch.

"This is a very sensitive system that allows the cell to dynamically respond to different attachment problems," says Julie Welburn, first author of the *Molecular Cell* paper and a postdoctoral researcher in the Cheeseman lab.

But for this system to function properly, phosphates also need to be removed from the KMN network to allow new microtubule attachments to form. In a recent Journal of Cell Biology article, the Cheeseman lab collaborated with researchers at the University of Pennsylvania to show

that another enzyme, protein phosphatase 1 (PP1), counteracts Aurora B's activity. As tension increases at a properly attached microtubule, one KMN network subunit recruits PP1. PP1 then removes the phosphates from the molecules phosphorylated by Aurora B, thereby stabilizing the microtubule's attachment to the kinetochore. However, the recruitment of PP1 itself to kinetochores is controlled by Aurora B activity.

"I think it's really cool that this process is not a simple tug of war between adding a phosphate and taking it away," says Cheeseman, who is also an associate professor of biology at MIT. "But that PP1 itself is sensitive to the overall level of Aurora B activity. So, the higher the Aurora B activity, the lower the PP1 activity, and vice versa. It sets up this balance between them, so that you can switch between high phosphorylation and no phosphorylation very quickly."

Although the two papers clarify certain aspects of the microtubule interface, the picture is not yet complete.

"We're slowly finding the other targets in this process and understanding even better how this mechanism works to correct microtubule attachments," says Welburn.

More information:

"Aurora B phosphorylates spatially distinct targets to differentially regulate the kinetochoremicrotubule interface" Molecular Cell, May 14, 2010

"Regulated targeting of protein phosphatase 1 to the outer kinetochore by KNL1 opposes Aurora B kinase", Journal of Cell Biology, March 22, 2010

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