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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.

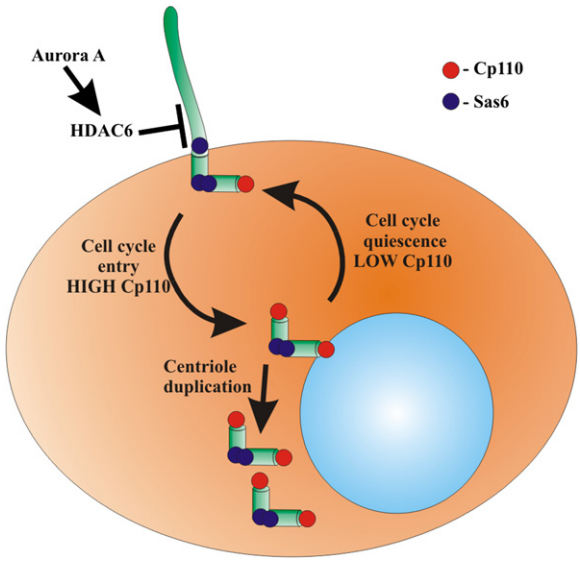

Figure 1. Regulating Centriole Duplication and Ciliogenesis
Centriole duplication is facilitated, in part, by Sas6 (blue). The transition from centrioles to basal bodies for ciliogenesis requires the movement of centrioles to the cell cortex. This transition is negatively regulated by CP110 complex binding to centrioles (red). Ciliary resorption prior to cell cycle reentry is promoted by Aurora A induced tubulin deacetylation.

Centrosomes are microtubule-organizing centers

(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 centrosomes, 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 ciliogenesis (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 ciliogenesis is inhibited. These studies provide an exciting model for the regulation of ciliogenesis 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 centrosome 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 cilia 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 deacetylase HDAC6, thereby destabilizing axonemal microtubules for ciliary resorption (Figure 1). Study of the coordination of the Aurora A-dependent ciliary disassembly with the CP110 complex for regulation of ciliogenesis 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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Self-Renewal in the Fly Kidney

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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.

Tissue stem cells are among the most intriguing cells found in adult organisms, as they generate precisely the different cell types needed to ensure tissue renewal (for review, see Blanpain et al., 2007). Remarkably, these cells maintain their proliferative capacity for the lifespan of the organism, generally without leading to the development of tumors. Vertebrates seem to have solved the challenge of keeping multipotent cells alive with an unlimited, but regulated, self-renewal potential by sequestering these cells in "niches" that isolate them from environmental cues that might lead to uncontrolled cell division and/or differentiation along unwanted lineages (Spradling et al., 2001). Stem cell niches do not only exist in vertebrates, however, and some of the best descriptions of the cellular and molecular components of a particular niche come from work on ovary and testis development in *Drosophila melanogaster* (reviewed in Ohlstein et al., 2004).

Although studies on stem cells in flies have proven invaluable to better understand the reproductive system, until recently the existence of multipotent cells in adult *Drosophila* epithelial tissues had not been apparent. However, in this issue of *Cell Stem Cell*, Steven Hou and colleagues report on the identification of multipotent cells in the Malpighian tubules (MT) (Singh et al., 2007). This fly equivalent of the mammalian kidney had previously been thought to be highly stable, rather than an organ under the remodeling control of a dividing cell population. The MT consists of different cell types, some of which are derived from the everting epithelial tube proper and others from the neighboring mesoderm, which become incorporated into the epithelium upon a mesenchymal-to-epithelial transition. Singh et al. performed lineage-tracing experiments, BrdU incorporation, and marker analyses to follow the fate of cells in the MT of adult flies over time. This work led to the unambiguous identification of multipotent cells in the lower region of the fly MT that are able to generate all cell types of the adult organ. These cells were designated "renal and nephric stem cells" (RNSC), and no fewer than 100 RNSC were found in one pair of anterior MT. This is a remarkable number given that an entire pair of anterior tubules only contains about 500 cells.

The study by Hou and colleagues also identifies the JAK-STAT signaling pathway as being of critical importance in regulating RNSC renewal in the lower tubule. Although the absence of signaling promotes the differentiation of RNSC, and the concomitant loss of the stem cell population, ectopic activation of the cytokine-type receptor Domeless by overexpression of its ligand Unpaired increases the size of the MT by accelerating the rate of RNSC division. Because RNSCs express both the ligand and the receptor, self-renewal is controlled by autocrine JAK-STAT signaling. The finding that the JAK-STAT pathway is important for maintaining the population of RNSCs is notable, because the same signaling system has been found to play a similar role in a number of other systems, for example in the testis for the maintenance of both somatic and germline stem cells (Tulina and Matunis, 2001; Kiger et al., 2001) and in the ovary for the maintenance of so-called "escort stem cells" (Decotto and Spradling, 2005). And, of course, it has long been known that mouse embryonic stem cells will only proliferate indefinitely without differentiating as long as the JAK-STAT pathway is kept active by leukemia inhibitory factor (Smith, 2001). In contrast to these latter cases, in which the ligand is expressed by support cells within the niche or added to the culture medium, RNSCs are capable of secreting their own self-renewal factor. How