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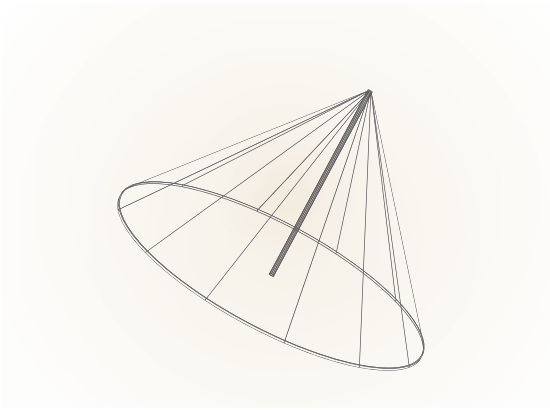
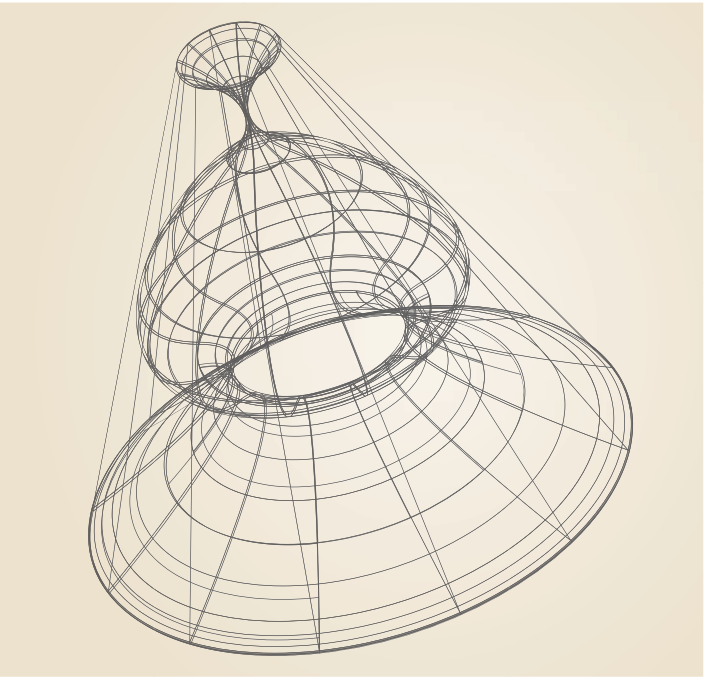


CHROMOSOMAL INSTABILITY

It's about the geometry

Chromosomal instability is a hallmark of many cancers and correlates with the presence of extra centrosomes. A direct link between the two has now been established by David Pellman and colleagues, who have defined an unanticipated mechanism through which extra centrosomes cause chromosome missegregation and aneuploidy.

By using long-term live-cell imaging to visualize thousands of cell divisions in cancer cell lines, the authors found that cells with multiple centrosomes rarely undergo multipolar cell divisions and, even when they do, they produce progeny that usually die or arrest, challenging the commonly held belief that multipolar mitosis is responsible for chromosomal instability. Instead, Ganem *et al.* proposed that during bipolar cell division, cells with extra centrosomes can form transient multipolar intermediate structures, the geometry of which predisposes kinetochores to attach to microtubules that originate from different spindle poles (merotelic attachments). Although the extra centrosomes eventually cluster into two poles to form a functional bipolar spindle, some of the abnormally attached chromosomes persist and lag behind the normally attached chromosomes, increasing the probability of missegregation. In support of their hypothesis, the authors found that cells with extra centrosomes spent most of mitosis in a multipolar arrangement and had many merotelic attachments and lagging chromosomes.



Are extra centrosomes sufficient to promote chromosome missegregation during bipolar cell division? Ganem *et al.* generated tetraploid human BJ and RPE-1 cell lines by inhibiting cytokinesis with cytochalasin D and used fluorescence-activated cell sorting to isolate pure populations of tetraploid cells with two or more centrosomes at mitosis. They found that tetraploid cells with extra centrosomes had an increased rate of lagging chromosomes and chromosome missegregation compared with tetraploid cells with a normal complement of centrosomes. This indicates that lagging chromosomes and chromosomal missegregation are caused by the presence of extra centrosomes rather than a duplicated genome.

The authors then tested the effect of overexpressing the kinase PLK4, which amplifies centrioles (an essential component of centromeres), in a U2OS osteosarcoma cell line over two generations of mitosis. During the first cell division, because the extra centrioles assembled before mitosis and remained engaged with their microtubules, bipolar spindle assembly occurred without the formation of a multipolar spindle intermediate. The frequency of lagging chromosomes in these cells was similar to that observed in control U2OS cells with two centrosomes. By contrast, in the second cell division after centriole amplification, the extra centrioles disengaged from the microtubules before cell duplication and the numbers of multipolar intermediates and lagging chromosomes in these cells were greater than in control cells. Together these findings suggest that spindle geometry may play as important a part as genetic mutations in generating chromosomal instability in human cancers.

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ORIGINAL RESEARCH PAPER Ganem, N. J. *et al.* A mechanism linking extra centrosomes to chromosomal instability. *Nature* 7 Jun 2009 (doi: 10.1038/nature08136)