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Centrioles in the mouse: cilia and beyond

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Centrioles, triplet microtubule structures, form the core of centrosomes, which are the dominant microtubule organizing centers of animal cells. Centrioles arise either through a canonical pathway with a centriolar template, or *de novo* without preexisting centrioles. Studies carried out in *C. elegans* and cultured mammalian cell lines have shown that centriole formation requires the sequential activities of a defined set of proteins, including PLK4 (aka Sak/Zyg1), CEP152 (aka Asl), SAS-6, STIL (aka Ana2/Sas-5) and SAS-4 (aka CPAP/CENPJ). Many studies have shown that centrioles have 2 major functions. During interphase and in differentiated cells, centrioles are the template for cilia and flagella, and cilia detect specific signals and generate fluid flow in specific organs. During mitosis, centrioles organize the pericentriolar material (PCM) and form mature centrosomes that help organize the spindle microtubules.

Although centrioles are essential to provide the basal body of cilia and flagella, other functions of centrioles, including in cell division, appear to vary between organisms and cell types. Absence of centrioles in *C. elegans* causes embryonic arrest at the 2-cell stage. In contrast, zygotic loss of centrioles in *Drosophila* is compatible with survival, although loss of the maternal contribution to centrioles in *Drosophila* also causes early embryonic arrest due to cell division failure. These findings demonstrate that centrioles are essential for cell division in some cell types but not others. Indeed, some cell types like mammalian oocytes do not have centrioles and meiotic divisions are acentriolar.

The functions of centrioles in mammals are now being defined for the first time. *Stil* mutant embryos arrest at midgestation with disrupted Hedgehog (Hh) signaling 1,2. In this issue of *Cell Cycle*, David et al use elegant electron microscopy techniques to demonstrate that *Stil* mutant mouse embryos completely lack centrioles and cilia.[3] David et al show that the absence of cilia accounts for the defects in Hh signaling, as expected because the Hh signal propagation requires cilia. We recently showed that removal of another protein essential for centriole duplication, SAS-4, also causes midgestation lethality, associated with complete loss of centrioles, cilia and disrupted Hh signaling.[4] Mutations in mouse *Plk4* and *Cep152* also cause midgestation lethality,[4,5] suggesting that removal of centrioles causes a common lethal syndrome in the mouse.

Despite the absence of centrioles, *Stil* mutant mouse embryonic fibroblasts (MEFs) can assemble PCM that includes the Pericentrin protein into distinct foci. These findings appear to differ from our findings in *Sas-4* mutants, as the *Stil* mutants appear to have interphase PCM foci, whereas *Sas-4* mutants assemble PCM aggregates mainly during mitosis, when the PCM becomes associated with the spindle poles. This suggests and confirms data in the literature that that there may be distinct requirements for different components of the centriole in PCM recruitment. David et al go on to show that while knockdown of the PCM protein Pericentrin does not affect the growth of MEFs, knockdown of Pericentrin in $Stil^{-/-}$ MEFs greatly reduced proliferation, suggesting that Pericentrin is required for the division of acentriolar cells.

Overexpression of a handful of centriole duplication proteins, including PLK4 and SAS-6, has been shown to be sufficient to induce centriole amplification in mammalian cells. David et al confirm previous findings from the group, showing that STIL is also sufficient to cause centriole amplification, even in the acentriolar $Stil^{-/-}$ MEFs.

In total, 5 genes known to be required for centriole formation have been inactivated in the mouse, *Plk4*, *Cep152*, *Stil*, *Sas-4*, and *Rttn* (*Ana3*). Each of these null mutants arrests at midgestation (~e9.5); in all cases examined, embryonic lethality is associated with loss of Hh signaling and cell death.[1-6] In contrast, human mutations in genes encoding centrosomal and centriolar proteins, including STIL, CEP152 and SAS-4 cause primary microcephaly or microcephaly in the context of dwarfism.[7] Because the human mutations are compatible with survival, it is possible that they represent partial loss-of-function alleles. David et al show that they can partially rescue the centrosome and cilia in $Stil^{-/-}$ MEFs by expressing truncated human microcephaly-associated forms of STIL. Thus the data suggest that the human microcephaly mutations that affect STIL, and perhaps other centriolar proteins, only partially disrupt centrioles, and that complete loss of centriole function in humans, as in mice, would cause lethality during gestation.

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