PERSPECTIVE

Multiple centrosomes: together they stand, divided they fall

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Cells with extra centrosomes rely entirely on centrosome clustering mechanisms to assemble a bipolar spindle and to divide in a bipolar fashion. To identify the pathways involved in suppression of multipolarity, Kwon, Godinho, and colleagues (pp. 2189–2203) have set up a genome-wide screen in *Drosophila* S2 cells. Surprisingly, they found that efficient clustering requires a large number of proteins associated with a variety of cellular functions.

The majority of cells in our body contain either one or two centrosomes, depending on their position within the cell cycle. A G1 cell contains a single centrosome composed of two centrioles. During S phase, two new (daughter) centrioles assemble in the close proximity of pre-existing (mother) centrioles, therefore generating two centrosomes that remain together until the end of G2. As mitosis is initiated, the two centrosomes move apart to form the poles of a bipolar mitotic spindle (Doxsey et al. 2005; Azimzadeh and Bornens 2007; Bettencourt-Dias and Glover 2007).

Centrosome number is maintained by the tight control of the centrosome replication cycle. Although in the past few years, our understanding of the mechanisms that regulate centrosome replication have improved considerably, how cells manage to restrict the formation of daughter centrioles to only two per cell cycle is still unclear (Tsou and Stearns 2006; Azimzadeh and Bornens 2007; Bettencourt-Dias and Glover 2007; Nigg 2007).

Increased centrosome number, or centrosome amplification, is a common characteristic of several human tumors. The general perception is that elevated centrosome numbers are associated with multipolar mitosis and consequently with abnormal cell division (D'Assoro et al. 2002a,b; Boveri 2008). The cause for centrosome amplification in tumors is not known, but, in principle, the presence of multiple centrosomes could result from defects in the control of the centrosome replication cycle, failure in cytokinesis, or, alternatively, cell fusion.

The exact contribution of extra centrosomes to tumor initiation is still a matter for discussion. The coexistence, in certain tumors and in tumor-derived cell lines, of multiple centrosomes together with high levels of aneuploidy suggests a positive correlation between centrosome amplification and chromosome instability (Lingle et al. 2002). However, the presence of extra centrosomes could also disrupt cell polarity and consequently interfere with normal cell behavior and tissue architecture. In vivo, centrosome amplification has been recently shown to drive tumorigenesis in flies (Basto et al. 2008), but it is too early to say if this holds true in other model organisms.

In theory, the presence of extra centrosomes within tumor cells could also prove to be deleterious. Multipolar mitosis, for instance, may generate sufficiently high levels of aneuploidy to pose a challenge for cell viability. Interestingly, several cancer cell lines seem to overcome this problem by clustering their extra centrosomes at the two poles of the spindle during mitosis, thus ensuring bipolar chromosome segregation (Ring et al. 1982; Quintyne et al. 2005; Saunders 2005).

Although centrosome clustering occurs both in vivo (Murphy 2003; Basto et al. 2008) and in tissue culture cells (Ring et al. 1982; Quintyne et al. 2005), the molecular mechanism responsible is poorly understood. Previous work has implicated the minus-end-directed motor Dynein and the spindle pole-associated protein NuMA in this process, but further proteins and pathways are also likely to be involved (Quintyne et al. 2005; Saunders 2005).

To investigate the mechanisms that regulate centrosome clustering, Kwon and Godinho from the Pellman laboratory have set up a clever screen in *Drosophila* S2 culture cells (Kwon et al. 2008). S2 cells are ideal for such a screen for two major reasons. First, more than 50% of these cells contain multiple centrosomes. Second, S2 cells are extremely efficient at clustering extra centrosomes, since 95% of the cells assemble a bipolar mitotic spindle (Fig. 1A). The investigators screened a total of 23,172 genes, which correspond to the majority of the *Drosophila* genome (99%), by RNAi. Careful visual analysis of ~96,000 images identified 133 genes with roles in centrosome clustering implicated in a variety of cellular functions.

