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The Centrosome and Its Duplication Cycle

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The centrosome was discovered in the late 19th century when mitosis was first described. Long recognized as a key organelle of the spindle pole, its core component, the centriole, was realized more than 50 or so years later also to comprise the basal body of the cilium. Here, we chart the more recent acquisition of a molecular understanding of centrosome structure and function. The strategies for gaining such knowledge were quickly developed in the yeasts to decipher the structure and function of their distinctive spindle pole bodies. Only within the past decade have studies with model eukaryotes and cultured cells brought a similar degree of sophistication to our understanding of the centrosome duplication cycle and the multiple roles of this organelle and its component parts in cell division and signaling. Now as we begin to understand these functions in the context of development, the way is being opened up for studies of the roles of centrosomes in human disease.

HISTORICAL BACKGROUND

Pioneering work from Boveri, van Benenden, and others in the 1880s saw the discovery of centrosomes, descriptions of how they enlarged before mitosis, and that they were associated with multipolar mitoses in tumor cells. Only now, more than a century later, are we beginning to have an understanding of how the organelle is pieced together and how it functions as a fundamental part of the cell-division machinery.

The explosion of the study of biological structures by electron microscopy (EM) in the 1950s revealed that centrosome has at its core the ninefold symmetrical centriole (Fig. 1A). A typical human centriole is a cylinder ~200 nm in diameter and 500 nm long. At the most interior and the proximal-most part of the centriole is a cartwheel that has nine spokes, each linked to microtubule blades that form the microtubule wall (see Fig. 4B). It is surrounded by electron dense pericentriolar material (PCM) that increases in amount in mitosis providing the nucleating center for spindle and astral microtubules. In quiescent cells, a mature centriole can become associated with the plasma membrane to template cilia or flagella that function in signal transduction and cell motility. Defects in ciliogenesis lead to a group of disorders collectively known as the ciliopathies.

Centrioles are present in metazoans and a variety of unicellular eukaryotes but are absent in the majority of land plants. Their ninefold symmetry is highly conserved but they do

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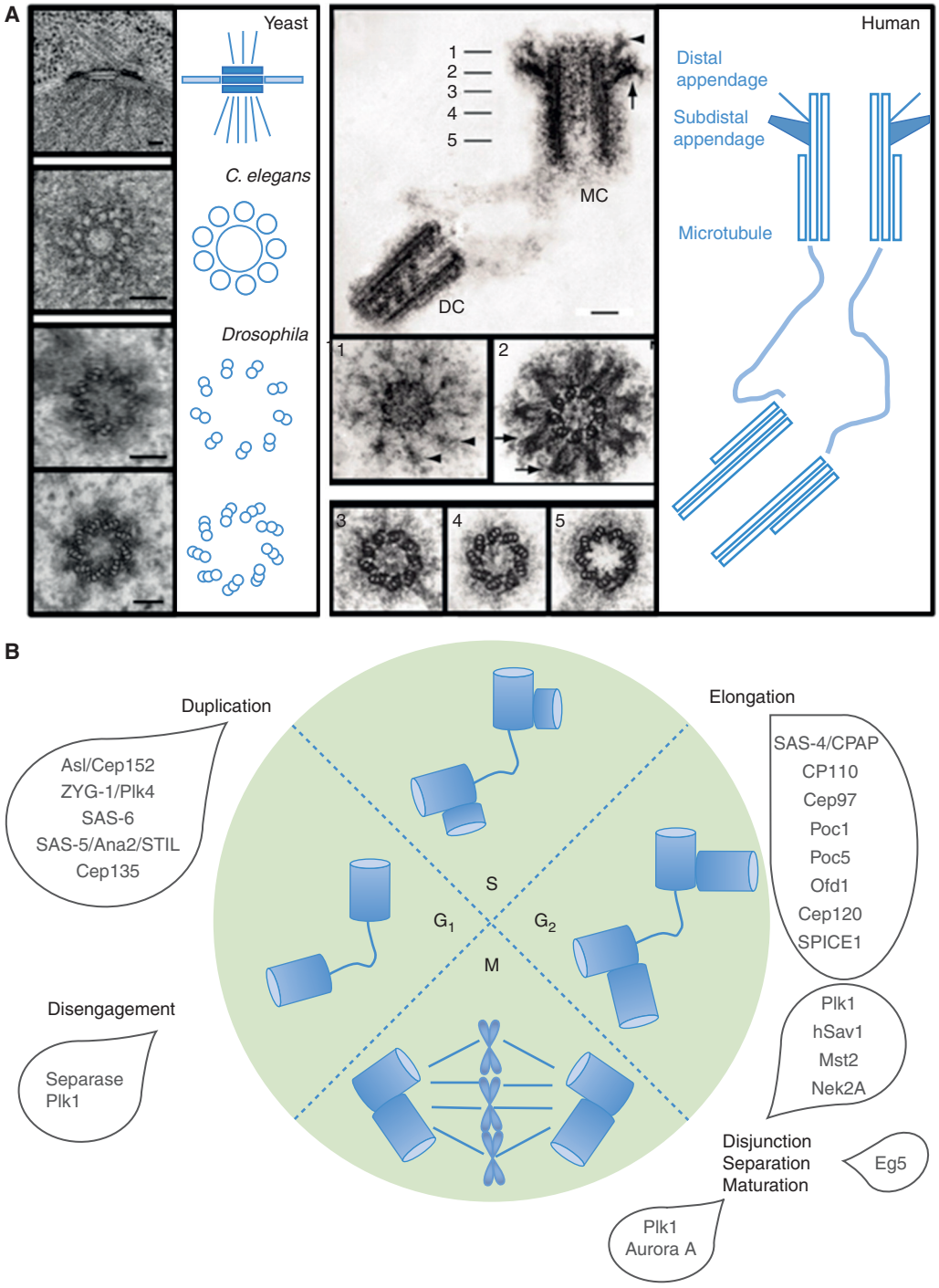

Figure 1. The structure and duplication cycle of centrosomes. (*A*) Electron microscopy reveals the structures of the spindle pole body (SPB) centrosome with ninefold symmetrical centriole as its core. Scale bars, 100 nm. (*B*) *C. elegans, Caenorhabditis elegans*; DC, daughter centriole; MC, mother centriole. The centrosome duplication cycle occurs in concert with the cell-division cycle. Key events and players in the centrosome cycle are indicated.

show structural differences among organisms. These differences are reflected in the molecular parts catalog for the centrioles of different organisms and give some clues to their evolution (Carvalho-Santos et al. 2010). The yeasts have evolved quite a different structure: the spindle pole body (SPB), a plate-like structure inserted into the nuclear envelope (Fig. 1A), and an ability to nucleate microtubules on its cytoplasmic and nuclear sides in the "closed" mitoses of yeast cells where the nuclear envelope does not break down. The SPBs carry much of the analogous machinery to the centriole and/or centrosome, and so it is of growing interest to compare their structure and function with centriole-containing centrosomes.

STRUCTURE AND DUPLICATION CYCLE OF YEAST SPBs

The budding yeast SPB nucleates both the nuclear spindle microtubules that segregate the genome and the cytoplasmic, astral microtubules that guide the spindle through the cytoplasm. As the nuclear envelope does not break down during mitosis, the planar trilaminar SPB is maintained within a specialized "polar fenestra" in the nuclear envelope throughout the cell-division cycle (Byers and Goetsch 1974, 1975; Heath 1980). Receptors for the γ-tubulin complexes sit on the opposing cytoplasmic and nuclear faces to nucleate the two sets of microtubules (Fig. 2). The nuclear receptor, Spc110 is a member of the pericentrin family of microtubule-nucleating proteins in which microtubule-nucleating motifs are separated from anchors by extended coiled-coil spacers (Kilmartin et al. 1993; Kilmartin and Goh 1996; Knop and Schiebel 1997; Sundberg and Davis 1997). These γ-tubulin docking motifs are highly conserved from human pericentrin and kendrin through *Drosophila* centrosomin (CNN) to fission yeast Mto1 and Pcp1 (Flory et al. 2002; Zhang and Megraw 2007; Fong et al. 2008; Samejima et al. 2008; Lin et al. 2014). Spc29 links Spc110 to the hexagonal crystalline lattice of Spc42 that comprises the central plaque in a coupling that relies on association of Spc110 with calmodulin (Geiser et al. 1993; Stirling et al. 1994; Donaldson and Kilmartin 1996; Spang et al. 1996; Bullit et al. 1997; Sundberg and Davis 1997; Elliott et al. 1999). On the cytoplasmic side of the central plaque, Spc42 anchors the Cnm67 linker protein that recruits Nud1 to the base of the outer plaque (Adams and Kilmartin 1999; Elliott et al. 1999; Schaerer et al. 2001). In turn, Nud1 recruits both the mitotic exit network (MEN) that regulates cell-cycle events at the end of the cycle (see the section on signaling from poles below) and the γ-tubulin complex receptor Spc72 (Knop and Schiebel 1998; Gruneberg et al. 2000).

γ-Tubulin recruits αβ-tubulin heterodimers to nucleate microtubules at the spindle poles of all eukaryotes (Kollman et al. 2011; Teixido-Travesa et al. 2012). Comprehensive molecular genetic analysis in budding yeast led to the characterization of the first γ-tubulin complex, the γ-tubulin small complex (γ-TuSC) (Geissler et al. 1996; Knop et al. 1997; Knop and Schiebel 1997, 1998). The γ-TuSC is conserved throughout eukaryotes and comprises two molecules of γ-tubulin and one each of the Spc97 and Spc98. Many other eukaryotes generate a larger γ-tubulin complex, the γ-tubulin ring complex (γ-TuRC) that contains Spc97/Spc98 orthologs and three further molecules that share the Grip motifs of Spc97 and Spc98 (GCP2-GCP6 [GCP2 and GCP3 being orthologous to Spc97 and Spc98, respectively]) alongside two or three additional components (Kollman et al. 2011; Teixido-Travesa et al. 2012). As its name suggests the γ-TuRC is a lock-washer-shaped ring in which the positioning of 13 γ-tubulin molecules serves as a template to recruit 13 αβ-tubulin heterodimers that seed the nucleation of 13 protofilament microtubules (Moritz et al. 1995; Kollman et al. 2011; Teixido-Travesa et al. 2012). The conserved γ-TuSC is Y shaped with Spc97/GCP2 and Spc98/GCP3 at the base of two γ-tubulin arms (Kollman et al. 2008). Because expression of the yeast γ-TuSC in baculovirus promotes the assembly of ring-like structures with 13-fold symmetry, the presence of the Grip domains in the GCP3-6 components of the γ-TuRC has been taken to infer that they act as variants of GCP2 and GCP3 to extend this core γ-TuSC complex into the larger

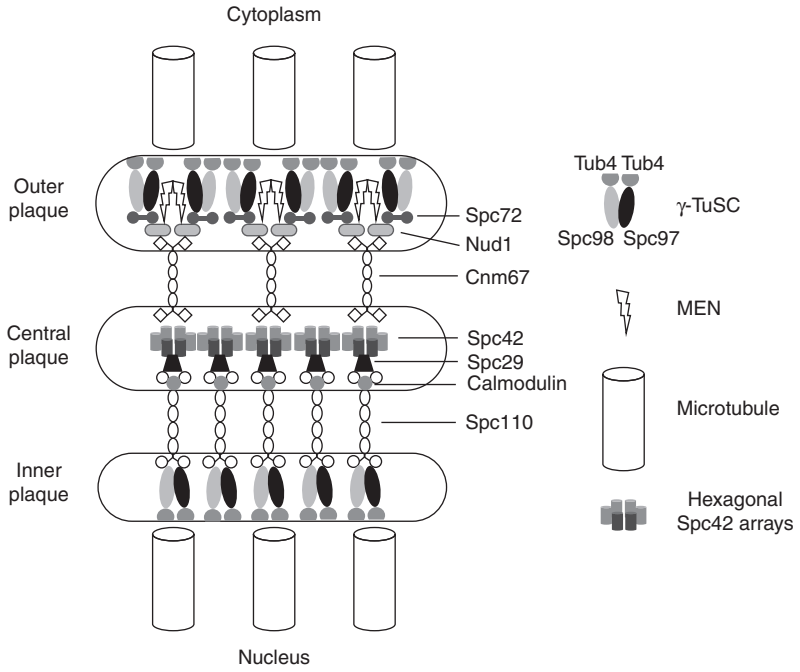

Figure 2. A highly schematic representation of molecular architecture of the budding yeast spindle pole body (SPB). A hexagonal crystalline array of Spc42 units associate with Spc29/Spc110 complexes on the nuclear side and cnm67 dimers on the cytoplasmic side of the SPB. These spacer proteins separate the central Spc42 plaque from the γ-TuSC microtubule-nucleating centers at the inner and outer plaques. At the inner plaque the interaction between the spacer Spc110 is direct with one Spc110 dimer associating with a single γ-TuSC (Erlemann et al. 2012). It is estimated that a functional microtubule nucleation unit comprises seven γ-TuSCs, two additional Spc98, and three extra γ-tubulins (Erlemann et al. 2012). This estimate agrees well with the reconstitution of 13-fold symmetric γ-tubulin microtubule-nucleating units in vitro (Kollman et al. 2008, 2010). At the cytoplasmic outer plaque, the association between the spacer and the γ-TuSC is mediated through the association of Nud1 with Spc72. Despite the fact that Spc72 interacts with both Spc97 and Spc98 in two hybrid assays (Knop and Schiebel 1998), in vivo measurements suggest that one Spc72 dimer interacts with a single γ-TuSC (Erlemann et al. 2012). Nud1 also acts as a scaffolding molecule for the mitotic exit network (MEN) that couples the SPB position with cell-cycle control. The stoichiometries of other associations remain to be established. The representation of Spc29 in between Spc110 and Spc42 is highly schematic, as the exact nature of its function as part of the Spc110 complex remains to be established.

