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A Kinesin in Command of Primary Ciliogenesis

Chad G. Pearson[1,*]
[1]Department of Cell and Developmental Biology, University of Colorado at Denver, Aurora, CO 80045, USA
*Correspondence: chad.pearson@ucdenver.edu
DOI 10.1016/j.cell.2011.05.023

Primary cilia sense extracellular cues and in response transmit signals required for development and tissue homeostasis. A new study by Kobayashi et al. (2011) reports that the kinesin Kif24 controls the formation of primary cilia by restricting the nucleation of cilia at centrioles.

Centriole duplication and function are temporally coupled with the cell cycle. In cycling cells, centrioles function as the centrosome core for cytoplasmic microtubule organization, whereas in quiescent cells (G_0) and cells in G_1, the centriole functions as a basal body for the nucleation of axoneme microtubules of the primary cilium. This switch in function is important for early development (the basal bodies of the sperm flagellum become centrioles after fertilization) and for the proper coordination of chemical and mechanical signaling events through different stages of both development and the cell cycle.

New studies have begun to uncover the mechanisms that control the centriole to basal body switch. The cyclin-dependent kinase substrate CP110 is a previously known regulator of primary ciliogenesis that was initially identified for its role in centrosome duplication (Spektor et al., 2007). In complex with Cep97, CP110 localizes to the distal end of centrioles during the assembly of new centrioles. During ciliogenesis, CP110 is specifically eliminated from the mother centriole—the one destined to become the basal body for the primary cilium. CP110-Cep97 levels are low during G_0, when cilia are formed and depletion of CP110 leads to the promiscuous formation of primary cilia in cycling cells. In order to restrict cilia formation in cycling cells, this complex may cap the distal end of centrioles to limit axoneme microtubule assembly and/or inhibit proteins required for ciliogenesis, such as Cep290 and Rab8a (Kleylein-Sohn et al., 2007; Schmidt et al., 2009; Tsang et al., 2008). However, an enzymatic activity for the CP110-dependent regulation of ciliary axoneme microtubules has not been identified.

The exciting new study by Dynlacht and colleagues (Kobayashi et al., 2011) demonstrates that a member of the kinesin-13 family functions with CP110 to suppress cilia formation. In contrast to canonical kinesin-driven cargo transport along microtubules, kinesin-13 subfamily members regulate microtubule length by disassembling microtubule ends. Humans express four kinesin-13 motor proteins, and the three extensively studied subfamily members (Kif2A, Kif2B, and Kif2C/MCAK) function in mitotic chromosome segregation and neurodevelopment. The fourth deeply conserved kinesin-13, Kif24, has distinct functions. In protists, Kif24 subfamily members localize to flagella, and overexpression or knockdown causes decreased or increased flagella length, respectively (Blaineau et al., 2007; Dawson et al., 2007; Piao et al., 2009). Thus, kinesin-13s also modulate the balance of axoneme microtubule dynamics to maintain normal flagella and ciliary length.

Consistent with this role for Kif24 proteins in protists, the authors show that human Kif24 antagonizes primary cilia formation by regulating centriole microtubules. Kif24 preferentially localizes to the distal end of mother centrioles and coimmunoprecipitates with CP110 and Cep97 (Kobayashi et al., 2011). Kif24 recruits and/or maintains CP110 at mother centrioles, and overexpression of Kif24 restricts ciliogenesis in quiescent cells. In vitro, Kif24 binds to and destabilizes microtubules, though not to the extent