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Time is everything

A group of genes identified by this screen are members of the Spindle Assembly Checkpoint (SAC) required for controlling the timing of anaphase onset. The SAC is a surveillance mechanism that monitors the kinetochore–microtubule (MT) attachment status of all chromosomes within a cell (Musacchio and Salmon 2007). This checkpoint delays anaphase onset by maintaining the Anaphase-Promoting Complex/Cyclosome (APC/C, an E3 ubiquitin ligase) in an inactive form (Acquaviva and Pines 2006). When the SAC is absent in cells containing extra centrosomes, multipolarity is maintained throughout mitosis and chromosomes are segregated in a multipolar fashion. Interestingly, comparing the time elapsed between nuclear envelope breakdown (NEBD) and anaphase onset in S2 cells with two centrosomes or more revealed a positive correlation between the presence of extra centrosome and the length of mitosis. To investigate the role of SAC in promoting centrosome clustering, the investigators blocked anaphase progression (in SAC-

depleted cells) with a proteasome inhibitor. Interestingly, suppression of multipolarity was partially rescued, which suggests that it is not the presence of extra centrosomes that is being monitored by the SAC. Instead, kinetochore–MT attachment, in these multipolar arrangements, might maintain the SAC in an active state, which in turn provides the cell with sufficient time to cluster supernumerary centrosomes and to assemble a bipolar spindle (Fig. 1B). The dependence of centrosome clustering and bipolar spindle formation on a functional SAC also has been described recently in other models (Basto et al. 2008; Yang et al. 2008).

Motors and forces: a fine balancing act

Another class of proteins identified by this screen are MT-binding proteins with roles in spindle pole focusing. One of the strongest hits identified was a molecular motor, the minus-end kinesin Ncd or HSET, which belongs to the Kinesin-14 family. This result is particularly in-

Figure 1. Genome-wide screen in cells with supernumerary centrosomes identifies three major pathways required for centrosome clustering. (A) In interphase, several centrosomes (green dots) can be detected, randomly distributed in the cytoplasm of S2 cells. Cells were incubated with dsRNA for 4 d and stained for DNA, MTs, and centrosomes. Using high throughput automated microscopy to acquire ~96000 images, Kwon et al. (2008) quantified the percentage of multipolar spindles for each gene knock down. A secondary screen confirmed that 133 genes are required to cluster multiple centrosomes and to assemble a bipolar mitotic spindle. (B) Mechanisms required for centrosome clustering. (1) The SAC. The presence of multipolar spindles is likely to perturb kinetochore–MT attachment, and cells arrest in a prometaphase like state with an active checkpoint that inhibits the APC/C. With enough time, centrosomes cluster and a bipolar spindle is assembled. Kinetochore–MT attachment is then likely to satisfy the checkpoint, and the APC/C can now be activated to trigger anaphase and mitotic exit. (2) MAPs as Ncd/HSET facilitate centrosome clustering. As cells enter in mitosis, Ncd is required to block centrosome movement away from the poles (toward the cortex). These proteins probably contribute to generate spindle forces that maintain the extra centrosomes together throughout mitosis. (3) Cell adhesion, the actin, and MT cytoskeleton cooperate to promote clustering. Cortical landmarks that form on the proximal sides of interphase adhesion sites recruit a large amount of factors that organize the actin and microtubule cytoskeleton. In a cell with multiple centrosomes, these landmarks generate a cortical force that exerts a pulling force on stable astral microtubules. Whether landmarks and cortical forces promote or suppress clustering depends on the arrangements of landmarks (e.g., two on opposite sides of the cell would favor clustering, whereas three or four arranged in a symmetric fashion would impede clustering).