γ-TuRC (Kollman et al. 2010). The extension of the templating function from a dimer to 13-mer that is conferred by the presence of the additional γ-TuRC components appears to be fulfilled in yeast by the γ-TuSC recruiting components of the SPB, as co-expression of the γ-TuSC with the interacting domain of the pericentrin molecule Spc110 in baculovirus generates extended γ-TuSC filaments (Kollman et al. 2010). This impact of Spc110 enhances the microtubule nucleation capacity of γ-TuSCs. Perhaps the simplicity of the budding yeast cytoskeleton with its permanent anchorage of microtubules to γ-TuSC receptors throughout the cell cycle has dispensed with the need for the complexity of the γ-TuRC that facilitates greater levels of control over microtubule nucleation.

SPB duplication is conservative as a new SPB forms at the end of a "half-bridge" that extends along the inner and outer faces of the nuclear envelope from one side of the central layer of the old SPB (Fig. 3) (Byers and Goetsch 1974, 1975; Adams and Kilmartin 2000; Kilmartin 2014). The half-bridge principally comprises

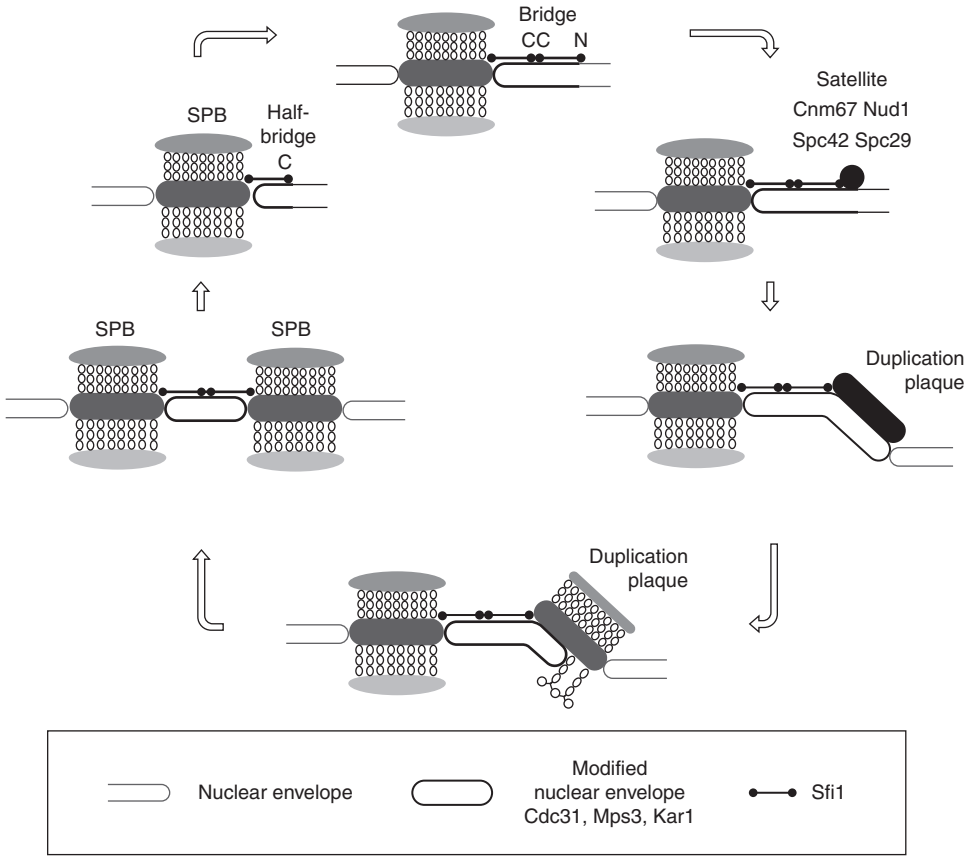

Figure 3. Budding yeast spindle pole body (SPB) duplication. A highly schematic representation of SPB duplication in budding yeast. The key role played by Sfi1 C-C homotypic dimerization in establishing a point for the formation of the satellite that expands to form the duplication plaque is shown in the *top* panel. Immunoelectron microscopy indicates that this satellite contains at least Cnm67, Nud1, Spc42, and Spc29. (For full details, see Adams and Kilmartin 1999, 2000; Kilmartin 2014.)

Cdc31, Kar1, Mps3, and Sfi1 (Baum et al. 1986; Rose and Fink 1987; Spang et al. 1993, 1995; Biggins and Rose 1994; Jaspersen et al. 2002; Kilmartin 2003; Li et al. 2006). Kar1 and the SUN domain protein Mps3 each contain a single membrane-spanning domain (Rose and Fink 1987; Jaspersen et al. 2002). Sfi1 is a long, flexible molecule principally composed of 20 Cdc31-binding repeats (Kilmartin 2003). Cdc31 is a member of the centrin family of calmodulin-related proteins that are found at spindle poles of all eukaryotes (Salisbury 2007). Sfi1-related molecules with multiple centrin-binding motifs accompany centrins at human centrosomes; however, their function remains to be determined (Kilmartin 2003; Azimzadeh et al. 2009). In budding yeast, the amino terminus of Sfi1 is anchored at the SPB, while the carboxyl terminus defines the end of the half-bridge extension. SPB duplication in the G_1 phase of the cell cycle is assumed to be initiated by the end on recruitment of a second Sfi1 molecule to the free carboxyl terminus via homotypic C-C dimerization (Kilmartin 2003; Li et al. 2006). Central SPB components then bind the amino terminus of this newly docked Sfi1 to form a small satellite on the cytoplasmic face of the nuclear envelope that subsequently expands to form a complete duplication plaque on the outer face of the nuclear envelope

(Adams and Kilmartin 1999). The duplication plaque is drawn into the nuclear envelope to generate side-by-side SPBs within the nuclear envelope, which are connected by an intact bridge (Byers and Goetsch 1974, 1975; Adams and Kilmartin 1999, 2000). The subsequent fission of the Sfi1–Sfi1 interface in the bridge generates two independent, half-bridge-bearing SPBs, which nucleate the microtubules of the bipolar spindle.

STRUCTURE AND DUPLICATION CYCLES OF CENTRIOLAR CENTROSOMES

The advances in recent years of genomics and proteomics have led to identification of the multiple protein components of centrosomes and centrioles, and these, coupled with so-called superresolution light microscopy, are bringing our understanding of the functional biology of the centrosome toward the understanding that we have of yeast SPBs. Superresolution techniques overcome the limits imposed on conventional microscopy by diffraction of light and resolve what was previously seen by conventional immunostaining as an unstructured blob into a tiny cylinder (Sillibourne et al. 2011; Fu and Glover 2012; Lau et al. 2012; Lawo et al. 2012; Mennella et al. 2012; Sonnen et al. 2012). In this way, the mature *Drosophila* centrosome, for example, has been resolved into five major regions and three for its engaged daughter (see Fig. 6A). This places us in a position to understand precisely how the centrosome matures and how its molecular organization changes in anticipation of cell division as anticipated more than a century ago.

The centrosome duplication cycle occurs in concert with the cell-division cycle. Newly born cells have a pair of centrioles, one engaged orthogonally to the other. This arrangement is lost as centrioles disengage in early G_1 (Fig. 1B), and the two wander apart in G_1 now linked by a loose fibrous connection. Assembly of a procentriole perpendicular to each mother begins in G_1/S and the procentrioles subsequently elongate throughout G_2 until a similar size to their mothers. Before mitosis, the mother centrioles begin to accumulate more PCM and are able to nucleate increased microtubules in preparation for spindle assembly. The fibrous tether among centrosomes resolves permitting centrosomes to disjoin and separate to opposite sides of the cell as the spindle poles. Preparation for centriole duplication takes place in concert with preparation for S phase.

Tying Centriole Duplication to S Phase

Centrosome duplication shares key regulators with DNA replication and yet the two processes can be uncoupled to reveal that both are dependent on Cdk2/cyclin E. Treatment of *Drosophila* embryos or *Xenopus* egg extracts with the α-DNA polymerase inhibitor, aphidicolin, for example, leads to the repeated rounds of centrosome assembly (Raff and Glover 1988; Hinchcliffe et al. 1999). If, in the latter system, Cdk2-cyclin E activity was blocked with a Cdk inhibitor derived from p57, then the multiple rounds of centrosome reproduction could be prevented and then restored by addition of purified Cdk2-cyclin E. Accordingly, injection of the Cdk inhibitor p21 or p27 into an individual blastomere of a dividing *Xenopus* embryo blocks centrosome duplication in that blastomere (Lacey et al. 1999). Similarly, when Chinese hamster ovary (CHO) cells are arrested in S phase by hydroxyurea (HU), then inhibition of Cdk2 activity blocks the continued centrosome duplication (Matsumoto et al. 1999; Meraldi et al. 1999). Together, these findings lead to a model in which activation of Cdk2 ensures the centrosome duplication usually in phase with DNA replication.

Although several centrosome-associated Cdk2 substrates have been identified, including NPM/B23 (nucleophosmin) (Okuda et al. 2000; Tokuyama et al. 2001), Mps1 (Fisk and Winey 2001; Fisk et al. 2003), and CP110 (Chen et al. 2002), the role of Cdk2 phosphorylation in the duplication cycle is far from clear. However, some clues are emerging from the direct involvement of proteins required to control the initiation of DNA replication in both processes. Cdk2's partners, cyclin E and cyclin A, both interact with MCM5 and recruit it to the centrosome where they repress centrosome am-

plification in S phase–arrested CHO cells (Ferguson and Maller 2008; Ferguson et al. 2010). Moreover, cyclin A has been found to promote Orc1 localization to centrosomes where Orc1 prevents cyclin E–dependent reduplication of centrosomes (Hemerly et al. 2009). Finally, a direct link to the licensing of DNA replication emerges from experiments to deplete cells of Geminin, a negative regulator of the initiation of DNA replication. Geminin depletion leads to multiple DNA endoreduplication cycles at the expense of mitosis that in U2OS, HCT116 colorectal cancer cells and TIG-3 diploid fibroblasts have been shown to be accompanied with centrosome reduplication (Tachibana et al. 2005). In contrast, overexpression of Geminin inhibits centrosome reduplication in the human breast cancer cell line MDA-MB-231 (Lu et al. 2009). However, the details of the link between these licensing proteins and the centriole duplication machinery are still not clear.

