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Cep152 and Plk4 form a double act

Two centrosomal proteins work together to duplicate centrioles.

In addition to their DNA, cells must duplicate their centrioles once—and only once—per cell cycle. These structures assemble centrosomes and nucleate cilia, so too many or too few centrioles can disrupt both the mitotic spindle and cell signaling. The kinase Plk4 is critical to the control of centriole number, though its precise function in the structure's biogenesis is unclear. Two studies now identify a Plk4-binding protein that helps the kinase build new centrioles (1, 2).

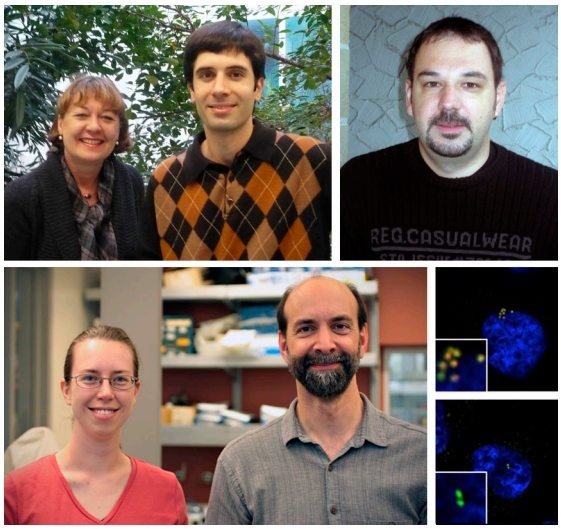
"Plk4 has the remarkable ability to generate extra centrioles in almost any animal cell in which it's overexpressed," says Stanford University's Tim Stearns. "Whereas, if you deplete the protein, cells are unable to make new centrioles. Plk4 therefore has all the hallmarks of a master regulator of centriole duplication." Plk4 even regulates its own activity to ensure that centrioles are only duplicated once per cell cycle, phosphorylating itself to trigger its own ubiquitination and degradation (3).

Plk4's critical role in centriole biogenesis was first reported in 2005 (4, 5). "People have been looking for substrates or binding partners of Plk4 ever since," explains Ingrid Hoffmann, from the German Cancer Research Center in Heidelberg. The search had been largely unsuccessful until both Hoffmann's and Stearns' groups—as well as a third team from the University of Cambridge (6)—found that Plk4 interacts with a centrosomal protein called Cep152.

The N terminus of Cep152 bound to Plk4's cryptic Polo-box domain, and depleting Cep152 blocked centriole duplication in mammalian cells. Moreover, Plk4 could no longer stimulate the formation of extra centrioles in the absence of Cep152, suggesting that the two proteins act together in centriole biogenesis. One possibility is that Cep152 recruits Plk4 to centrosomes—a key step because new centrioles usually form at the base of preexisting "mother" centrioles.

"A protein with a phenotype as striking as Plk4's can't have just one interaction partner!"

Focal Point



Two groups find that the centrosomal protein Cep152 binds to the kinase Plk4 to promote centriole duplication. In the absence (bottom right, lower panel) of Cep152 (red), Plk4 overexpression no longer causes centrioles (green) to overduplicate. (Top row, L-R) Ingrid Hoffmann, Onur Cizmecioglu, Marc Arnold, and colleagues (not shown) report that Cep152 acts as a scaffold to recruit both Plk4 and CPAP to the centrosome. (Bottom row, L-R) Emily Hatch, Tim Stearns, and coworkers (not shown) find that Cep152 is phosphorylated by Plk4 in vitro and is required to localize Sas6 to centrioles.

This seems to be Cep152's job in *Drosophila* cells, in which Plk4 no longer localizes to centrosomes in the absence of Asterless, the fly Cep152 homologue (6).

The situation is less clear in mammalian cells, however. Although Hoffmann's team found that newly synthesized Plk4 wasn't recruited to centrioles in Cep152's absence, both groups saw that Cep152 knockdown didn't result in the loss of stably associated Plk4 from the organelles. This may reflect the limitations of RNAi, or may indicate that mammalian Cep152 has a slightly different function compared to the fly version. Stearns suggests that Plk4's cryptic Polo-box may bind to more than one mammalian centriolar protein because—in contrast to Cep152 depletion—overexpressing an N-terminal fragment of Cep152 was able to completely strip Plk4 from centrioles, perhaps by out-competing both endogenous Cep152 and an additional Plk4-binding partner.

On the other hand, depletion of mammalian Cep152 was sufficient to disrupt two downstream components of the centriole-duplication pathway. Hatch et al. (1) found that cells lacking Cep152 failed to recruit a protein called Sas6 to centrioles, while Cizmecioglu et al. (2) discovered that Cep152 depletion prevented the centriolar localization of CPAP, a potential substrate of Plk4 that regulates centriole length. Cep152 bound CPAP directly, suggesting that Cep152 acts as a scaffold to recruit both Plk4 and CPAP to centrioles.

Meanwhile, Hatch et al. found that Cep152 itself is phosphorylated by Plk4 in vitro. Stearns now wants to determine whether Cep152 is also an in vivo substrate of Plk4 and to investigate what other centriole components the two proteins interact with. Hoffmann also wants to look for additional targets of Plk4. "I think that a protein with a phenotype as striking as Plk4's can't have just one interaction partner!" Hoffmann says.

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3. Holland, A.J., et al. 2010. *J. Cell Biol.* 188:191–198.
4. Bettencourt-Dias, M., et al. 2005. *Curr. Biol.* 15:2199–2207.
5. Habedanck, R., et al. 2005. *Nat. Cell Biol.* 7:1140–1146.
6. Dzhindzhev, N.S., et al. 2010. *Nature.* 467:714–718.