Figure 2. Centrosome amplification and cancer therapy. The presence, within a tumor, of a high portion of cells with extra centrosomes that rely on centrosome clustering mechanisms to continue to divide and thus to proliferate might be of therapeutic interest. In principle, inhibition of centrosome clustering mechanisms may result in multipolar spindle assembly and abnormal cell division and consequently in the production of low-viability progeny. As shown by Kwon et al. (2008), HSET is essential for the survival of cancer cells with extra centrosomes but is dispensable for mitosis in cells with only two centrosomes.

teresting, since *Drosophila ncd* mutants are viable but female sterile (Endow and Komma 1998). Previous work has shown that in *Drosophila* somatic cells that contain normal centrosome number Ncd is dispensable. The activity of this motor is, however, essential to focus the MT-minus ends of the acentrosomal female meiotic spindle (Skold et al. 2005). In *Drosophila*, like in the majority of animal species, female meiotic spindles do not contain centrosomes. In this case, MT nucleation entirely depends on the chromatin-mediated pathway and on the role of additional molecular motors to focus MTs at the spindle poles (Heald et al. 1996, 1997; Skold et al. 2005; Barr and Gergely 2007).

Live analysis of *ncd*-depleted S2 cells revealed increased centrosome mobility toward the cell cortex, away from the spindle. Thus, Ncd activity is important for both suppressing centrosome movement and constraining its position, most likely by balancing cortical forces acting on the centrosomes (Fig. 1B). Interestingly, while certain MT-associated proteins (MAPs) such as Asp, Myo10A, Clip-190, and Tankyrase are among the candidates required for suppression of multipolarity, other MAPs with well-known roles in mitosis such as EB1 (Vaughan 2005), Msps/ChTog (Cullen et al. 1999; Gergely et al. 2003), or D-TACC (Gergely et al. 2000; Raff 2002) have either been identified as a weak hit or not identified at all. This suggests a requirement for a specific small subset of MAPs in centrosome clustering.

Centrosome clustering and spindle positioning: two sides of the same coin?

As described above, cell autonomous factors such as the SAC and intrinsic spindle forces can facilitate the clustering of centrosomes. Environmental cues, however, seem to play just as an important role according to the RNAi screen by Kwon et al. (2008). In fact, >30% of candidate proteins, with known functions, identified by the screen are involved in the regulation of the actin cytoskeleton, cell polarity, adhesion, or cortical contractility. A closer look at the list of factors within these categories reveals a striking overlap with a group of proteins involved in cell adhesion-dependent spindle positioning (Thery et al. 2005; Toyoshima and Nishida 2007). Hence, cells with extra centrosomes seem to have “hi-

jack” the spindle positioning mechanism to promote their survival. As detailed below, this clustering mechanism relies on adhesion- and actin-dependent generation of heterogeneous cortical forces that organize astral MTs and thereby guide centrosome movement.

While the actin cytoskeleton has a well-established role in cell shape, motility, cytokinesis, and spindle positioning, the current study is the first to suggest that it promotes centrosome clustering in cells with extra centrosomes (Kwon et al. 2008). Disrupting the actin cytoskeleton by the depolymerizing agent Latrunculin A (Lat A) causes a twofold increase in multipolar mitoses in both S2 and mammalian cells. Lat A treatment of *Ncd*/HSET-depleted cells revealed a synergistic effect on multipolarity, whereas Lat A treatment did not further increase multipolarity in cells depleted of factors involved in cell adhesion and contractility. Therefore, centrosome clustering by *Ncd*/HSET occurs independently of the actin cytoskeleton, while cell adhesion and contractility factors facilitate clustering in an actin-dependent manner (Kwon et al. 2008). So, how can cell adhesion and cortical contractility link the actin cytoskeleton to centrosome clustering?