Elevated levels of Cdk2/cyclin E activity have been proposed to underlie the overduplication of centrosomes seen in most p53-deficient cell lines (reviewed by Fukasawa 2008). In normal cells, this would be reflected as part of a stress response in which elevated levels of p53 would depress Cdk2 levels via the activation of p21, thus creating an environment that is not permissive for centriole duplication. However, how exactly p53 exerts its function at the centrosome is not clear. There does, however, appear to be a link between p53 and the regulation of Polo-like kinase 4 (Plk4), which, as we will see below, is a master regulator of centriole formation. The autoregulated instability of Plk4 controls its abundance, and thus preventing Plk4 autoregulation leads to centrosome amplification. This is normally associated with stabilization of p53 and loss of cell proliferation. In the absence of p53, function cells carrying amplified centrosomes are able to proliferate (Holland et al. 2012). The complexity of this regulative network is heightened by the recent report that Plk4 is directly phosphorylated and activated by stress-activated protein kinase kinase kinases (SAPKKKs) to promote centrosome duplication (Nakamura et al. 2013). However, this is balanced early in the stress response by stress-induced SAPK activation that prevents centrosome duplication. In the late stages of the stress response, however, p53 down-regulates Plk4 expression, thereby preventing sustained Plk4 activity and centrosome amplification. In cancer cells, both p53 and the SAPKK MKK4 are frequently inactivated leading to continued Plk4 activity and centrosome duplication in the absence of SAPK-mediated inhibition.

The Core Pathway of Centriole Assembly

The core pathway for centriole duplication was first elucidated in *Caenorhabditis elegans* as a series of dependent steps. The coiled-coil protein SPD-2 (spindle defective 2) was required to recruit the ZYG-1 protein kinase that, in turn, recruits the spindle assembly abnormal proteins SAS-6 and SAS-5 as a prerequisite for procentriole assembly and, finally, SAS-4, required for the addition of centriolar microtubules (Fig. 4A) (O'Connell et al. 2001; Kirkham et al. 2003; Leidel and Gonczy 2003; Dammermann et al. 2004; Delattre et al. 2004, 2006; Kemp et al. 2004; Pelletier et al. 2004, 2006; Leidel et al. 2005). The functional homologs of these five proteins are highly conserved (Fig. 4A) (Goshima et al. 2007; Dobbelaere et al. 2008; Balestra et al. 2013).

The Cartwheel

The protein at the innermost core of the centriole is Sas-6 (zone I in *Drosophila*; Sonnen et al. 2012; Dzhindzhev et al. 2014). Indications for its importance in establishing ninefold symmetry first came from studies of loss of its function in *Chlamydomonas*, *Paramecium*, and from *Drosophila*, in which loss of, or abnormalities in, the cartwheel structure were observed (Nakazawa et al. 2007; Rodrigues-Martins et al. 2007a; Jerka-Dziadosz et al. 2010). When its structure was unveiled through crystallography of large fragments of the zebrafish and *Chlamydomonas* proteins, this revealed the head-to-head dimerization of its amino-terminal part and a parallel coiled-coil dimer; the ninefold symmetry could be accounted for by nine such Sas-6 homodimers interacting through ad-

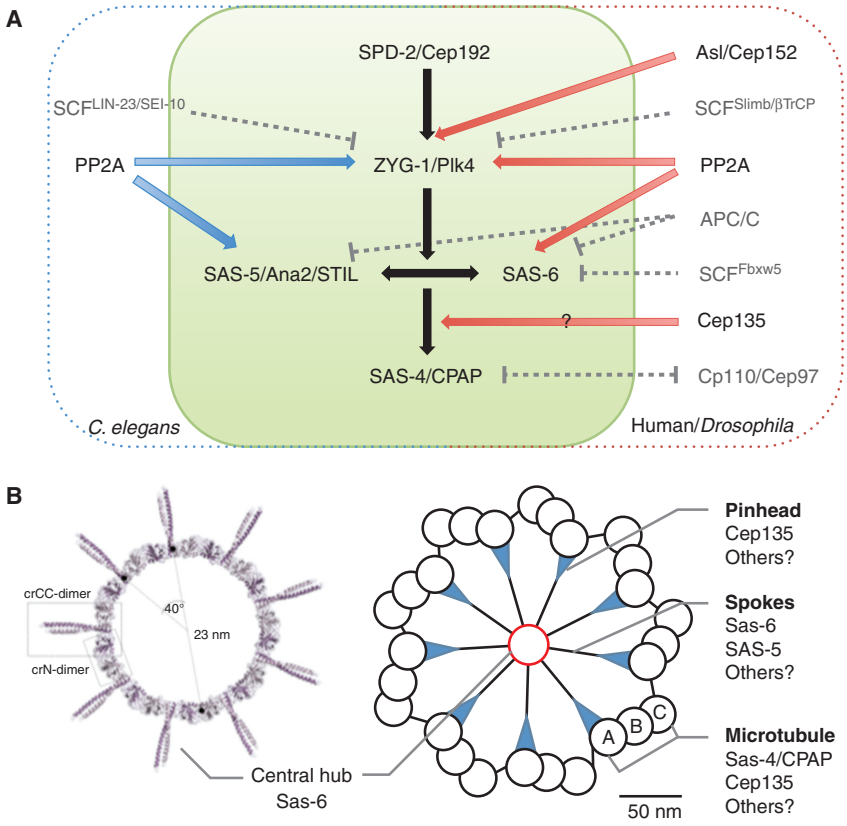

Figure 4. Centriole assembly. (*A*) Comparison of *Caenorhabditis elegans* (*C. elegans*) and Human/*Drosophila* pathways. Common elements are in the green box. (*B*) Structure organization of nine Sas-6 dimers (*left*) (Kitagawa et al. 2011c), and the relationship of cartwheel to centriole wall/microtubules (*right*). Molecular components are indicated.

jacent amino termini to give a ring-like central hub with the carboxy-terminal coiled-coil dimers radiating outward as nine spokes (Fig. 4B) (Cottee et al. 2011; Kitagawa et al. 2011c; Schuldt 2011; van Breugel et al. 2011). Indeed, Sas-6 protein could self-assemble into ring-like structures having similar diameters to the central hub and cartwheel in solution. The cartwheel height could then be accounted for by the stacking of such structures as later revealed by electron tomography of the cartwheel in the *Trichonympha* basal body (Guichard et al. 2012). This may not be the only way to establish the core structure, as analogous studies revealed that the *C. elegans* SAS-6 also forms N-N homodimers and coiled-coil dimers but these assemble into filamentous spiral oligomers instead of rings. Such a structure could be the underlying reason for the lack of the cartwheel structure in this organism and its replacement by a central tube (Hilbert et al. 2013). However, although the detailed arrangements of Sas-6 may vary among different species, its role in dictating centriolar ninefold symmetry seems now indisputable.

The close cooperation between SAS-5 and SAS-6 in centriole duplication in *C. elegans* is also seen with the human and *Drosophila* counterparts of SAS-5, STIL, and Ana2, respectively (Stevens et al. 2010; Kitagawa et al. 2011a; Tang et al. 2011; Arquint et al. 2012; Vulprecht et al. 2012). Overexpression of SAS-6 in *Drosophila* syncytial embryos led to the de novo formation of tube- or vesicle-like structures that are surrounded by microtubule asters (Rodrigues-

Martins et al. 2007a). However, coexpression of Sas-6 and Ana2 in *Drosophila* spermatocytes leads to the assembly of cartwheel-like structures (Stevens et al. 2010). Overexpression of STIL or Sas-6 in other systems leads to centriole overduplication (Kitagawa et al. 2011a; Tang et al. 2011; Arquint et al. 2012; Vulprecht et al. 2012). Both Ana2 and STIL localize to the innermost region of the centriole (Sonnen et al. 2012; Dzhindzhev et al. 2014), raising the possibility that Ana2/STIL might be part of the cartwheel structure. Indeed, the *C. elegans* SAS-5 physically binds a narrow central region of the SAS-6 coiled-coil domain, and is able to prevent the coiled-coil dimer from forming a tetramer in vitro (Qiao et al. 2012). Moreover, once phosphorylated by Plk4, *Drosophila* Ana2 becomes able to bind Sas-6 (see below) (Dzhindzhev et al. 2014).

Although SAS-6 and SAS-5/Ana2/STIL are components of the innermost part of the centriole, SAS-4 colocalizes with its microtubule wall (zone II in *Drosophila* cells; Fu and Glover 2012). Indeed, SAS-4 promotes polymerization of centriolar microtubules, and overexpression of its human homolog, CPAP, leads to centriole elongation (Kohlmaier et al. 2009; Schmidt et al. 2009; Tang et al. 2009). A tubulin-binding domain is critical for this function (Hsu et al. 2008; Cormier et al. 2009), and its stable incorporation into centrioles is dependent on γ-tubulin and microtubule assembly (Dammermann et al. 2008). CPAP is reported to interact with STIL and another centriole protein, Cep135 (Tang et al. 2011; Cottee et al. 2013; Hatzopoulos et al. 2013; Lin et al. 2013a), but how these molecules cooperate to regulate procentriole assembly requires further analysis. The functional importance of Cep135 was first shown by the requirement for its ortholog, Bld10p, for cartwheel formation in *Chlamydomonas* and *Paramecium* (Hiraki et al. 2007; Jerka-Dziadosz et al. 2010). *Drosophila* centrioles are still able to form in the absence of Cep135 but are short (Mottier-Pavie and Megraw 2009; Carvalho-Santos et al. 2010). Similarly, when Cep135 was disrupted in the chicken DT40 cell line, there was only a small decrease in the centriole number with no major defects in centrosome composition or structure (Inanc et al. 2013). However, human Cep135 is required for excessive centriole duplication following Plk4 overexpression (Kleylein-Sohn et al. 2007), and a recent report showed that depletion of Cep135 reduces the centrosome number (Lin et al. 2013a). Thus, although a common function of Cep135 seems to ensure the intact structure of centrioles, in most cases, its loss does not have a devastating effect (Roque et al. 2012; Inanc et al. 2013; Lin et al. 2013a).

Plk4

The protein kinase ZYG-1 that lies at the head of the centriole formation pathway in *C. elegans* is a distant member of the Plk4 family, a family of Polo-like kinases that have three Polo box domains within their carboxy-terminal domain (Slevin et al. 2012). Like ZYG-1, Plk4 lies at the head of the pathway for centriole assembly in *Drosophila* and human cells (Bettencourt-Dias et al. 2005; Habedanck et al. 2005; Kleylein-Sohn et al. 2007; Rodrigues-Martins et al. 2007b). When Plk4 is down-regulated, centriole duplication fails, and when it is overexpressed in *Drosophila* embryos, it promotes overduplication of sperm-derived centrioles (Bettencourt-Dias et al. 2005; Rodrigues-Martins et al. 2007b; Cunha-Ferreira et al. 2009). Strikingly, Plk4 was also found to drive de novo centriole formation when overexpressed in unfertilized eggs (Rodrigues-Martins et al. 2007b). Contemporaneous findings in human cells showed that Plk4 overexpression causes centrioles to overduplicate into flower-like arrays with mother centrioles in the center (Kleylein-Sohn et al. 2007). However, how Plk4 exerts this function remains largely unknown. In *C. elegans,* ZYG-1 binds directly to SAS-6 and recruits the SAS-6–SAS-5 complex to the centriole, independent of its kinase activity (Lettman et al. 2013). Consistently, overexpression of Plk4 can promote the recruitment of Ana2/STIL and Sas-6 to supernumerary centrioles (Kleylein-Sohn et al. 2007; Stevens et al. 2010). A number of Plk4/ZYG-1 substrates have been identified—SAS-6 (Kitagawa et al. 2009), Cep152 (Hatch et al. 2010), and a component of γ-TuRC GCP6

(Bahtz et al. 2012), but their significance is not clear. More recently, it has been shown in *Drosophila* that Plk4 phosphorylates Ana2 in its conserved STAN motif to enable it to bind to Sas-6. Both Ana2 and Sas-6 become recruited to the daughter centriole once it has disengaged from the mother at the end of mitosis. If the Plk4 sites in Ana2 are mutated to *nonphosphorylatable* residues, it can still bind to the daughter centriole but it cannot recruit Sas-6, and centriole duplication fails (Dzhindzhev et al. 2014). In contrast to *Drosophila*, where some Sas-6 remains at the core of the centriole once it is incorporated, in human cells, Sas-6 is destroyed during G_1 (Strnad et al. 2007) and is transiently recruited to the lumen of the mother centriole in S phase (Fong et al. 2014). The human Sas-6 is then repositioned to the site of procentriole formation in a process that is dependent on STIL/Ana2) and Plk4 (Fong et al. 2014).

