Centrioles Want to Move Out and Make Cilia

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Cilia formation in mammalian cells requires basal bodies that are either derived from centrioles that transition from their cytoplasmic role in centrosome organization or that form en masse in multiciliated cells. Several recent studies have begun to uncover the links between centriole duplication and their transformation to basal bodies.

Motile cilia, as in multiciliated epithelial cells, and immotile primary cilia with sensory function comprise the two general classes of cilia in mammalian cells. The critical nature of cilia formation is becoming increasingly apparent with the identification of a number of ciliary-based diseases exhibiting a pleiotropic array of pathologies (Badano et al., 2006). The diseases associated with defective ciliary function include polycystic kidney disease (PKD), Bardet-Biedl Syndrome (BBS), Jeune asphyxiating thoracic dystrophy, and Meckel-Gruber syndrome. Beyond the connection to human diseases, there are many outstanding fundamental questions regarding cilia formation and function. Particularly interesting is the poorly understood conversion cells undergo from unciliated to ciliated. Cilia formation studies have primarily focused on the molecular components responsible for intraflagellar transport (IFT), which is the bidirectional transport of proteins within cilia. This process is essential for ciliogenesis and is evident in the observation that IFT genes are mutated in human ciliary disease (Beales et al., 2007). Furthermore, IFT is necessary for transporting signaling molecules in cilia that are likely responsible for transmitting both mechanical and chemical signals from the surrounding cellular environment. In addition, intracellular transport of membranes to growing cilia is essential for ciliary biogenesis. This process is carried out, in part, by a subset of conserved BBS proteins (Nachury et al., 2007). While each of the above events is crucial for ciliogenesis, the cellular cues initiating ciliary formation are likely coming from the organelle at the base of the cilia, the basal body.
(MTOC) composed of two centrioles, which are barrel shaped structures with nine-triplet microtubules, and a pericentriolar matrix that is responsible for nucleating microtubules and organizing the mitotic spindle. In addition to their role in organizing centrocentres, centrioles can migrate to the cell cortex to become a basal body for the formation of cilia during cell-cycle quiescence. The duality of centriole function must therefore be regulated so that cilia formation is restricted to stationary phases of the cell cycle.

The regulation of both centriole/basal body duplication and nucleation of cilia is essential for defining the number of cilia in a single cell. Controls must be in place for cells with primary cilia and for multiciliated epithelial cells such that one or a limited density of basal bodies is assembled, respectively. A myriad of recent papers have studied the mechanisms both for the duplication and assembly of centrioles and for their transformation to basal bodies.

For centriole duplication, the structural steps defining assembly have been described. Recently, several studies in C. elegans have identified a number of critical molecules for early centriole assembly intermediates. In particular, the conserved Sas-6 protein is necessary for centriole assembly in worms, flies, and humans, while overexpression of Sas-6 causes the overduplication of centrioles (Strnad et al., 2007). In multiciliated epithelial cells, the typical centriole duplication cycle is altered to assemble hundreds of centrioles that become basal bodies. Sas-6 was found to localize to centrioles, basal bodies, and axonemes in epithelial cells. Furthermore, Sas-6-depleted cells do not form cilia (Vladar and Stearns, 2007). While basal body assembly is regulated by centriole components, such as Sas-6, the direct regulation of centrioles to enable the transformation to basal bodies must be facilitated by the recruitment or loss of components for each respective MTOC function.

Surprisingly, Spektor and colleagues discovered a complex of two centriolar proteins (CP110 and Cep97) that inhibit cillogenesis (Spektor et al., 2007). Previously, this group identified CP110 and found that its depletion causes cytokinesis and centrosome separation and duplication defects (Chen et al., 2002). They now report that CP110 interacts with Cep97 and that depletion of the complex members causes aberrant cilia formation in proliferating cells, whereas expression of CP110 suppresses cilia formation in quiescent cells (Spektor et al., 2007). Perhaps the most compelling evidence for the CP110 inhibition of ciliary formation is the specific localization of CP110 to centrioles without a cilium, while the mother centriole turned basal body that nucleates the primary cilium lacks CP110 (Figure 1). CP110 localizes to the distal end of centrioles near the transition zone (Kleylein-Sohn et al., 2007) and may limit axoneme nucleation. CP110 activity is regulated such that its protein levels are low during quiescence and, upon cell cycle reentry, CP110 levels increase and cillogenesis is inhibited. These studies provide an exciting model for the regulation of cillogenesis through the cell cycle. In addition to the regulation of the CP110 complex through protein levels, there is likely a spatial component to its regulation based on the selective localization of CP110 to unciliated basal bodies. Finally, determining the regulation of ciliary formation by the CP110/Cep97 complex in the context of multiciliated epithelial cells will determine whether this system is specific to primary cilia or is conserved and can direct the density of cilia in multiciliated cells.

This negative regulation suggests that the default or dominant cellular pathway for basal bodies/centrioles is to form cilia. The CP110 complex is required to suppress cilia formation, allowing basal bodies to act as centrioles for centrosome function. This is consistent with the hypothesis that the basal body/MTOC at the cell cortex was the evolutionary precursor to centrosomes roles in the cytoplasm (Azimzadeh and Bornens, 2004). Perhaps the development of ciliary regulation by the CP110 complex was a critical evolutionary step in moving this organelle into the cytoplasm to function as a centrosome.

In addition to the negative regulation of cilium formation by the CP110 complex, recent studies find that cilia resorption during cell cycle reentry is regulated by Aurora A (Pugacheva et al., 2007). Active Aurora A phosphorylates and activates the tubulin deacteylase HDAC6, thereby destabilizing axonemal microtubules for ciliary disassembly (Figure 1). Study of the coordination of the Aurora A-dependent ciliary disassembly with the CP110 complex for regulation of cillogenesis will inform our understanding of the transition from quiescence to cell cycle reentry (Figure 1).

With the addition of negative regulators of ciliary formation, the management of centrioles and basal bodies becomes even more complex. There are mature versus new centrioles in cycling cells, and their ability to be converted to basal bodies, or not, in quiescent cells, plus the centrioles that arise via massive reduplication mechanisms yield at least five functionally distinct types of centriole structures. The goal now is to determine how similar or different these structures are depending on their associated positive and negative regulators.

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REFERENCES


Tissue stem cells are typically rare and located in niches that prescribe low rates of cell division and survival. In this issue of Cell Stem Cell, Singh et al. (2007) demonstrate that, in the adult fly, epithelial cells exist that are neither in niches nor in small numbers, divide at high rates, and are multipotent.