Most adherent cell types in tissue culture adopt a round morphology during mitosis, a shape that promotes the stability of mitotic spindles (Kunda et al. 2008). Cell rounding is accompanied by the detachment of the plasma membrane from the substrate as a result of actomyosin-dependent cortical contractions. Stable anchoring sites, however, resist these forces, allowing the formation of actin-based retraction fibers (RFs) that persist throughout mitosis (Mitchison 1992). Cell-matrix adhesion molecules are paramount in the establishment of these RFs (Thery et al. 2005). The FERM-domain protein Fit1A identified in the screen is a good candidate for such a role, since its mammalian homolog, Mig-2, is required for cell spreading possibly by providing a link between integrins and the actin cytoskeleton (Tu et al. 2003; Shi et al. 2007). To directly address the connection between cell adhesion, RF assembly and clustering, Kwon et al. (2008) performed a series of elegant experiments using time-lapse microscopy methods to follow live human cells on fibronectin-coated surfaces. The investigators noticed that extra centrosome-containing human breast cancer cells with elongated interphase morphology as-

semble multipolar spindles less frequently than cells with round morphology. Therefore, interphase cell shape exerts a strong influence on the efficiency of centrosome clustering in the subsequent mitosis. In addition, bipolar spindle formation is clearly favored when cells are grown on fibronectin micropatterns with a two-pole symmetry (I or H shape). Patterns such as Y and O are sufficient to cause a threefold increase in the frequency of multipolar spindles. These results cumulatively suggest that the physical environment of an interphase cell has a major impact on how effectively extra centrosomes can cluster during spindle assembly. But, how can the distribution of RFs influence centrosome clustering?

The ability of RFs to modulate the actin and MT cytoskeletons plays an important role in spindle positioning (Thery et al. 2005, 2007; Toyoshima and Nishida 2007), and it may also be exploited in centrosome clustering (Kwon et al. 2008). RFs generate a heterogeneous cortex by selectively accumulating factors such as members of the ezrin/radixin/moesin (ERM) family, hence turning cell adhesion patterns into cortical landmarks (Bretscher et al. 2002; Thery and Bornens 2006). These landmarks are important for cortical contractility, MT organization, and stable spindle positioning (Carreno et al. 2008; Kunda et al. 2008). A positive relation was demonstrated between cortical contractility and centrosome clustering in drug-based assays that modulate contractility; impaired contractility reduced clustering, whereas increased contractility was associated with improved clustering. A direct role for contractility in centrosome clustering was also suggested by the presence of Myo10A—a member of the atypical myosin family—among the high-scoring candidate proteins. Importantly, drug-induced contractility restored normal centrosome clustering in Myo10A-depleted cells, indicating that the primary role of Myo10A in clustering is to facilitate cortical contractions (Kwon et al. 2008). The function of contractility in centrosome clustering is evolutionarily conserved, as depletion of Myo-10, a related atypical myosin in mammals with an established role in spindle positioning (Toyoshima and Nishida 2007), suppressed clustering in human cells with supernumerary centrosomes.

Astral MTs seem to play a crucial role in centrosome clustering since their selective depolymerization increased the frequency of multipolar spindles (Kwon et al. 2008). The RFs could locally influence astral MT stability via the recruitment of stabilizing proteins. Stable astral MTs establish a positive feedback loop by transporting further stabilizing factors from the spindle poles to the RF (Thery and Bornens 2006), leading to the enrichment of MT plus-end stabilizing complexes such as CLIP-170/IQGAP/Rac1/cdc42 (Fukata et al. 2002) at these sites. This complex may play a role in centrosome clustering, since the *Drosophila* CLIP-170 homolog, CLIP-190, has been identified as a high-scoring candidate protein in the siRNA screen. The similarities between the molecular pathways involved in spindle positioning and centrosome clustering are so intriguing that it might be worthwhile testing certain candidates identified in

the Kwon and Godinho screen for their potential role in spindle positioning (Kwon et al. 2008).

Interestingly, polarity proteins such as Crumbs (Tepass et al. 1990), Cornetto (Bulgheresi et al. 2001), and PAR-1 (Shulman et al. 2000; Doerflinger et al. 2003) have also been isolated as candidate proteins in centrosome clustering. Besides the role of PAR-1 in epithelial polarity, MT cytoskeleton polarization, and asymmetric cell division (Margolis and Borg 2005), there is also evidence for the involvement of PAR-1 in cell–matrix adhesion (Kiger et al. 2003). These polarity proteins must influence centrosome clustering through the actin cytoskeleton, since depleting them in the presence of Lat A does not cause a synergistic increase in multipolar spindles (Kwon et al. 2008).