Since the original studies in *C. elegans,* it has become clear that centriole assembly requires additional factors. One of these, Asterless (Asl, *Drosophila*)/Cep152 (vertebrates) has particular importance in recruiting Plk4 to the centrosome. The interaction of two of the Polo boxes of Plk4 (the cryptic Polo-box domain) with Asl/Cep152 is conserved in *Drosophila*, human, and *Xenopus* cells, although their codependency for localization differs (Cizmecioglu et al. 2010; Dzhindzhev et al. 2010; Hatch et al. 2010). Asl also has additional roles in binding Sas-4 to help establish the PCM (see below). Cep192 also binds to Plk4 and so cooperates with Cep152 in recruiting Plk4 to the centriole (Sonnen et al. 2013; Firat-Karalar et al. 2014). This echoes the finding of the dependency of ZYG-1 recruitment on SPD-2 in *C. elegans.* However, in *Drosophila*, Spd-2 barely plays any role in centriole assembly but is instead required for PCM recruitment on mitotic entry (Dix and Raff 2007; Giansanti et al. 2008). In Planarians where the canonical centriole duplication pathway was abandoned during evolution and centrioles are only assembled in terminally differentiating ciliated cells through an acentriolar pathway, Spd-2/Cep192 along with CNN/CDK5RAP2 and Nek2 are all absent from the genome (Azimzadeh et al. 2012). This raises the possibility that Spd-2 is not needed for de novo centriole formation, but for canonical duplication.

To ensure that proliferating cells have only a single pair of functional centrosomes, it is crucial to tightly regulate the levels of centriolar proteins, particularly Plk4. How Plk4 becomes activated and then how its activity might be restricted to one part of the centriole at which the procentriole forms is not yet understood. In some way, licensing of duplication is linked to the disengagement of centrioles at the end of mitosis (see below) but the molecular details of this process have to be elucidated.

In contrast, we know quite a lot about the controlled proteolysis of Plk4 kinase that is achieved in both *Drosophila* and human cells via the $SCF^{Slimb/\beta TrCP}$ ubiquitin ligase complex (Cunha-Ferreira et al. 2009; Rogers et al. 2009; Guderian et al. 2010). If this system fails, the consequence is development of multiple centrioles both in *Drosophila* and human cells. Plk4 degradation first requires that Plk4 forms a homodimer through its carboxy-terminal coiled-coil region (Leung et al. 2002; Habedanck et al. 2005), where it is able to autophosphorylate a phosphodegron enabling the binding of $SCF^{Slimb/\beta TrCP}$ to promote its own destruction (Guderian et al. 2010; Holland et al. 2010, 2012; Sillibourne et al. 2010). Consistently, the ZYG-1 kinase of *C. elegans* is also down-regulated by the Slimb/βTrCP homolog, LIN-23, and also a second F-box protein, SEL-10 (Peel et al. 2012).

The autophosphorylation of *Drosophila* Plk4 is counteracted by the protein phosphatase PP2A and its B55 regulatory subunit Twins, that thereby act to stabilize Plk4 during mitosis (Brownlee et al. 2011). Plk4 is not the only centriolar protein to be targeted by PP2A. In *C. elegans*, PP2A's association with the SAS-5–SAS-6 complex is instrumental in targeting SAS-5 and, hence, SAS-6 to the centriole (Kitagawa et al. 2011a), and its activity protects SAS-5 as well as ZYG-1 from degradation by the proteasome (Song et al. 2011). PP2A is similarly required for human Sas-6 to localize to centrioles (Kitagawa et al. 2011a), although it is not clear whether this is mediated through STIL.

Levels of Plk4 appear to decrease at the centrosome as cells exit mitosis, suggesting that the

APC/C might also regulate Plk4 levels. Similar reductions occur for CPAP, STIL, and human Sas-6 and each of these molecules is targeted by APC/C-Cdh1 or Cdc20 (Strnad et al. 2007; Tang et al. 2009, 2011; Puklowski et al. 2011; Arquint et al. 2012; Arquint and Nigg 2014). Interplay between APC/C and SCF pathways has also been reported to regulate levels of Sas-6 (Puklowski et al. 2011). Sas-6 forms a complex with Fbxw5 to target its destruction. However, Fbxw5 is negatively regulated by Plk4 and it is also targeted for destruction by the APC/C. Thus, the Fbxw5-mediated destruction of Sas-6 would be promoted at mitotic exit and at times when Plk4 activity is minimal. However, further work is needed before we have a coordinated picture of the spatial and temporal regulation of the stability and activity of these proteins.

Centriole Elongation

Once the cartwheel of the procentriole is established, then the A, B, and C centriolar microtubules are added and begin growth (Guichard et al. 2010). Some of the components identified as essential for centriole assembly also contribute to centriolar microtubule elongation. Sas-4/CPAP, for example, promotes the polymerization of centriolar microtubules in cooperation with CEP120, which localizes preferentially to the daughter centriole (Mahjoub et al. 2010; Comartin et al. 2013; Lin et al. 2013b). Overexpression of either CPAP or CEP120 results in excessively long centrioles and their depletion abolishes this phenotype (Comartin et al. 2013; Lin et al. 2013b). CEP120 also interacts with SPICE1 that is required for centriole duplication, spindle formation, and chromosome congression (Archinti et al. 2010). Depletion of SPICE1 also results in short procentrioles, although, in contrast to its partners, overexpression of SPICE1 does not cause centriole elongation (Comartin et al. 2013). The existence of a second mechanism controlling the length of the distal part of the centriole is suggested in HeLa cells where short procentrioles or centrioles with defective distal structures accumulate in the absence of POC5 (Azimzadeh et al. 2009) and in Ofd1 mutants of mouse cells that display an abnormally elongated distal portion of centriole (Singla et al. 2010).

The elongation of centrioles brought about by overexpression of CPAP can be counteracted by another centriolar protein, CP110 (Kohlmaier et al. 2009; Schmidt et al. 2009; Tang et al. 2009). CP110 is required for the formation of supernumerary centrioles resulting from excessive Plk4 or from S-phase arrest (Chen et al. 2002; Kleylein-Sohn et al. 2007) but it also limits centriole length in HeLa and U2OS cells, where its depletion leads to abnormally long centrioles (Schmidt et al. 2009). It may act as a physical barrier for elongation as it localizes to the distal end of the centriole (zone V) as a cap (human) or plug (*Drosophila*) (Kleylein-Sohn et al. 2007; Fu and Glover 2012). The Cep97 protein is required to target CP110 to this distal part of the centriole and overexpression of these proteins can prevent the formation of primary cilia in RPE1 cells (Spektor et al. 2007; Tsang et al. 2008). This is suggested to occur by opposing CEP290, whose depletion prevents ciliogenesis, by interfering with Rab8a's localization to centrosomes and cilia (Tsang et al. 2008). Depletion of a kinesin-13 subfamily member, Kif24, also induces the formation of primary cilia, but not elongated centrioles, apparently by displacing CP110 and Cep97 from the mother centriole (Kobayashi et al. 2011). Together, this indicates that the removal of CP110 and Cep97 from the centriole tip is a critical early step for ciliogenesis. A depolymerizing kinesin-like protein, Klp10A, has been found to restrict centriolar microtubule length in *Drosophila* cells. However, in this case, depletion of CP110 shortens centriole microtubules, apparently by exposing them to Klp10A (Delgehyr et al. 2012).

CP110 is also targeted for degradation by the SCF through the F-box protein cyclin F/Fbxo1 and if allowed to accumulate it induces centrosome overduplication in G_2 (D'Angiolella et al. 2010). A deubiquitinating enzyme, USP33, antagonizes $SCF^{cyclinF}$-mediated ubiquitination and stabilizes CP110 possibly during S and G_2/M phases (Li et al. 2013). Consequently, depletion of USP33 inhibits centrosome amplification in S-phase-arrested U2OS cells or in cyclin-F knockdown cells.

How ubiquitin ligase and deubiquitinating enzyme counteract each other's function as the cell cycle progresses needs further exploration. However, it seems clear that the regulated destruction of centriolar proteins plays a role not only in centriole duplication, but also in elongation. Thus, pharmacological inhibition of cellular proteolysis by Z-L_3VS or MG132 not only causes assembly of multiple daughter centrioles but also their abnormal elongation. A siRNA screen for genes affecting centriole length in Z-L_3VS-treated cells has revealed additional players to CPAP, CP110, and Cep97, which include the centriolar protein Sas-6, centrosomal proteins FOP and CAP350, the cohesion protein C-Nap1, as well as appendage proteins Cep170 and ninein (Korzeniewski et al. 2010). It will be fascinating to see how these fit into the regulatory network that controls centriole length.

Centrosome Disjunction at G_2/M

When mother and daughter centrioles lose their orthogonal arrangement during mitotic exit, a second proteinaceous linker, containing C-Nap1 and rootletin, is established that connects them at their proximal ends and persists until G_2/M (Fig. 5A) (Fry et al. 1998; Mayor et al. 2000; Bahe et al. 2005; Yang et al. 2006). Depletion of C-Nap1 or rootletin causes centrosome splitting regardless of the cell-cycle stage (Mayor et al. 2000; Bahe et al. 2005). Immuno-EM revealed C-Nap1's localization to the proximal ends of the connected centrioles but not between them, whereas rootletin is present both at ends and between the centriole pairs in nonciliated cells and, in addition, connected to basal bodies in ciliated cells (Fry et al. 1998; Mayor et al. 2000; Bahe et al. 2005; Yang et al. 2006). The overexpression of rootletin produces fibers that are able to recruit Nek2A and C-Nap1. Cep68 also decorates fibers emanating from the proximal ends of centrioles, dissociates from centrosomes during mitosis, and requires rootletin and C-Nap1 for centrosome localization. Depletion of rootletin does not affect the association of C-Nap1 with centrosomes, whereas either depletion of C-Nap1 or overexpression of its fragments affects the centrosomal localization of rootletin (Bahe et al. 2005; Yang et al. 2006). Phosphorylation of both proteins by Nek2A (Fry et al. 1998; Helps et al. 2000; Bahe

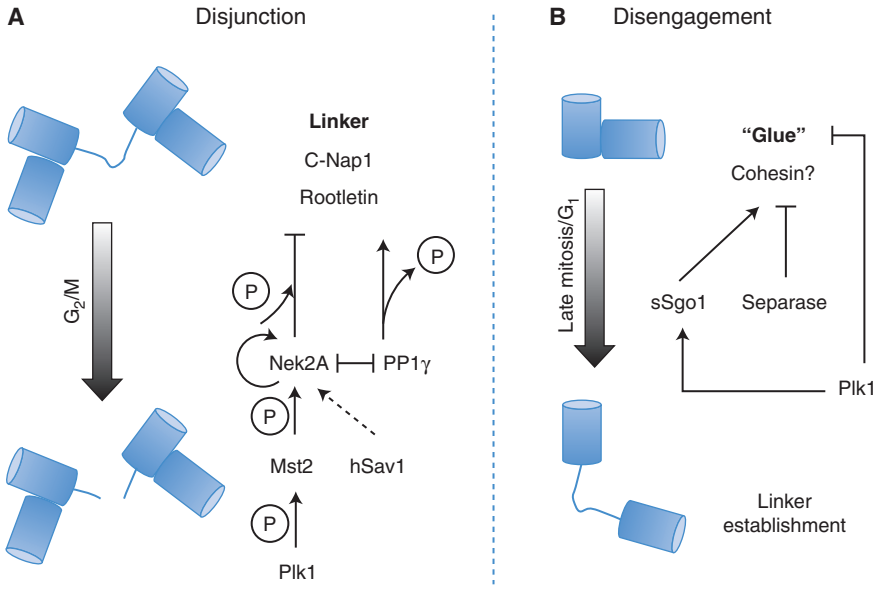

Figure 5. Centrosome disjunction and centriole disengagement. (*A*) Series of upstream events trigger the dissociation of C-Nap1 and rootletin from the centrosome leading to loss of centrosome cohesion. Main players are depicted. (*B*) Roles of Plk1 and separase in disjoining mother and daughter centrioles.

et al. 2005) promotes centrosome disjunction at the G_2/M transition; overexpression of wild-type Nek2A will stimulate centrosome splitting in interphase, whereas the kinase-dead mutant leads to monopolar spindles with unseparated spindle poles (Faragher and Fry 2003). Together, this has led to a model whereby C-Nap1 provides a docking site for rootletin fibers to connect the proximal ends of centrioles, Nek2A phosphorylates both C-Nap1 and rootletin, promoting their dissociation from the centrosome and leading to loss of centrosome cohesion.

