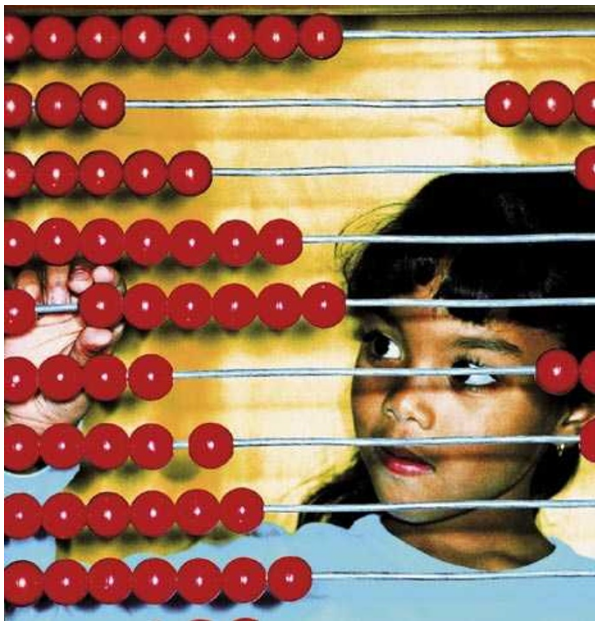
CANCER BIOLOGY

The counting game



Stockbye

Centrosomes — the main microtubule-organizing centres in cells — are important for the accurate segregation of chromosomes during cell division. Their number is tightly regulated to avoid multipolar mitoses, which cause aneuploidy and ultimately cell death. However, cancer cells can avoid multipolar mitosis by clustering the extra centrosomes, although the underlying mechanism has been elusive. Researchers have now examined the process of centrosome clustering, which has provided new leads for therapeutic approaches.

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Pellman and colleagues carried out a genome-wide RNA interference (RNAi) screen for factors that are required for centrosome clustering in *Drosophila melanogaster* S2 cells. The visual screen, which was based on the identification of multipolar spindle phenotypes, identified 133 factors that regulate diverse cellular processes, such as the spindle assembly checkpoint (SAC; which prevents the onset of anaphase until chromosomes are bipolar), the bundling of spindle microtubules (MTs), actin regulation and cell adhesion. Of these, 82 have mammalian homologues and could be relevant therapeutic targets.

Using time-lapse imaging and green fluorescent protein-tagged markers, the authors visualized the nuclear envelope breakdown and the onset of anaphase in cells with two or more centrosomes, and measured the interval between the two processes. Anaphase was delayed in cells with multiple centrosomes, but not in SAC mutants, which formed multipolar spindles. So, the SAC seems to allow sufficient time for other compensatory mechanisms to cluster centrosomes before cell division.

NCD, a kinesin that bundles MTs at the spindle poles, was identified in the screen: live imaging of centrosomes in NCD-depleted cells showed the formation of multipolar spindles. So, NCD has a crucial role in cells containing multiple centrosomes, yet it is not essential for cell division in normal cells. This makes NCD a selective target to treat cancer. Indeed, short interfering RNA-mediated depletion of HSET (the human NCD homologue) in human cancer cells with multiple centrosomes induced multipolar spindles and cell death, but had no effect on normal cells.

Treatment of S2 cells with actin inhibitors or chemicals that block cortical contractions prevented centrosome clustering and caused multipolar mitoses. Furthermore, chemicals that block MT bundling in combination with the depletion of MYO10, a myosin that binds to MTs and affects spindle positioning in human cells, caused similar phenotypes and suggested that actin-dependent and MT-dependent forces act together to organize multiple centrosomes.

At least some of these actin-dependent forces seem to originate from sites of strong cell matrix adhesion. Using fibronectin micropatterns to manipulate interphase cell shape and adhesion pattern, Pellman and colleagues showed that the geometry of adhesive contacts can determine whether cancer cells with extra centrosomes undergo a bipolar or multipolar mitosis. These results suggest novel mechanisms by which the tumour microenvironment might influence the genetic stability and the survival of cancer cells.

Identifying the molecular differences between cancer cells and the normal cells from which they are derived is essential for designing selective therapeutic strategies. These findings suggest that blocking centrosome clustering and promoting multipolar mitoses might be a promising strategy to induce death in tumours that contain multiple centrosomes.

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ORIGINAL RESEARCH PAPER Kwon, M. *et al.* Mechanisms to suppress multipolar divisions in cancer cells with extra centrosomes. *Genes Dev.* 28 July 2008 (doi:10.1101/gad.1700908)