Viewpoint

Centrosome cycle studies reveal promising candidates for anti-cancer drug design

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Centrosomes are complex cellular substructures that are dynamically regulated by a series of biochemical and morphological changes that parallel the progression of the cell cycle. In addition to organizing cytoplasmic microtubule arrays during interphase, centrosomes direct formation and positioning of the bipolar mitotic spindle and thereby enable equal partitioning of chromosomal material during mitosis. Because impaired centrosomal function during cell division has the potential to cause chromosomal missegregation, and thus lead to genetic instability, the centrosome has become an important focus for cancer research. In fact, many tumor cells, including those from the breast, exhibit excessive numbers of centrosomes and/or centrosomes with aberrant morphologies. A collection of recent papers, some of which challenge prevailing dogmas, provide new insight into the biology of the metazoan centrosome cycle (i.e., duplication, maturation and separation) and elucidate novel regulatory pathways that are reasonable targets for oncogenic therapy development.

Given the correlation between centrosome number and tumor progression, molecules regulating centrosomal duplication at the G1/S transition have been under considerable scrutiny. Fisk and Winey recently used a culture-based assay of centrosome duplication to query the relevance of mMps-1p, the mouse orthologue of the *Saccharomyces cerevisiae* MPS1p protein kinase, a protein known to regulate spindle pole body replication (*Cell* 2001, 106:95-104). While overexpression of wild-type mMps-1p promotes excessive duplication events, a kinase-inactive form of mMps-1p exerts a dominant negative effect antagonizing centrosome replication. Furthermore, mMps-1p protein stability, and thus function, is regulated via phosphorylation through cyclin-dependent kinase 2 (CDK2), a known mediator, and possible coordinator, of DNA replication and centrosomal duplication. Matsumoto and Maller have demonstrated that, in the context of S-phase-arrested Xenopus extracts, it is calcium/calmodulin-dependent kinase (CaMKII), and not CDK2, that actually initiates centrosomal duplication (*Science* 2002, 295:499-502). CaMKII is likely triggered in response to the periodic calcium oscillations that occur at the G1/S transition and are required for centrosome duplication. Finally, a provocative study by Khodjakov *et al.* challenges the concept that centrosome replication is an obligate semi-conservative process (*J Cell Biol* 2002, 158:1171-1181). They show that new centrosomes form *de novo* in S phase-arrested cells in which centrosomes have been removed by laser ablation. This finding not only raises important questions regarding centrosome duplication checkpoints but also suggests that tumor-associated centrosome amplification could conceivably be attributed to *de novo* synthesis events.

Aurora serine/threonine kinases have received recent attention as critical regulators of the cell and centrosome cycle. One family member, called Aurora A, is over-expressed in many tumors and is found in the 20q13 breast cancer amplicon. In cultured cells, over-expression of Aurora A results in centrosome amplification and aneuploidy. Recent results indicate that Aurora A is an important determinant of centrosome maturation. Hannak *et al.* employed an RNAi strategy to query the role of *Caenorhabditis elegans* Aurora A (or AIR-1) during the first embryonic cell division (*J Cell Biol* 2001, 155:1109-1116). AIR-1 depletion resulted in the incomplete separation of centrosomes, an event likely due to the impaired accumulation of γ-tubulin and other pericentriolar components required for centrosome maturation. Aurora A depletion in *Drosophila* also induces centrosomal maturation and spindle defects. For example, Giet and colleagues showed that in both neuroblasts and syncytial embryos, mutations in Aurora A lead to a decrease in the length of astral microtubules and to a disorganization of centro-

CDK2 = cyclin-dependent kinase 2; CAMKII = calcium/calmodulin-dependent kinase; C-Nap1 = centrosomal Nek2-associated protein 1.

somes (*J Cell Biol* 2002, 156:437-451). Aurora A-depleted cells also displayed mitotic spindles with gross metaphase defects. Moreover, reduced Aurora A function correlated with aberrant centrosomal recruitment of the D-TACC/MSPS complex, which plays a role in the regulation of astral microtubules of the spindle. Likewise, in an independent study of *Drosophila* sensory organ precursor cells, Berdnik and Knoblich showed that mutations in Aurora A impair centrosomal accumulation of both centrosomin and γ-tubulin and give rise to spindle defects (*Curr Biol* 2002, 12:640-647).

The genetic models described above argue strongly for a role for Aurora A in centrosome maturation and suggest that perturbed Aurora A function has severe consequences on spindle function during subsequent mitotic progression. A recent study by Meraldi *et al.* in cultured cells has suggested that Aurora A over-expression induces centrosomal amplification, not by modulating duplication machinery, but by promoting aberrant mitosis and cytokinesis (*Embo J* 2002, 21:483-492). Aurora A-induced malfunctions lead to an abundance of multinucleated cells and a seeming amplification of what are actually normally duplicated centrosomes. This assessment is further supported by the fact that centrosome amplification is exacerbated in cells defective in the mitotic checkpoint protein p53. Collectively, these studies demonstrate the importance of Aurora A as a target for cancer study. In this regard, a recent structural analysis, by Cheetham and colleagues, of Aurora A highlights a number of features unique to this kinase (*J Biol Chem* 2002, 277:42419-42422), and in doing so provides potentially useful information for the development of specific Aurora A modulators.

Other centrosomal constituents of recent notice are centrosomal Nek2-associated protein 1(C-Nap1) and the Rho-dependent protein kinase, p160ROCK, both of which appear to be involved in centrosome organization via their contributions to intercentriolar linkages. C-Nap1 localizes preferentially to the ends of parental centrioles and has been implicated in cell-cycle-regulated cohesion of centrosomes following duplication. Mayor and colleagues recently showed that C-Nap1 is phosphorylated at the onset of mitosis. This phosphorylation drives dissociation of C-Nap1 from the centrioles, and may thereby contribute to centrosome separation leading to bipolar spindle formation (*J Cell Sci* 2002, 115:3275-3284). p160ROCK, which was originally identified from a panel of centrosome-directed monoclonal antibodies, plays a role in intercentriolar positioning. Chevrier *et al.* have shown that within a single centrosome, p160ROCK localizes to the maternal centriole and the intercentriolar linker (*J Cell Biol* 2002, 157:807-817). p160ROCK-specific inhibitors induced centriole separation in G1 cells and caused accelerated movement of the maternal centriole to the midplate after mitosis. Thus, p160ROCK is an important regulator of centrosome organization and positioning throughout the cell cycle.

Clearly, irregularities in centrosome duplication, maturation and/or separation have potential to wreak havoc on the fidelity of mitotic events. Presumably, these centrosomal defects contribute to tumor cell aneuploidy, which is observed in many human cancers. Given the abundance of centrosome cycle regulators, it is likely that studies such as those described above will contribute to the development of important cancer diagnostics and/or therapies.

Articles selected from Faculty of 1000:

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