Two Hippo pathway components, Mst2 kinase (mammalian sterile 20–like kinase 2) and the scaffold protein hSav1 (scaffold protein Salvador), directly interact with Nek2A and regulate its ability to localize to centrosomes. Phosphorylation of Nek2A by Mts2 promotes its ability to induce centrosome disjunction. Depletion of Mst2, hSav1, or Nek2A results in a reduction of C-Nap1 phosphorylation and the continued association of C-Nap1 and rootletin with centrosomes that are still able to separate and form a spindle through the Eg5 pathway (Mardin et al. 2010). It seems that Plk1 functions upstream of the Mst2-Nek2A pathway. Phosphorylation of Mst2 by Plk1 blocks formation of a Nek2A–PP1γ–Mst2 complex in which Nek2 phosphorylation of C-Nap1 is counteracted by PP1 (Helps et al. 2000; Mardin et al. 2011). Nek2 also associates with two structural proteins that block its activity, namely, the focal adhesion scaffolding protein, HEF1 (Pugacheva and Golemis 2005) and pericentrin/kendrin (Matsuo et al. 2010). It has been proposed that pericentrin/kendrin serves to anchor Nek2 at the centrosome and suppress its activity.

After centrosome disjunction, the further separation of two centrosomes is mediated mainly by the kinesin-5 subfamily member, Eg5 (for review, see Ferenz et al. 2010). Eg5 homotetramers cross-link antiparallel microtubules so that when the motors walk toward microtubule plus ends, the antiparallel microtubules slide apart and centrosomes get pushed away from each other (Kashina et al. 1996). Inhibition of Eg5 by small molecule inhibitors monastrol results in prometaphase-arrested cells with monopolar spindles (Kapoor et al. 2000).

PCM Assembly

The enlargement of the centrosome that begins before mitosis results from recruitment of PCM first thought to be amorphous, but more recently revealed by 3D-structured illumination microscopy to be organized in layers that have a clear hierarchy (Fig. 6A,B) (Fu and Glover 2012; Lawo et al. 2012; Mennella et al. 2012; Sonnen et al. 2012). It is helpful to consider PCM in terms of two groups of proteins. One group of PCM proteins, including Dplp/pericentrin, Asl/Cep152, and Plk4, are associated with the mother centriole where, throughout the cell cycle, they reside in the region adjacent to the centriole microtubules. The other group, including Spd-2/Cep192, CNN/CDK5RAP2, and γ-tubulin are robustly recruited only on mitotic entry, again predominantly around the mother centriole, when the centrosome begins to nucleate increased numbers of microtubules.[3]

Although Asl is essential for Plk4 function (Dzhindzhev et al. 2010), pointers to another of its functions—recruiting PCM—came from early studies of *asl* mutants (Varmark et al. 2007). Other indications came from the discovery that CNN failed to be recruited to centrosomes following the injection of antibodies against Asl into *Drosophila* (Conduit et al. 2010). These findings can largely be accounted for by a direct interaction between Asl and Sas-4 and the bridging role played by Sas-4 in linking the centriole with PCM (Dzhindzhev et al. 2010). When expressed in *Drosophila* embryos, either Sas-4 alone or a mutant form of Asl able to bind Sas-4 but not Plk4 can promote formation of acentriolar PCM aggregates that nucleate cytoplasmic microtubules (Dzhindzhev et al. 2010). Moreover, Sas-4 null mutant flies show a reduction of PCM components in testes (Gopalakrishnan et al. 2011, 2012). This reflects the ability of Sas-4 to form complexes with CNN and Dplp; centrosomes with mutant Sas-4 unable to form such complexes have reduced PCM (Dzhindzhev et al. 2010; Gopalakrishnan et al. 2011). A double mutation in Sas-4 protein se-

[3]This is in addition to Spd-2 present within zone II throughout the cell cycle.

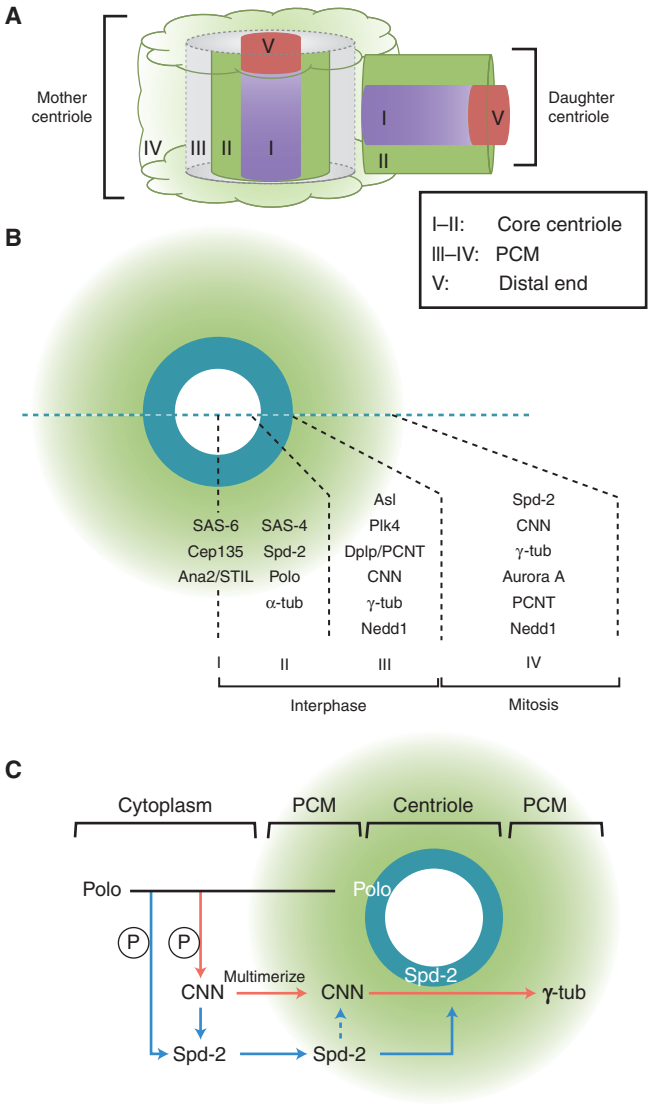

Figure 6. Pericentriolar material (PCM) assembly. (*A*) The zones of the *Drosophila* centrosome (Fu and Glover 2012). (*B*) Expansion of the PCM in mitosis. Comparison of human and *Drosophila* components. (*C*) Pathway of PCM assembly deduced from studies in *Drosophila* (Fu and Glover 2012; Conduit et al. 2014a,b). tub, Tubulin.

quence that abolishes its binding to tubulin enhances centrosomal protein complex formation leading to abnormally large centrosomes and asters (Gopalakrishnan et al. 2012). Thus, tubulin binding may interfere with Sas-4-mediated PCM assembly. Sas-4 is recruited to both mother and daughter centrioles at a very early stage, and how it specifically initiates PCM assembly around mother but not daughter centrioles needs further study.

Surprisingly, a whole genome siRNA screen with *Drosophila* cells identified only three components, Polo, Spd-2, and CNN, that are required for the second phase—the expansion of the PCM for mitosis (Fig. 6C) (Dobbelaere et al. 2008). Polo kinase or Plk1 (Polo-like kinase 1) is

the major kinase required for the dramatic increase of PCM that occurs before mitotic entry (Blagden and Glover 2003; Glover 2005). Its kinase activity is needed for the normal localization of Spd-2/Cep192, CNN/CDK5RAP2, pericentrin, and Nedd1 (Haren et al. 2009; Zhang et al. 2009; Hatch et al. 2010; Lee and Rhee 2011; Fu and Glover 2012). Interestingly, *Drosophila* Polo is restricted to zone II (i.e., the vicinity of the microtubule wall). As Polo phosphorylates both Spd-2 and CNN, this suggests the existence of a phosphorylation gradient as PCM assembles. In accord with this notion, a FRAP experiment indicated that CNN is recruited first to the vicinity of centriole before spreading out into the PCM (Conduit et al. 2010). Continuous Plk1 activity is required during mitosis to maintain PCM structure after centrosome maturation (Mahen et al. 2011). PCM is present only around the mother centriole as cells progress through mitosis but as the mother and daughter disengage, then the daughter becomes competent to recruit PCM in the following G_1 phase. This process requires Plk1, as does the accompanying process of centriole disengagement (see below), although what exactly Plk1's substrate might be in this process remains unknown (Wang et al. 2011). In *C. elegans*, Plk1 is targeted to the centrosome by Spd-2, which, when overexpressed, can increase the centrosome volume (Decker et al. 2011). However, whether Plk1 is targeted by this route in other organisms is not yet clear.

There is some interdependency for recruitment of Polo's substrates Spd-2 and CNN to the PCM; localization of Spd-2 to PCM requires CNN, whereas CNN can partially support its own recruitment in cultured *Drosophila* cells (Fu and Glover 2012). This may vary a little among different cell types, as in the embryo, Conduit and colleagues suggest that Asl initially helps recruit Spd-2, which, in turn, recruits CNN. CNN, on the other hand, was not required to recruit Asl or Spd-2, but was required to maintain Spd-2 in the PCM (Conduit et al. 2014a). *CNN* mutants show reduced γ-tubulin and Aurora A at the embryonic centrosome (Megraw et al. 1999; Zhang and Megraw 2007), and a conserved motif near the amino terminus of CNN has been identified as essential for recruitment of γ-tubulin, D-TACC (transforming acidic coiled-coil proteins), and the Ch-TOG family microtubule polymerase Msps (Minispindles) (Zhang and Megraw 2007). Spd-2 mutant flies have reduced CNN and γ-tubulin in several cell types (Dix and Raff 2007; Giansanti et al. 2008), and injection of antibodies against Spd-2 into *Drosophila* embryos prevents CNN recruitment in the vicinity of the centriole (Conduit et al. 2010). CDKRAP2 and Cep192, human counterparts of CNN and Spd-2, also increase on centrosome maturation as does pericentrin, and the proteins show interdependency for the recruitment of γ-tubulin (Haren et al. 2009; Lee and Rhee 2011). In part, this reflects the physical association of γ-tubulin with the amino-terminal part, and pericentrin with the carboxy-terminal part of CDKRAP2 (Fong et al. 2008; Choi et al. 2010; Wang et al. 2010).

Aurora A kinase also contributes to centrosome maturation. In part, this may be because of its role together with Bora in activating Plk1 by phosphorylating Thr210 at the G_2/M transition (Macurek et al. 2008; Seki et al. 2008). Secondly, Aurora A has a role in the enrichment of multiple centrosomal factors onto the centrosome. Key to this is the phosphorylation and recruitment of the transforming acidic coiled-coil protein 3 (TACC3; D-TACC in *Drosophila*) and its partner proteins that influence the properties of microtubules nucleated by the PCM (Giet et al. 2002; Terada et al. 2003; Barros et al. 2005; Kinoshita et al. 2005; Mori et al. 2007; Fu et al. 2010).