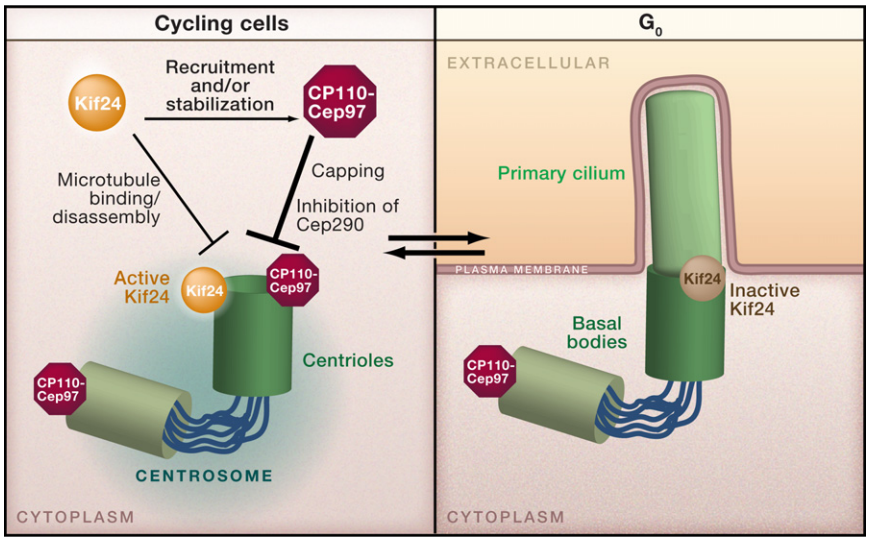

Figure 1. The Transition from Centriole to Basal Body

A model for Kif24 regulation of the transition between centriole and basal body functions. Kif24 limits ciliogenesis by recruiting and/or maintaining CP110 at the mother centriole. Coincident with the loss of CP110 from the mother centriole, the centriole becomes a basal body for primary ciliogenesis during the G_0 and G_1 phases of the cell cycle. Kif24 also binds α/β-tubulin and, through its depolymerase activity, regulates γ-tubulin and posttranslationally modified centriole microtubules to limit ciliogenesis.

of kinesin-13, Kif2C. Overexpression of Kif24 specifically decreases the levels of γ-tubulin and posttranslationally modified forms of α/β-tubulin at the mother centriole, leading the authors to conclude that Kif24 specifically modulates centriole microtubules.

CP110's negative regulation of cilia formation is specific to cell types that form primary cilia (ciliated cells; RPE1 and NIH 3T3 cell lines). In contrast, long and structurally deviant centrioles are assembled when CP110 is depleted from transformed culture cells that do not form cilia (nonciliated cells; U2OS cell line) (Kohlmaier et al., 2009; Schmidt et al., 2009). Nonciliated cells are either not competent to assemble primary cilia or additional negative regulators of cilia remain to be discovered in these cells. In contrast, Kif24 depletion in U2OS cells does not affect centriole length or CP110 localization (Kobayashi et al., 2011), indicating that CP110 localization to the distal end of centrioles is not mediated by Kif24 in these cells. Thus, Kif24 regulates ciliogenesis, whereas CP110 has additional functions in centriole duplication, length control, and ciliogenesis.

However, overexpression of Kif24 shortens the elongated centrioles found upon CP110 depletion, further supporting a role for Kif24 depolymerization of centriolar microtubules (Kobayashi et al., 2011). Because centriole microtubules are stable, these studies raise interesting questions about which subclasses of microtubules are recognized by the Kif24 depolymerase activity. As with other microtubule motor proteins and depolymerases, Kif24 may target specific posttranslationally modified microtubules. Once targeted to microtubules, it is unclear how Kif24 depolymerizes and regulates microtubules such that cilia formation is limited and centriole length is controlled. Finally, the dissimilar phenotypes associated with the loss of CP110 at the centriole distal end in divergent cell types (either promiscuous cilia or elongated centrioles) introduce interesting questions about how cilia formation and centriole length control are alternatively regulated. These events remain to be studied in the context of multicellular model systems with cell-cycle regulation of primary cilia formation. Such efforts will likely contribute to understanding the misregulation of ciliogenesis in cancer cells where cellular transformation can inhibit cilia formation (Seeley et al., 2009).

The discovery of a microtubule depolymerase that recognizes centriole microtubules reveals a new activity for the kinesin-13 subfamily in limiting cilia formation. Centrioles in ciliated cells are poised to form cilia, and the CP110-Cep97-Kif24 complex suppresses this (Kobayashi et al., 2011). Furthermore, Kif24 recruits and/or maintains CP110-Cep97 at mother centrioles, and double knockdown of CP110 and Kif24 has a similar effect on ciliogenesis compared to the single knockdown of Kif24. Thus, Kif24's role in the localization of CP110 is its key function in limiting promiscuous cilia formation. In addition, a role for Kif24-depolymerizing activity in regulating ciliogenesis is also evident (Figure 1).

Unlike CP110, Kif24 is detected at the basal body of the primary cilium, albeit at reduced levels, suggesting that a threshold level of Kif24 is required to limit cilia formation or that Kif24 activity is regulated by additional mechanisms. The upstream regulatory elements that recruit, activate, and/or repress Kif24's tubulin remodeling remain to be discovered. Given that mitotic kinesin-13s are regulated by the Aurora B kinase, perhaps Aurora kinases also modulate Kif24 function to only allow cilia formation during the G_0 and G_1 phases of the cell cycle. This is consistent with the repression of cilia via activating phosphorylation of the tubulin deacetylase (HDAC6) by Aurora A kinase. Furthermore, cilia formation and length regulation by *Chlamydomonas* kinesin-13 are likely regulated by phosphorylation and intraflagellar transport (Piao et al., 2009). Similar mechanisms providing temporally controlled phosphoregulation and spatial positioning of Kif24 may also be required for the motor to define when a primary cilium is projected from the cell to act as a cellular antenna.

ACKNOWLEDGMENTS

I thank Jennifer Deluca, Jason Stumpff, and Alex Stemm-Wolf for fantastic discussions and comments. I apologize to the many authors that were not referenced due to space limitations. C.G.P. is supported by the American Cancer Society (ACS-IRG#57-001-50).

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