While it is clear that actin-driven forces contribute to the clustering of extra centrosomes, the precise molecular mechanisms involved remain to be established. Thery et al. (2007) have suggested recently that heterogeneous cortical forces exert a pulling force on astral MTs, hence producing a torque on the mitotic spindle, which rotates it until stable spindle orientation is achieved. It is possible that centrosome clustering occurs via a similar mechanism. It will be crucial to determine the identity of the major players involved in the generation of these forces. Since such factors may be among the 43% of candidate proteins that have no known function, screening this panel in the presence of Lat A could be a quick way to identify missing molecular links.

The Kwon and Godinho screen may also have broader implications on environment-induced centrosome positioning within cells (Kwon et al. 2008). For instance, centrosome movement during epithelial polarization, membrane targeting of the centrosome in preparation to form the primary cilium, and centrosome positioning during the process of wound healing could all require some extent of actin remodeling. It is therefore feasible that a universal pathway exists to link the remodeling of the cortical actin cytoskeleton to MT organization and centrosome positioning in cells.

Centrosome clustering and cancer therapeutics

Centrosome amplification is a common occurrence in a variety of human cancers. As discussed above, the success of cell division in the presence of supernumerary centrosomes depends entirely on efficient centrosome clustering mechanisms that promote bipolar spindle assembly and accurate distribution of sister chromatids during anaphase. This could make the clustering ability of a cancer cell with excess number of centrosomes its Achilles heel (Fig. 2; Kwon et al. 2008). The finding that centrosome clustering pathways are dispensable in cells containing normal centrosome number establishes the process of centrosome clustering as an attractive, tumor cell-specific therapeutic target. Indeed, as demonstrated by Kwon et al. (2008), HSET depletion blocks centrosome clustering and promotes multipolar divisions and hence abnormal chromosome segregation or aneuploidy. Most importantly, HSET depletion selectively kills cells with

extra centrosomes without affecting the viability of cells that contain normal centrosome numbers. Consequently, based on the *in vitro* data, the incidence of toxicity may be markedly lower with a hypothetical HSET inhibitor than with other mitosis-blocking agents currently in clinical use. HSET is therefore an exciting new therapeutic target, and being a kinesin, it is also a great candidate for small molecule inhibitor-based approaches. In summary, inhibiting centrosome clustering could turn out to be a very powerful way to shrink tumors, in particular those with a high penetrance of centrosome amplification.

It is worth a mention, however, that aneuploidy does not only act as a tumor suppressor (Sotillo et al. 2007; Weaver et al. 2007) but can also behave as a tumor initiator at least in certain tissues of aged animals (Weaver et al. 2007). It will be critical, therefore, to ensure that a potential HSET inhibitor does not generate excessive amounts of low degree aneuploidy within tumors.

It is important to recall that centrosome clustering can occur via at least two distinct mechanisms: One is intrinsic to the spindle, whereas the other relies on actin-generated forces in response to environmental cues. These two pathways cooperate under tissue culture conditions to bring about efficient clustering, but *in vivo* cells may utilize one or the other pathway depending on their shape and environment. It would be particularly interesting to see which pathway prevails in cells with multiple centrosomes when grown in a three-dimensional tissue culture system or in *in vivo* vertebrate models. A preferential use of clustering pathways is already apparent in two-dimensional culture conditions where the small, round, and nonadherent neuroblastoma cell line relies on HSET almost entirely for centrosome clustering, whereas adherent cells seem to tolerate the absence of HSET better (Kwon et al. 2008). Tumor cells with supernumerary centrosomes will therefore select clustering pathways that afford the best chance for survival within their particular environment.

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Gergely and Basto

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