Disengagement of the Mother–Daughter Linkage

At the end of S phase, the cell has two centrosomes, each comprising a mother–daughter pair of centrioles (technically, one of these mothers is a grandmother). The pairs remain tightly linked at the poles of the spindle for mitosis, after which they disengage (Fig. 5B). Centriole disengagement has been described as a licensing step that enables the duplication of centrioles purified from S-phase-arrested

HeLa cells and placed in a *Xenopus* egg extract (Tsou and Stearns 2006). In these experiments, disengaged centrioles could duplicate during the first interphase of a cycling extract, whereas engaged centrioles required an extra cycle to become disengaged. It has been suggested that recruitment of Asl onto the daughter centriole in *Drosophila* embryos occurs only once mother and daughter have separated at the end of mitosis and that this provides a duplication license (Novak et al. 2014). However, it is notable that in cultured cells, the incorporation of Ana2 and Sas-6 onto the daughter's procentriole once it has disengaged from the mother in telophase appears to mark the very first event in the duplication process (Dzhindzhev et al. 2014).

Disengagement in late mitosis requires the activity of separase, the protease that promotes sister chromatid separation, and Plk1 (Tsou et al. 2009). Although the notion that centriole disengagement and chromatid separation might share common machinery appears elegant, whether cohesin is a separase substrate in both processes remains confusing. Although one study has reported that a noncleavable cohesin subunit Scc1 would not prevent disengagement in HeLa cells (Tsou et al. 2009), another suggested otherwise in Hek293 cells (Schockel et al. 2011). If endogenous Scc1 was replaced by a variant carrying a recognition site for human rhinovirus HRV protease or if its partner protein, Smc3, carried a site for TEV protease, these molecules could be cleaved by the appropriate protease resulting in centriole disengagement. However, similar experiments in *Drosophila* embryos have challenged the involvement of cohesin in centriole engagement. *Drosophila* embryos expressing TEV-cleavable Rad21 (corresponding to human Scc1) were arrested at metaphase by the catalytically inactive E2 ubiquitin ligase, Ubch10^{C114S} (Cabral et al. 2013; Oliveira and Nasmyth 2013). Centriole disengagement could be observed after treatment with the Cdk inhibitor, p21, to drive mitotic exit but not after by TEV protease treatment that leads to sister chromatid separation (Oliveira and Nasmyth 2013). Depletion of the *C. elegans* separase, sep-1, impairs the separation and consequent duplication of sperm-derived centrioles at the meiosis–mitosis transition, but subsequent cycles proceed normally (Cabral et al. 2013). To date, searches for alternative separase substrates in centriole disengagement have identified kendrin/pericentrin B (Lee and Rhee 2012; Matsuo et al. 2012). However, much remains to be done before we understand the nature of this process.

Although most engagements are eventually dissolved even without separase, the requirement for Plk1 appears absolute. Inhibition of Plk1 in a *Xenopus* CSF extract, for example, will block disengagement in the presence of separase (Schockel et al. 2011), and overexpression of Plk1 will promote centriole disengagement in G_2 (Loncarek et al. 2010). It also seems that APC/C activity contributes to disengagement (Prosser et al. 2012), and that Plk1 and APC/C-Cdh1 activities can independently achieve this (Hatano and Sluder 2012). The duality of the regulation of sister chromatid separation and centriole disengagement is echoed in the suggestion of a role for Plk1 in localizing the small isoform of Shugoshin1 (sSgo1). Mutation of sSgo1's putative Plk1 phosphorylation sites results in weaker localization at centrosome and promotes centriole splitting in mitosis (Wang et al. 2008). Further work is required to determine the detail and universality of this potential regulatory system and the nature of Plk1's substrates in centriole disengagement.

Plk1 may well have multiple roles at the centrosome toward the end of mitosis that relate to the differential behavior of mother and daughter centrioles. The disengagement of the procentriole by Plk1 is hypothesized to expose a site on the mother, enabling it once again to be able to initiate formation of a new procentriole. At the same time, Plk1 is proposed to modify the daughter centriole in some way as to render it competent for the initiation for procentriole formation in the next cycle (Loncarek et al. 2010; Wang et al. 2011).

THE CILIUM CYCLE

Primary cilia are present on most cell types in vertebrates where they function in signal sensing and transduction. In quiescent, G_1 or

G_0, cells, the mother centriole associates with the ciliary vesicle at its distal end, migrates to the cell surface, and docks at the plasma membrane to become a basal body competent for cilium formation. The distal appendage proteins Cep83/ccdc41, SCLT1, FBF1 (Tanos et al. 2013), Cep89/ccdc123 (Sillibourne et al. 2011), and Cep164 (Graser et al. 2007) are all required for cilium formation (Tanos et al. 2013). CEP83 is specifically required for centriole-to-membrane docking (Joo et al. 2013; Tanos et al. 2013). The subsequent elongation of the ciliary axoneme depends on intraflagellar transport (IFT), a microtubule motor-based delivery system that transports cargos from outside the cilia to the growing tip, or retrieves them to the cell body (reviewed by Pedersen and Rosenbaum 2008; Ishikawa and Marshall 2011; Avasthi and Marshall 2012).

Ciliogenesis first requires the removal of CP110 and Cep97 from the distal end of the centriole (Fig. 7). This is promoted by Tau-tubulin kinase 2 (TTBK2); in TTBK2 null mouse embryo, E10.5 neural cilia are missing in 10.5-day-old embryos, and yet basal bodies dock to the cell cortex (Goetz et al. 2012). Cep83 appears to be upstream of this process because its depletion blocks centrosome-to-membrane association, and the undocked centrioles fail either to recruit TTBK2 or release CP110 (Ri-parbelli et al. 2012). It has been reported that, after cytokinesis, cilia arise considerably faster in cells inheriting the older mother centriole and that these cells are more responsive to Sonic Hedgehog signals that require receptors on the cilia (Anderson and Stearns 2009). This suggests the centriole age might transmit asymmetry to sister cells and potentially influence their ability to respond to environmental signals and so alter cell fate.

To regain its function as a centriole at the spindle pole, the basal body needs to dissociate from the cell cortex usually with loss of the cilium (Fig. 7). In mammalian cells, active Aurora A kinase associates with basal bodies to induce cilia disassembly by phosphorylating HDAC6 (histone deacetylase 6) to activate its tubulin deacetylase activity, necessary for primary cilia resorption (Pugacheva et al. 2007). HEF1, a transducer of integrin-initiated attachment, migration, and antiapoptotic signals at focal adhesions, appears to be required to stabilize and activate Aurora A for cilia disassembly (Pugacheva et al. 2007). In *Chlamydomonas*, cilia are cleaved from the basal body at the distal end of the transition zone (Parker et al. 2010) in a process requiring the scaffold protein Fa1, the NIMA family kinase Fa2 (Finst et al. 1998, 2000; Mahjoub et al. 2002), and the microtubule-severing protein katanin (Quarmby 2000). The

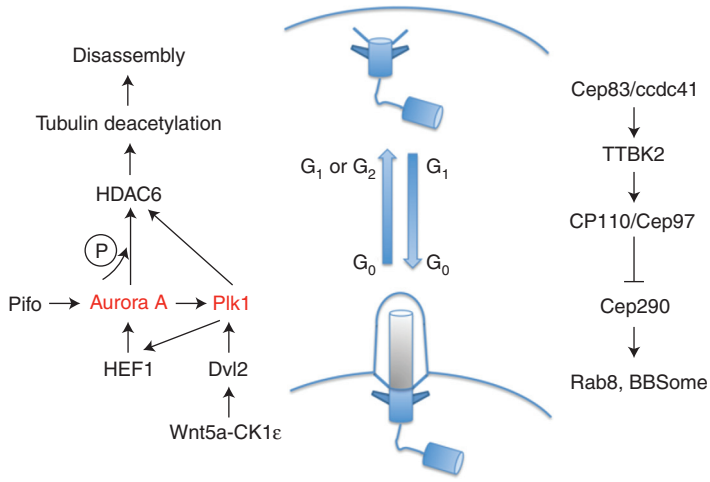

Figure 7. Cilia assembly and disassembly cycle. Role of Plk1 and Aurora A in activating tubulin deacetylation for cilia disassembly (*left*). Cilia assembly pathway (*right*).

Chlamydomonas Aurora A–like kinase, CALK, is also required for cilia excision and disassembly (Pan et al. 2004), suggesting that this is an evolutionarily conserved mechanism.

Plk1 also participates in the disassembly process by interacting with phosphorylated Dvl2 (Dishevelled 2), which is primed by both noncanonical Wnt5a signaling and CK1ε (casein kinase 1 epsilon). Depletion of Plk1, Dvl2, or disruption of their interaction leads to lower HEF1 levels and reduced Aurora A activity (Lee et al. 2012). Plk1, recruited by PCM1 to the PCM in G_2, is also required for a second wave of cilia resorption (Wang et al. 2013). Plk1 appears also to interact with HDAC6 and promote tubulin deacetylation independently of Aurora A because activated Plk1 induces cilia disassembly in the presence of an Aurora A kinase inhibitor (Wang et al. 2013). This points to cooperation between Aurora A and Plk1 in centriole disassembly just as there is in centrosome maturation.

There is growing evidence that cell-cycle progression can be held up to accommodate cilia formation. When cells are depleted of Nde1 (nuclear distribution gene E homolog 1), cells develop longer cilia and cells are delayed in cell-cycle reentry (Kim et al. 2011). Cilia disassembly can also influence cycle progression; a phosphomimic mutant of the dynein-associated protein, Tctex-1, is recruited to the transition zone, where it accelerates both cilium disassembly and S-phase entry (Li et al. 2011). Suppression of Aurora A or HDAC6 activities will also inhibit both ciliary resorption and S phase (Li et al. 2011), thus pointing to an inhibitory effect of cilia on cell-cycle progression.

THE CENTROSOME AND SPB AS CONTROL CENTERS

The catalog of proteins that associate with the centrosome is very large. As the cell's principal microtubule-organizing center (MTOC), it is a hub for microtubule-associated molecules and has great potential as a center for regulatory function.

Just as seminal advances in our understanding of cell-cycle progression came from studies with the budding yeast (*Saccharomyces cerevisiae*) and fission yeast (*Schizosacharomyces pombe*) in the 1980s, in more recent years, clues to the overriding importance of the centrosome in signaling mitotic entry have also emerged largely from studies in yeasts. To briefly recap, the universal cell-cycle controls owe much to fission yeast studies by Nurse and colleagues. Cdk1-cyclin B activity is restrained throughout interphase via phosphorylation of Cdk1 by Wee1 kinases. Removal of this phosphate from stockpiled Cdk1/cyclin B complexes by Cdc25 phosphatases then unleashes a wave of Cdk1-cyclin B activity that promotes mitotic commitment (Nurse 1990). Work in *Xenopus laevis* oocyte/egg extracts established that an initial impact of newly activated Cdk1-cyclin B is to use Polo kinase to enhance Cdc25 and repress Wee1 activities (Hoffmann et al. 1993; Izumi and Maller 1993, 1995; Strausfeld et al. 1994; Kovelman and Russell 1996; Kumagai and Dunphy 1996; Abrieu et al. 1998; Karaiskou et al. 1999, 2004; Lindqvist et al. 2009). These feedback loops convert mitotic commitment into a bistable, all or nothing, switch (Ferrell 2008).

It was clear from its discovery that the fission yeast Polo kinase, $Polo^{Plo1}$, has roles at the SPB in both mitotic entry and exit (Ohkura et al. 1995; Tanaka et al. 2001). The first clue to $Polo^{Plo1}$'s role in mitotic entry was its recruitment to the SPB with 15% of G_2 phase remaining. This period of $Polo^{Plo1}$ residence on the G_2 spindle pole was doubled to occupy 30% of G_2 phase by the *cut12.s11* mutation in the SPB component Cut12 (Bridge et al. 1998; Mulvihill et al. 1999). This particular *cut12* allele was originally named *suppressor of cdc25*, *stf1.1* and, as its name suggests, is able to compensate for the loss of Cdc25 (Hudson et al. 1990). This implied that mitotic entry could be accomplished solely by the known ability of Wee1 inactivation to regulate mitotic entry in the absence of Cdc25 (Fantes 1979) when regulation of the spindle-pole-associated Cdk1/cyclin B changed (Alfa et al. 1990). The clear conservation of Cdk1/cyclin B feedback loops in fission yeast (Kovelman and Russell 1996; Tanaka et al. 2001) suggested that *cut12.s11* may be exploiting these switches to inhibit Wee1 and drive mitosis.

