Centrosome signaling pathways consult on their decision

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Study reveals unexpected dialog between mitotic entrance and exit pathway proteins on yeast spindle pole bodies.

Centrosomes recruit many different signaling proteins that control progression through the cell cycle. For example, spindle pole bodies (SPBs), the yeast equivalent of centrosomes, are associated with two distinct scaffold proteins that regulate either entry into or exit from mitosis. In this issue, Chan et al. reveal that, in fission yeast, the mitotic exit scaffold influences the activity of the mitotic entry scaffold, suggesting that the concentration of signaling components on centrosomes helps cells integrate multiple signals when making important cell fate decisions, such as whether or not to enter mitosis (1).

The SPB-associated scaffold protein Cut12 promotes mitotic commitment by regulating the activity of Polo kinase, which, in turn, promotes the full activation of Cdk1–Cyclin B to drive mitotic entry. A temperature-sensitive mutant, *cut12.1*, compromises local Cdk1–Cyclin B activation at the restrictive temperature, preventing daughter SPBs from nucleating microtubules so that cells form monopolar spindles and undergo cell cycle arrest (2).

A second SPB scaffold protein, Sid4, regulates mitotic exit and cytokinesis by recruiting a signaling network called the septum initiation network (SIN; 3). "The perception has been that the two scaffolds work independently," explains Iain Hagan, from Cancer Research UK and the University of Manchester. "They are both on the SPB, but it's unclear why this is the best place for them."

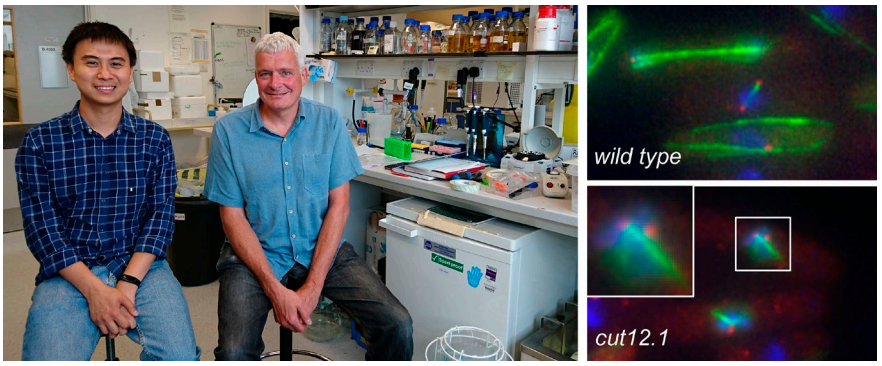
Hagan and colleagues, led by Dr. Kuan Yoow Chan, wanted to investigate how the *cut12.1* mutation affects Polo's recruitment to the SPB and so, because Sid4 also recruits Polo, they introduced an inactivating mutation into this second scaffold protein. To their surprise, the researchers saw that inactivating *sid4* suppressed the *cut12.1* mutation, allowing cells to form a bipolar spindle (1). "The cells were now able to enter mitosis just fine," says Hagan. "The deficiency in Cut12 function and Cdk1–Cyclin B activity is somehow compensated for when *sid4* is mutated."

This compensation wasn't caused by a loss of SIN activity, because mutations in other SIN components failed to suppress the *cut12.1* phenotype. Moreover, the researchers were able to isolate *sid4* mutations that suppressed *cut12.1* while retaining SIN function. These mutations were all in Sid4's C-terminal domain, which anchors the protein to the SPB, and were clustered around a threonine residue (T584) that was phosphorylated in a cell cycle–dependent manner. Mutating T584 to a phosphomimetic glutamate residue also allowed *cut12.1* cells to enter mitosis, indicating that this residue is crucial for the dialog between Sid4 and Cut12.

Chan et al. found that Sid4 T584 is phosphorylated by the NIMA family kinase Fin1 (the fission yeast homologue of mammalian Nek2 kinase), initiating a kinase cascade that promotes mitotic entry. Casein kinase 1δ binds to Sid4 phosphorylated on T584 and phosphorylates the scaffold protein on two other residues. These residues can then bind to a third kinase, $Chk2^{Cds1}$, that is known to phosphorylate the protein phosphatase Flp1 and displace it from SPBs (4). Flp1, a member of the Cdc14 family of phosphatases, opposes Cdk1–Cyclin B activation and dephosphorylates many of its targets. "Evicting this phosphatase from the SPB therefore reduces the local threshold for Cdk1–Cyclin B activation and mitotic entry," Chan explains.

The dialog between Sid4 and Cut12 explains why these two signaling proteins are concentrated together on SPBs, because it allows the integration of outputs from the two scaffolds. Moreover, these pathways can be influenced by many other inputs; Sid4 is involved in a pathway that arrests cells in response to spindle assembly defects (5), whereas $Chk2^{Cds1}$ forms part of the DNA replication checkpoint (4). Polo activation by Cut12, meanwhile, has been linked to nutrient sensing pathways (6, 7). These different inputs could all be integrated at the SPB to determine whether or not a cell will divide.

Many of the mammalian homologues of these proteins localize to centrosomes. Indeed, Chan et al.'s observations may help provide a molecular insight into why mutations in the centrosomal protein pericentrin disrupt DNA checkpoint signaling and cause a disease called Seckel syndrome. The researchers now plan to investigate this by examining checkpoint signaling in their mutant fission yeast strains.



Focal Point Kuan Yoow Chan (left), Iain Hagan (right), and colleagues identify an unexpected dialog between two signaling scaffold proteins, explaining why these two proteins concentrate on fission yeast spindle pole bodies. Compared with wild-type cells (top), cells carrying a temperature-sensitive mutation in the mitotic commitment scaffold Cut12 (bottom) form a monopolar spindle (green) and fail to enter mitosis at the restrictive temperature. But Chan et al. find that mutations in the mitotic exit scaffold *sid4* suppress the *cut12.1* phenotype by initiating a kinase cascade that lowers the local threshold for Cdk1–Cyclin B activation and mitotic entry. PHOTO COURTESY OF THE AUTHORS.

1. Chan, K.Y., et al. 2017. *J. Cell Biol.*
2. Tallada, V.A., et al. 2009. *J. Cell Biol.* 185:875–888.
3. Morrell, J.L., et al. 2004. *Curr. Biol.* 14:579–584.
4. Díaz-Cuervo, H., and A. Bueno. 2008. *Mol. Biol. Cell.* 19:2488–2499.
5. Johnson, A.E., et al. 2013. *Curr. Biol.* 23:1920–1926.
6. Petersen, J., and I.M. Hagan. 2005. *Nature.* 435:507–512.
7. Petersen, J., and P. Nurse. 2007. *Nat. Cell Biol.* 9:1263–1272.

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