

## Discovery upends model for how dividing cells monitor equal distribution of their chromosomes

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Ludwig researchers Arshad Desai and Christopher Campbell, a postdoctoral fellow in his laboratory, were conducting an experiment to parse the molecular details of cell division about three years ago, when they engineered a mutant yeast cell as a control that, in theory, had no chance of surviving. Apparently unaware of this, the mutant thrived.

Intrigued, Campbell and Desai began exploring how it had defied its predicted fate. As detailed in the current issue of *Nature*, what they discovered has overturned the prevailing model of how dividing cells ensure that each of their daughter cells emerge with equal numbers of chromosomes, which together package the genome. "Getting the right number of chromosomes into each cell is absolutely essential to sustaining life," explains Desai, PhD, a Ludwig member at the University of California, San Diego, "but it is also something that goes terribly wrong in cancer. The kinds of mistakes that occur when this process isn't functioning properly are seen in about 90% of cancers, and very frequently in advanced and drug-resistant tumors."

Campbell and Desai's study focused in particular on four interacting proteins known as the chromosomal passenger complex (CPC) that monitor the appropriate parceling out of chromosomes. When cells initiate division, each chromosome is made of two connected, identical sister chromatids—roughly resembling a pair of baguettes joined in the middle. As the process of cell division advances, long <u>protein</u> ropes



known as <u>microtubules</u> that extend from opposite ends of the cell hook up to the chromosomes to yank each of the sister chromatids in opposite directions. The microtubules attach to the chromatids via an intricate disc-like structure called the <u>kinetochore</u>. When the protein ropes attach correctly to the sister chromatids, pulling at each from opposing sides, they generate tension on the chromosome. One of the four proteins of the CPC, Aurora B <u>kinase</u>, is an enzyme that monitors that tension. Aurora B is expressed at high levels in many cancers and has long been a target for the development of cancer therapies.

Aurora B is essentially a molecular detector. "If the chromosomes are not under tension," says Desai, "Aurora B forces the rope to release the kinetochore and try attaching over and over again, until they achieve that correct, tense attachment."

The question is how? Aurora B is ordinarily found between the two kinetochores in a region of the chromosome that links the sister chromatids, known as the centromere. The prevailing model held that the microtubule ropes would pull themselves, and the kinetochores, away from Aurora B's reach, so that it cannot force the microtubule ropes to detach from their captive chromosomes. In other words, the location of Aurora B between the two kinetochore discs was thought to be central to its role as a monitor of the requisite tension. "This matter was thought settled," says Desai.

Yet, as Campbell and Desai show through their experiments, <u>yeast cells</u> engineered to carry a mutant CPC that can't be targeted to the centromere survive quite vigorously. They demonstrate that in such cells Aurora B instead congregates on the microtubule ropes. There, it somehow still ensures that the required tension is achieved on <u>chromosomes</u> before they are parceled out to <u>daughter cells</u>.

How precisely it does this remains unclear. Campbell and Desai provide



evidence that the clustering of Aurora B on microtubules might be sufficient to activate its function. At the same time, they hypothesize, appropriate tension on the chromosome may induce structural changes in Aurora B's targets that make them resistant to its enzymatic activity. Campbell and Desai are now conducting experiments to test these ideas.

**More information:** Tension sensing by Aurora B kinase is independent of survivin-based centromere localization, <u>DOI:</u> <u>10.1038/nature12057</u>

## Provided by Ludwig Institute for Cancer Research

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