Although the *cut12.s11* mutation is an ostensibly innocuous glycine to valine change (Bridge et al. 1998), this particular glycine sits at the start of a bipartite docking site for protein phosphatase 1 (PP1) (Grallert et al. 2013a). This glycine/valine switch reduced PP1 recruitment to Cut12 leading to the revelation that a complete block to PP1 recruitment to Cut12 enabled cells to survive the otherwise lethal abolition of Cdc25 function (Grallert et al. 2013a). Thus, PP1 recruitment to Cut12 is integral to the mitotic commitment switch. The direct correlation between the degree of PP1 recruitment to Cut12 and the level of Polo^{Plo1} activity detected in whole cell extracts established that a primary impact of PP1 recruitment to Cut12 is to set the level of Polo^{Plo1} activity throughout the cell (Mulvihill et al. 1999; MacIver et al. 2003; Grallert et al. 2013a). PP1 recruitment to Cut12 also sets local Polo^{Plo1} activity at each individual SPB so that the temperature-sensitive loss-of-function *cut12.1* mutation that enhances PP1 affinity for Cut12 blocks the conversion of the new SPB into a mitotic pole (Bridge et al. 1998; MacIver et al. 2003; Tallada et al. 2009; Grallert et al. 2013a). Consequently, cells form monopolar rather than bipolar spindles and cells die. This defect stemmed from deficient Polo^{Plo1}-based feedback controls because a simple elevation of Cdc25 levels activated the new SPB to drive *cut12.1* cells through a functional mitosis (Tallada et al. 2007, 2009). This evidence for spindle pole–driven mitotic commitment was consolidated by the ability of ectopic activation of either Polo^{Plo1} or Cdk1 at interphase SPBs to inappropriately promote mitotic commitment (Grallert et al. 2013b). These data categorically establish that events on the spindle pole form an integral part of the switch that regulates mitotic commitment.

The Cut12/PP1/Polo^{Plo1} switch can be altered either at the level of Cut12 or Polo^{Plo1}. Phosphorylation within Cut12's bipartite PP1 docking motif by Cdk1-cyclin B or the NIMA kinase Fin1 reduces PP1 affinity for Cut12, whereas simultaneous phosphorylation by both kinases blocks it completely (Grallert et al. 2013a). Cdk1/cyclin B phosphorylation of Cut12 clearly constitutes another feedback control as the enhancement of Plo1 activity it will generate will, in turn, accelerate activation of further Cdk1-cyclin B reserves. It is unclear whether Fin1 is also another mode of feedback control, or whether it coordinates division with specific external cues. In contrast, direct control of Polo^{Plo1}'s SPB affinity clearly does couple division timing to environmental cues (Petersen and Hagan 2005; Petersen and Nurse 2007; Hartmuth and Petersen 2009; Halova and Petersen 2011). Phosphorylation of the conserved serine 402 between the kinase and Polo-box domains enhances SPB recruitment of Polo^{Plo1} in response to signaling flux through the Sty1 MAP kinase stress-response pathway (equivalent to p38 of higher eukaryotes) (Petersen and Hagan 2005; Halova and Petersen 2011). Heat, pressure, and nutritional signaling from the TOR network compromise the function of the protein phosphatase Pyp2 (equivalent to human DUSP65) toward the MAP kinase Sty1 (George et al. 2007; Petersen and Nurse 2007; Hartmuth and Petersen 2009; Halova and Petersen 2011). This reduction in Pyp2 function enhances MAP kinase signaling to boost serine 402 phosphorylation, thereby driving Polo^{Plo1} onto the SPB (Petersen and Nurse 2007) to couple division to at least three external cues: nutrition, heat, and pressure stresses.

Similar pathways may operate in animal cells but are less well characterized. It is long known that Cdk1/cyclin B associates with the centrosome (Bailly et al. 1989) and that its initial activation occurs here (Jackman et al. 2003). This appears to require the activity of the Cdc25B isoform (Gabrielli et al. 1996; De Souza et al. 2000; Lindqvist et al. 2005) whose association with centrosomes is promoted by Aurora A (Dutertre et al. 2004). Specific phosphorylation events on centrosomal Cdc25C in late G_2 phase could also play some role (Franckhauser et al. 2010). Although the relationship to the spindle pole is less well developed than in fission yeast, Plk1 activity levels do determine the timing of mitotic commitment in human cells (Gavet and Pines 2010). In a further echo, the role played by Polo^{Plo1}. S402 phosphorylation following heat stress in fission yeast; human Plk1 drives the first division after recov-

ery from DNA damage (Macurek et al. 2008; Seki et al. 2008). A firmer link to centrosomal activities sits at the heart of the promotion of mitotic commitment by Aurora A in *C. elegans* (Hachet et al. 2007), the acceleration of mitotic commitment in *Xenopus* egg extracts following the addition of centrosomes (Perez-Mongiovi et al. 2000), and in humans on removal of the centrosomal component MCPH1 (Gruber et al. 2011). Modeling experiments in *Xenopus* egg extracts now bring these diverse threads together into a coherent reiteration of the fission yeast data by supporting the concept of waves of Cdk1/cyclin B feedback loop activities emanating from the centrosome (Chang and Ferrell 2013).

A final twist to centrosomal control has been provided by the demonstration that pericentrin mutations alter the DNA damage checkpoint response (Griffith et al. 2008). This link had been anticipated by reports that centrosomal Chk1 played a critical role in determining the timing of mitotic commitment. However, concerns about the specificity of the antibody used for immunolocalization and the expression levels of centrosomally targeted Chk1 fusion proteins in the early studies has questioned whether Chk1 does indeed act at centrosomes (Matsuyama et al. 2011). Thus, the link between pericentrin and cell-cycle control remains enigmatic, although it is tempting to speculate that the potential coupling between fission yeast pericentrin and Cut12/Polo^{Plo1} controls could hold the key (Fong et al. 2010).

In summary, although less developed than the fission yeast data, the indications are that centrosomal triggering of mitotic commitment will be a universal phenomenon that may well involve the same players that operate in fission yeast.

CENTROSOME ASYMMETRIES

Cellular Asymmetry and Spindle Alignment in Budding Yeast

The two mitotic SPBs can have strikingly different impacts on yeast cell fate, even though they both reside within the same cytoplasm at the same point in the cell-division cycle. This distinctive behavior can arise from intrinsic differences in SPB maturation or extrinsic cues that influence the recruitment of SPB components or the modification of resident molecules. In the budding yeast *S. cerevisiae*, an initial intrinsic distinction between the old and new SPB is overwhelmed by extrinsic factors that arise from inherent cellular asymmetry to impose asymmetric behavior that is entirely dependent on SPB position rather than age. In contrast, intrinsic control predominates in the fission yeast *S. pombe*.

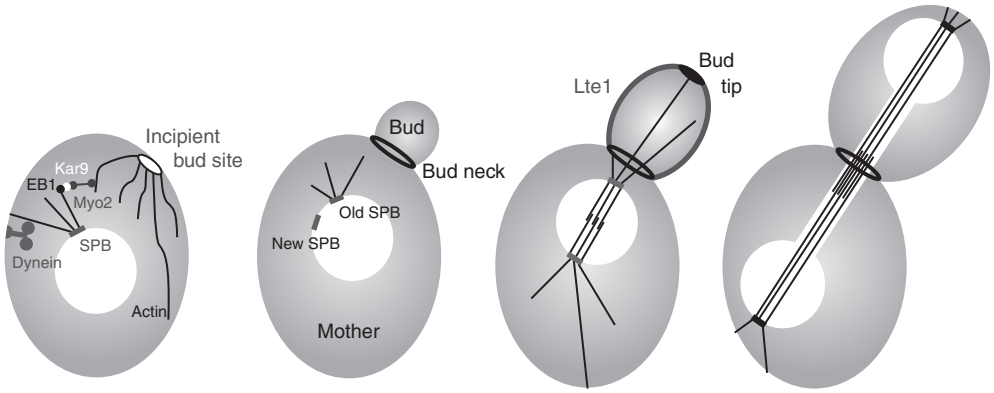

Figure 8. Key landmarks in the control of asymmetric spindle pole body (SPB) function in budding yeast. The figure shows the key landmarks that are referred to in the text imposed on depictions of bud growth from a mother yeast cell. See text for full details on how each of these molecules/features contributes to asymmetries of SPB function that ensure each daughter cell will inherit one genome.

The intrinsic asymmetry of budding yeast cells is generated through expansive growth at the tip of a bud that emerges from a defined zone of the mother cell cortex. The narrow channel connecting the mother and bud (the bud neck) presents a unique challenge for genome segregation as the mitotic spindle must be aligned to promote passage of one set of the duplicated chromosomes through the neck (Fig. 8). Two redundant pathways guide this alignment by directing the astral microtubules that emerge from the cytoplasmic face of one of the two SPBs through the narrow aperture. In one, Kar9 associates with both the microtubule plus end-binding protein EB1 and the myosin motor protein Myo2 to guide astral microtubules along actin filaments that emanate from the incipient bud site and growing bud tips (Beach et al. 2000; Lee et al. 2000; Yin et al. 2000). In the second pathway, dynein both guides the astral microtubules along the cell cortex and promotes instability of the plus ends to ensure end-on association of microtubules with the cortex (McMillan and Tatchell 1994; Carminati and Stearns 1997; Adames and Cooper 2000; Heil-Chapdelaine et al. 2000; Yeh et al. 2000). When astral guidance fails, the ensuing nuclear division within the mother cell blocks cytokinesis and mitotic exit through activation of the spindle orientation checkpoint (SPOC) (Yeh et al. 1995; Miller and Rose 1998; Miller et al. 1998; Bardin et al. 2000; Pereira et al. 2000; Caydasi and Pereira 2012).

SPB Asymmetry and Spindle Alignment in Budding Yeast

The strong tendency for the old SPB to lead the spindle into the bud (Pereira et al. 2001) stems from a delay in the recruitment of the Spc72 γ-tubulin docking component of the cytoplasmic outer plaque of the new SPB (Juanes et al. 2013). Because microtubules cannot be nucleated until γ-tubulin is recruited to Spc72 (Knop and Schiebel 1998), the inherent pause in Spc72 docking delays microtubule nucleation from the new SPB to allow the microtubules extending from the old SPB to be guided into the bud (Shaw et al. 1997; Juanes et al. 2013). However, if the connection between astral microtubules and the cortex is broken before the old SPB enters the bud (via transient dissolution of the microtubule cytoskeleton), then microtubules extending from either the old or the new SPB can lead spindle orientation into the bud (Pereira et al. 2001). Thus, although intrinsic asymmetry in SPB maturation drives spindle orientation in unperturbed divisions, extrinsic controls are equally competent to drive asymmetry of SPB function.

Extrinsic Control of Asymmetric SPB Behavior Drives the End of the Budding Yeast Cell Cycle

Exit from budding yeast mitosis is driven by the Hippo-signaling-related MEN that releases the protein phosphatase Cdc14 from sequestration in the nucleolus (Visintin et al. 1998; Pereira and Schiebel 2001; Stegmeier and Amon 2004; Hergovich et al. 2006). Newly released Cdc14 can then dephosphorylate sites that were initially phosphorylated by Cdk1/cyclins to promote the mitotic state. This impact of the MEN on Cdc14 release, and its coincident control of the cytokinetic machinery (Meitinger et al. 2012), acts at sites that are remote from the heart of MEN control on the SPBs. Whether or not an SPB resides within the mother or the bud determines its competence to promote MEN signaling.

MEN activity is controlled by a GTPase of the Ras superfamily called Tem1. Tem1 activation recruits the Pak kinase Cdc15 that then recruits the NDR kinase Dbf2/Mob1 kinase to drive Cdc14 from the nucleolus. Tem1 activation is promoted by $Polo^{Cdc5}$ phosphorylation of its Bfa1/Bub2 GAP complex (Hu et al. 2001; Pereira and Schiebel 2001; Geymonat et al. 2003; Simanis 2003; Stegmeier and Amon 2004; Maekawa et al. 2007). Once the GAP is inhibited, the intrinsic GTP exchange activity of Tem1 family GTPases (Furge et al. 1998; Geymonat et al. 2003) then flips Tem1 into an active GTP-bound form that drives MEN activation.

