Research Roundup

Don't cut too soon

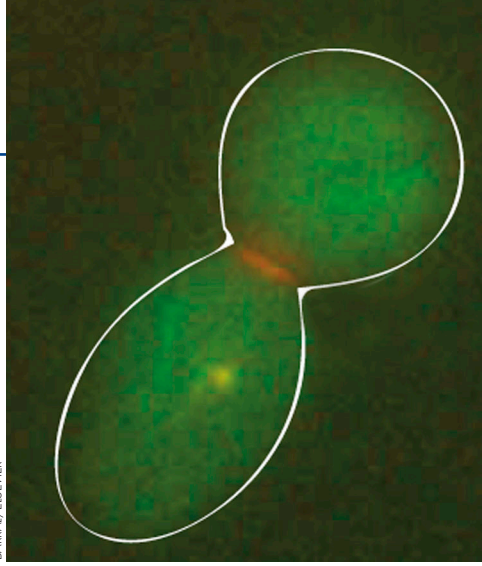
Caren Norden, Manuel Mendoza, Yves Barral (ETH, Zurich, Switzerland), and colleagues have found a new checkpoint in yeast cell division. Cytokinesis, they show, is delayed until chromosomes are out of the way, thanks to a pathway that monitors the spindle midzone.

If cytokinesis were to occur too soon, chromatids still lingering in the spindle midzone might get cut. Cytokinesis fails in animal cells with spindle midzone defects, and Barral's group now shows that the same is true for budding yeast. Although the actomyosin ring contracted normally, final membrane resolution (called abscission) was delayed in several mutants with altered midzone structure.

The midzone appears to be important for abscission perhaps by acting as a sink to inactivate the yeast Aurora kinase Ipl1. Although Ipl1 remained in the nucleus, it activated the export during mitosis of two anillin-like proteins called Boi1 and Boi2 that shuttled to the bud neck. There, they delayed abscission, as loss of the Boi proteins hastened cytokinesis, even in wild-type cells, thus causing chromosomal breaks.

At anaphase onset, Ipl1 is on chromosomes and is probably active. At telophase, Ipl1 accumulates at the midzone, where DNA is lacking, allowing its inactivation. Boi1 and Boi2 thus return to the nucleus.

Unlike other checkpoints, the delay did not stall mitotic progression; everything except cytokinesis went forward. "A yeast cell can survive if cytokinesis fails once," says Mendoza. "The worst that can happen is it becomes diploid or forms a chain of multiple nuclei in a common cytoplasm. It's not tragic. What would be tragic is if chromosomes were cut."



BARRAL/ELSEVIER

The continued presence of Boi1 (red) at the bud neck in midzone mutant cells at telophase prevents the completion of cytokinesis.

Mammalian Aurora B promotes initial furrow ingression and is thus required for cytokinesis. To determine whether it also prevents premature abscission, it will be necessary to knock out the kinase activity only after ingression. JCB

Reference: Norden, C., et al. 2006. *Cell.* 125:85–98.

Putting mitosis in reverse

Cells exiting mitosis are able to undo their work and return to metaphase if cyclin B is preserved, as revealed by a new study from Tamara Potapova, Gary Gorbsky (Oklahoma Medical Research Foundation, Oklahoma City, OK), and colleagues.

The destruction of cyclin B at anaphase, and the resulting inactivation of Cdk1, ushers in mitotic exit and cytokinesis. By tinkering with these mitotic regulators, Gorbsky's group reversed mitotic exit in vertebrate cells.

The authors first inhibited proteasome activity to preserve cyclin B at anaphase onset, creating a mitotic stall. They then forced these cells into cytokinesis by inhibiting Cdk1 activity. If they then withdrew the Cdk1 inhibitor, the cells reverted back into mitosis. The cleavage furrow opened, the nuclear envelope dissolved, chromatin recondensed, and the mitotic spindle reformed and recaptured the chromosomes.

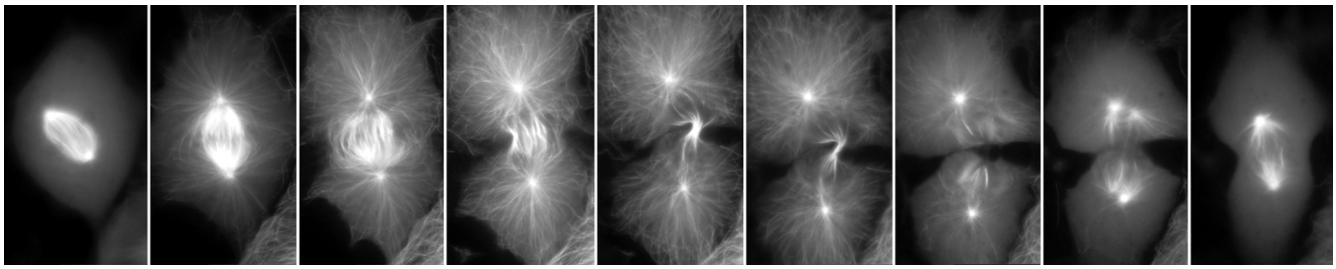
Cyclin B is not the whole story, however. "Clearly," says Gorbsky, "cyclin B is not the only thing, because it's not reversible if we wait too long." Another Cdk1 inhibitor might come into play later on, as Sic1 does in budding yeast. "Now that we have control of the first arrow of directionality, we can look at what's downstream of that."

When Tim Hunt first identified cyclin and its periodic destruction, the notion that cells would repeatedly make and destroy a protein to control its activity was rather shocking. But by the late 1980s, when it was shown that nondegradable cyclin prevented mitotic exit, the idea that proteolysis provides directionality in mitosis no longer seemed so far fetched.

"Some people, perhaps rightly so, just accepted the notion that protein degradation makes [mitosis] irreversible," says Gorbsky. "We just figured out that we could look at that. It could have turned out differently, if we couldn't reverse it."

Protein degradation uses up a lot of energy, but it is apparently preferable to a cheaper, sloppier mechanism of directionality. "Bad things [such as premature centrosome splitting] can happen during mitosis," says Gorbsky. "So reversing back into it is really not a good idea," as even the reversal process itself might be error prone. JCB

Reference: Potapova, T.A., et al. 2006. *Nature.* 440:954–958.



GORBSKY/MACMILLAN

Cdk inhibition induces reversal of mitotic exit and cytokinesis (left to right) if proteasome activity is also inhibited.