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Heidi Hehnly

University of Massachusetts Medical School

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One among many: ODF2 isoform 9, a.k.a. Cenexin-1, is required for ciliogenesis

Comment on: Chang J, et al. Cell Cycle 2013; 12:655–62; PMID:23343771; http://dx.doi.org/10.4161/cc.23585
Heidi Hehnly, Hui-Fang Hung and Stephen Doxsey*; Program in Molecular Medicine; University of Massachusetts Medical School at Worcester; Worcester, MA USA; *Email: Stephen.Doxsey@umassmed.edu; http://dx.doi.org/10.4161/cc.24330

An elegant study from the Kyung Lee laboratory resolves the confusion over the role of the centrosome protein "human outer dense fiber protein 2" (hOdf2) vs. its splice variant, Cenexin-1 (Odf2 isoform 9), in the assembly of centriolar appendages and primary cilia. Previous studies suggested that these polypeptides had overlapping or distinct functions in ciliogenesis, but the different isoforms led to uncertainty about this claim. The Lee group provides solid data to demonstrate that Cenexin-1 but not Odf2 is required for these functions.

Primary cilia are microtubule-based sensory organelles projecting from the surface of most cells. They assemble from the centrosome, more specifically from the mother centriole or basal body of the centrosome. This centriole contains specialized substructures called appendages that are lacking in the daughter centriole. Subdistal appendages appear to position the basal body at the cell cortex through contact with the microtubule cytoskeleton, whereas the distal appendages have been proposed to anchor the basal body to the plasma membrane. Chang et al., 2013 used an invaluable tool established by Ishikawa et al.—an Odf2/cenexin-1 null cell line (Odf2−/−) that lacks both appendage types and cannot make primary cilia. The authors use this cell line for complementation experiments designed to test whether expression of either hOdf2 or hCenexin-1 rescues the Odf2−/− phenotypes. The outcome of this experiment was difficult to predict because hOdf2 was primarily characterized in testes, where it played a role in sperm outer dense fiber component required for sperm tail function. On the other hand, hCenexin-1 was not examined in testes but was found to be the major ODF2 isoform in somatic cells, where its unique C-terminal extension was required for recruiting Plk1 during mitosis. A clue to their cilia functions was suggested by the localization of hCenexin-1 to the mother centriole, the site of cilia formation, and the localization of hOdf2 along the entire ciliary axoneme.

Results from the Odf2−/− complementation experiments show that hCenexin1 expression rescues subdistal appendage formation, whereas expression of hOdf2 does not. The Odf2 splice variant, hCenexin1, is able to rescue cilia formation. Other less direct data consistent with a role for cenexin1 in cilia formation is its interaction with Rab8 through its C-terminal extension, which is lacking in hOdf2. This may be an important interaction, as Rab8 is required for membrane trafficking during ciliogenesis. Another result suggests that hCenexin1 is required for localizing Chibby, an essential cilia component, to mother centrioles. This study redefines what was previously thought to be cooperative or distinct roles of hOdf2 and hCenexin-1 in the formation of centriolar appendages and cilia. The work shows that hCenexin-1 alone performs these functions arguing for hOdf2 function to be revisited, possibly through the use of the robust tools exploited in this study. It will also be of great interest to gain a better understanding of the molecular mechanism of hCenexin-1 control over centriolar appendage organization and how this, in turn, influences ciliogenesis. This will likely involve structural roles such as building appendages and anchoring microtubules, as well as molecular roles in binding to Rab8 and localization of Chibby to centrioles. In this regard, the C-terminal extension of hCenexin-1 is required for both mother-centriole-specific localization of the protein and for binding the activated form of the small GTPase, Rab8.

Other work on Rab8 as well as Rab11 suggests interesting GTPase control mechanisms for cilia formation. For example, a Rab11-Rab8 GTPase cascade has been proposed for primary ciliogenesis. Moreover, Rab8 associated with recycling endosomes localizes to the basal bodies of the growing primary cilium where it is thought to participate in ciliary vesicle formation. In addition, Rab11 (and possibly Rab8) associated with recycling endosomes localize specifically to the appendages of the mother centriole. These intriguing observations lead us to speculate that the mother centriole appendages, and more specifically, the Rab8-binding C-terminal extension of cenexin-1 at these appendages, may facilitate organization of the Rab11-Rab8 GTPase cascade at these sites for initiating ciliogenesis and the formation of the ciliary vesicle.

On a related topic, the ODF2 gene is required to establish planar cell polarity and basal foot formation at cilia. It is unclear if it is the hOdf2 isoform, the hCenexin1 isoform, or other Odf2 splice variants that are required for these cellular functions. At this juncture, the best candidate for initiating and regulating planar cell polarity is hCenexin1 since exogenously expressed hCenexin1 localizes to mother centriole appendages and contributes to microtubule organization.

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