The primary mode of spatial control of MEN activity is through modulation of Kin4 kinase activity (D'Aquino et al. 2005; Pereira

and Schiebel 2005). Kin4 phosphorylation of Bfa1 both blocks its ability to be inhibited through $Polo^{Cdc5}$ phosphorylation and promotes docking of 14-3-3 proteins to drive Bfa1 turnover at SPBs (Caydasi and Pereira 2009; Caydasi et al. 2014). Bfa1 phosphorylation by Kin4, therefore, locks MEN signaling in the off state. Kin4 is inhibited by Lte1 (Bertazzi et al. 2011). Lte1 accumulates on the bud cortex until one SPB enters the bud where upon it is released into the cytoplasm (Bardin et al. 2000; Pereira et al. 2000). Kin4, on the other hand, associates with both the cortex and SPB of the mother cell (D'Aquino et al. 2005; Pereira and Schiebel 2005). This partitioning of the kinase and its inhibitor ensures high levels Kin4 activity in the mother and very low levels in the daughter (Bertazzi et al. 2011). Spindle misalignment errors that result in the retention of both SPBs in the mother cell place these two SPBs in the zone of high Kin4 activity that drives Kin4 onto both SPBs to block mitotic exit. If one SPB eventually enters the bud, Kin4 activity will be inhibited on that SPB_{bud} by Lte1 to promote Kin4 departure and so drive MEN activation from this SPB_{bud} (Bertazzi et al. 2011; Falk et al. 2011; Caydasi et al. 2014).

Intrinsic Controls Set by SPB Maturation Establishes One SPB as the Signaling Center for Mitotic Exit in Fission Yeast

Although the asymmetric competence for signaling of two otherwise indistinguishable SPBs arises primarily from extrinsic, spatial context cues to drive mitotic exit of budding yeast, it is primarily the age of the SPB and not external cues that determines which of the two anaphase SPBs will host the active version of the fission yeast equivalent of the MEN (Simanis 2003; Grallert et al. 2004). Thus, even in the simple single-celled yeasts, different strategies can turn one of the two spindle poles into a unique signaling platform from which to determine cell fate.

Asymmetry of Centrioles, Centrosomes, and Fate Decisions

In animal cells, there is increasing evidence that stereotypical centrosome inheritance correlates with cell fate decisions. The *Drosophila* male germline stem cell (GSC) divides asymmetrically to produce one stem cell that is able to self-renew and one gonioblast that subsequently undergoes differentiation (Fig. 9A). GSCs attach

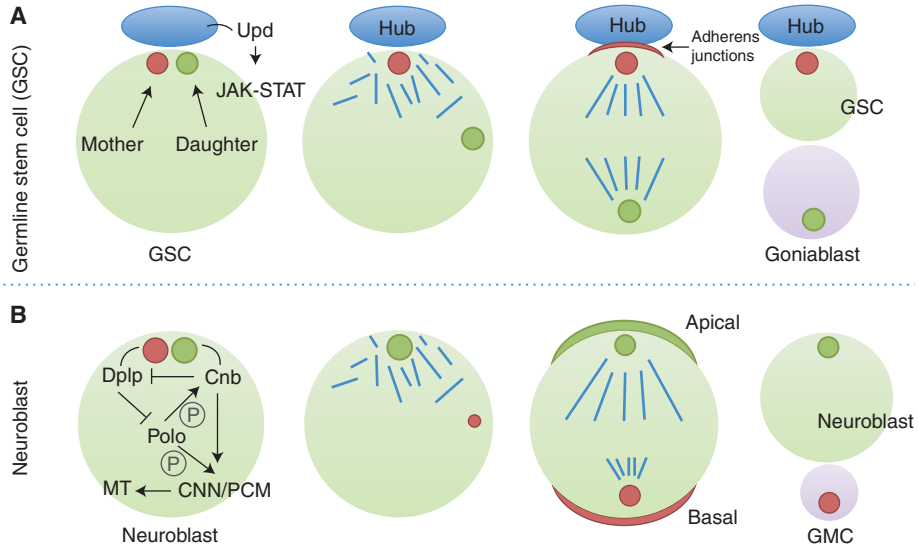

Figure 9. Inheritance of centrosomes in asymmetric cell division in *Drosophila*. The stem cells of the male germline inherit the mother centrosome (*A*) in contrast to the stem cell of the neuroblasts that inherit the daughter (*B*). GMC, ganglion mother cell; MT, microtubule; PCM, pericentriolar material.

to a cluster of support cells called the hub that secrete the signaling ligand Upd (Unpaired), which activates the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway in adjacent germ cells to specify stem cell identity (Kiger et al. 2001; Tulina and Matunis 2001). During cell division, the spindle is orientated perpendicular to the hub so that one daughter cell remains attached to the hub and the other is placed outside the niche. Using a heat shock–Gal4 control promoter, only the newly assembled centriole is labeled on pulse-chase heat shock by transient expression of a centrosomal marker, GFP-PACT (Yamashita et al. 2007). The mother centrosome was observed to be normally inherited by the GSC, whereas the daughter centrosome moves away from the hub and is inherited by the cell that commits to differentiation (Yamashita et al. 2007).

A similar finding was made in mouse radial glia progenitors that produce self-renewing radial glia in the ventricular zone and differentiating cells for the future neocortex (Fig. 9B) (Wang et al. 2009). Centrosomes were marked with photoconvertible Centrin1 that would change color from green to red when pulsed with violet light. Original centrioles (red) could then be distinguished from newly formed centrioles (green). During the peak phases of neurogenesis, mother centrosomes are preferentially inherited by radial glia progenitors that stay in the ventricular zone, whereas the daughter centrosomes mostly leave the ventricular zone and are associated with differentiating cells. Removal of the subdistal appendage protein, ninein, disrupts the asymmetric segregation and inheritance of the centrosome and causes premature depletion of progenitors from the ventricular zone.

The reverse pattern of inheritance is seen in *Drosophila* neuroblasts that function as stem cells for brain development, where the mother centrosome is inherited by the differentiating daughter cell. Mother and daughter centrosomes could be traced either by photoconvertible PACT and the daughter centriole marker Cnb (centrobin) (Januschke et al. 2011) or distinguished by the different fluorescence intensity of PACT (Conduit and Raff 2010). Early in the cell cycle, the daughter centrosome organizes an aster that remains by the apical cortex, whereas the mother loses PCM and microtubule-organizing activity and moves extensively throughout the cell (Rebollo et al. 2007). Before mitosis, the mother centrosome begins to recruit PCM and organizes a mitotic aster as it settles near the basal cortex. When the daughter centrosome-specific protein, Centrobin (Cnb), is depleted, both centrosomes are free to wander in the cells, and they lose their interphase association with centrosomal proteins Asl and CNN. Strikingly, when Cnb is ectopically targeted to both centrosomes by fusing to PACT, the mother centrosome is able to retain PCM and microtubule organizing activity. Cnb co-precipitates with a set of centrosomal proteins, including γ-tubulin, Ana2, CNN, Sas-4, Sas-6, Asl, DGrip71, and Polo. These data suggest that Cnb is both necessary and sufficient for centrosomes to retain microtubule organizing activity probably through interaction with PCM components (Januschke et al. 2013). Cnb is regulated by Polo in this process; following chemical inhibition of Polo or mutation of three Polo phosphorylation sites, the interphase microtubule aster is lost (Januschke et al. 2013). The centriolar protein, Cep135, is required to establish centrosome asymmetry in *Drosophila* neuroblasts through shedding of Polo from the mother centrosome (Singh et al. 2014). Dplp (pericentrin-like protein), on the other hand, is more enriched on the mother centrosome (Lerit and Rusan 2013). In Dplp mutant neuroblasts, the mother centrosome retains γ-tubulin and Polo levels comparable to the daughter. Targeting Cnb to both centrosomes abolishes the asymmetric distribution of Dplp, suggesting that Dplp is one of Cnb's targets to establish centrosome asymmetry.

Defects in Division Symmetry in Microcephaly

In contrast to the above examples of asymmetric centriolar behavior, the reasons why aberrant centrosome behavior might lead to the various forms of inherited microcephaly are less clear. Microcephaly develops as the result of a fail-

ure of neuroprogenitor cells to undertake sufficient symmetric divisions to generate sufficient numbers of cells before asymmetric, differentiating divisions to generate the cerebral cortex (Jeffers et al. 2008; Rai et al. 2008). It is generally thought that proper centrosomal function is required to ensure correct spindle orientation to prevent asymmetric divisions from occurring before the progenitor cell population has been sufficiently expanded (reviewed in Morrison and Kimble 2006). The most commonly affected gene in microcephaly is *aspm* (abnormal spindle-like microcephaly associated, MCPH5) (Thornton and Woods 2009). In cultured human cells, ASPM localizes to centrosomes and spindle poles, similar to its fly and worm ortholog (Saunders et al. 1997; Kouprina et al. 2005; van der Voet et al. 2009; Noatynska et al. 2012). Neuroprogenitors depleted of ASPM fail to orient the mitotic spindle perpendicular to the ventricular surface of the neuroepithelium giving asymmetric, rather than symmetric, divisions (Fish et al. 2006). Mutations in CPAP (MCPH6) and STIL (MCPH7) also affect spindle orientation (Kitagawa et al. 2011b; Brito et al. 2012). Other genes for centrosomal proteins that are mutated in microcephaly include the CNN homolog, CDK5RAP2 (MCPH3), required for centrosome maturation and DNA damage-induced G_2 arrest (Barr et al. 2010; Lizarraga et al. 2010), and CEP63 with its partner Cep152, which participate in centriole assembly (Sir et al. 2011). Centriole amplification has also been shown to be one cause of microcephaly in human patients that is triggered by mutants that stabilize STIL by removing a KEN destruction box (Arquint and Nigg 2014).

The link tying microcephaly mutations to spindle orientation in brain development may not be quite as straightforward as it seems. Not all forms of microcephaly are associated with defects in spindle orientation; a mutant encoding a truncated version of ASPM results in microcephaly without interfering with spindle orientation (Pulvers et al. 2010). Conversely, division orientation can be completely randomized in neuroprogenitor cells by mutations in LGN, a protein that helps orient the spindle with respect to the axis of cell polarity, and yet this does not lead to smaller brains. One of the genes mutated in microcephaly patients encodes MCPH1, which regulates several DNA damage response proteins. MCPH1 appears in radiation-induced nuclear foci (Rai et al. 2006) and specifically regulates levels of both BRCA1 and Chk1 (Xu et al. 2004; Lin et al. 2005; Tibelius et al. 2009). *MCPH1* knockdown cells show increased radiosensitivity (Peng et al. 2009; Liang et al. 2010) as well as recombination and chromosome condensation defects (Wood et al. 2008, Liang et al. 2010; Trimborn et al. 2010). MCPH1 also participates in altering the chromatin structure in response to DNA damage to allow DNA repair (Peng et al. 2009).

We, therefore, seem still not to fully understand the underlying causes of these defects in brain development and all of the roles of the centrosome in this process.

CONCLUDING REMARKS

We have come a long way in understanding centrosome structure and function, particularly with the explosion of molecular detail that has been added to the picture over the past decade. We are now beginning to piece together the molecular components of the organelle and their dynamic interactions during cell-cycle progression. As with many cell-cycle processes, the principal events of the centrosome cycle are regulated by a combination of protein phosphorylation/dephosphorylation and stability. We now have to find out exactly how and when centrosomal proteins become modified and how this affects their function. Only then will we be able to bring our level of understanding of the metazoan centrosome up to what we already have for yeast SPBs. We also have to fully appreciate the diversity of centrosomal function in different cell types of metazoans and their roles in development. Perhaps only when we have a greater understanding of these functions in normal cells will we be able to properly address how these processes go awry in the multiple types of tumor cells that show centrosomal abnormalities. Many challenges still lie ahead before we can come to grips with the many roles

of the centrosome uncovered at the end of the 19th century.

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