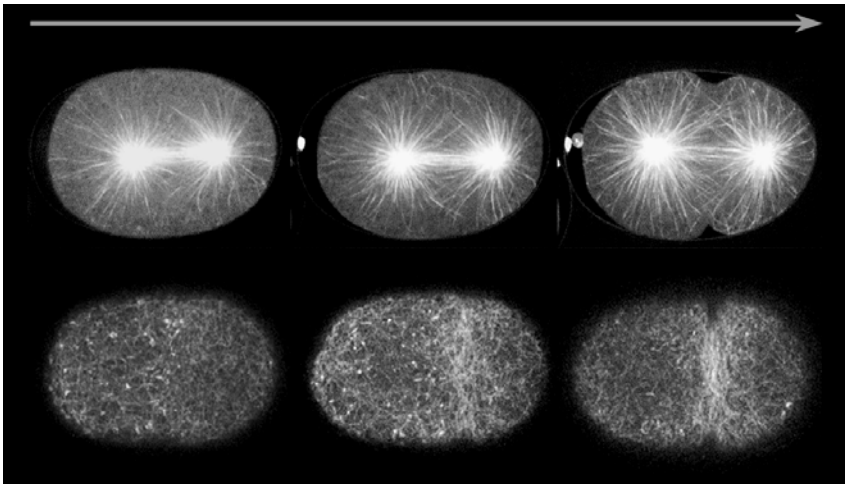
RIKEN Center for Developmental Biology (CDB)
2-2-3 Minatojima minamimachi, Chuo-ku, Kobe 650-0047, Japan

Astral tweaks: Refining the picture of microtubule activity in cytokinesis

April 20, 2006 – Cell division involves a pair of discrete mechanisms: mitosis, in which the nucleus divides and loses its membrane, and the freshly replicated chromosomes move toward opposite sides of the cell; and cytokinesis, in which the cell itself cleaves into two new cells. While the processes and their outcomes are distinct, there is nonetheless a considerable degree of carryover and coordination between the two. The cytoskeletal components known as microtubules are a prime example. Microtubules are central to mitotic division, in which they provide the guidance and support backbone used to segregate the replicated chromosomes, what is known as the mitotic spindle. But a large body of evidence points to a role for spindle microtubules in fixing the position of the cleavage furrow, which splits the cell along an axis set up by the actin-based contractile ring during cytokinesis, as well.

The question of how microtubules might determine the site of the nascent contractile ring has remained an open one for some years. One theory is that astral and/or central microtubules help to focus or hold the ring at the center of the cell, such that it forms perpendicular to the mitotic spindle pulling the chromosomes laterally to the poles. A second conjecture is the cleavage furrow forms due to a relaxation of tension at the cell's cortex at its poles, while a third ascribes a more actively inhibitory role to microtubules on cortical relaxation, such that the cleavage furrow is prevented from forming anywhere other than at the central plane of division.



Initiation of cytokinesis in the one-cell embryo of *C. elegans*. A mitotic spindle visualized by GFP-tubulin, is shown at top and filamentous actin visualized by GFP-moesin at bottom. A contractile ring forms at the spindle equator where the density of astral microtubules is high.

Now, in an article published in the April issue of *Developmental Cell*, Fumio Motegi and colleagues in the CDB Laboratory for Developmental Genomics (Asako Sugimoto; Team Leader) and New York University (USA) report findings that point to a new model for astral microtubule activity during cytokinesis. Working with the nematode *C. elegans*, Motegi finds that astral microtubules, which localize on opposing sides of the mitotic nucleus and help draw the chromosomes away from each other, in fact exhibit two separately mediated modes of action; one that localizes the contractile ring to the cell's equator, and a second that suppresses furrowing at all other regions of the cortex.

Contact: Douglas Sipp sipp@cdb.riken.jp TEL: +81-78-306-3043
RIKEN CDB, Office for Science Communications and International Affairs

"This is something of a reconciliation between a pair of rival theories, in the sense that Fumio was able to show that cortical relaxation and contractile ring induction, both of which are regulated by microtubules, could play complementary roles in a single dividing cell," says Sugimoto.

Early in the study, the team concentrated on the activity of astral microtubules at the cell cortex and, using GFP labeling to visualize the cells, they observed that these microtubules tended to behave differently at different stages of mitosis. In early anaphase, when the chromosomes are just beginning to separate, microtubules appeared had dots or comet-like in appearance, while in late anaphase, when the cleavage furrow begins to divide the cell into halves, the microtubules were filamentous and persisted longer. They also found that microtubules were most densely concentrated in the part of the cell where the contractile ring arises, and that, indeed, the early anaphase concentration of microtubules at the spindle equator appeared to promote the accumulation of RHO-1 (necessary for contractile ring formation).

A focused gene screen delivered them a trio of candidates for further study: *tbg-1*, which codes for γ-tubulin, *gip-1*, whose protein product interacts with γ-tubulin, and *air-1*, encoding aurora-A kinase. Interfering with the functions of these genes by RNAi, revealed very different patterns of phenotype. In the absence of γ-tubulin, the cleavage furrow frequently failed to form, whereas on *air-1* knockdown, the contractile ring assembled correctly at the central axis, but the cells later tended to exhibit furrow-like ingressions in multiple incorrect sites as well.

Sugimoto says "Our analysis of these findings led us to a new model for astral microtubule activity during cytokinesis, in which early anaphase activity by γ-tubulin causes the contractile ring to assemble where it should, in the center of the dividing cell, followed by later activity mediated by AIR-1, which prevents additional furrows from forming elsewhere by stabilizing the polar cortex."

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