How chromosomes 'cheat' for the chance to get into an egg

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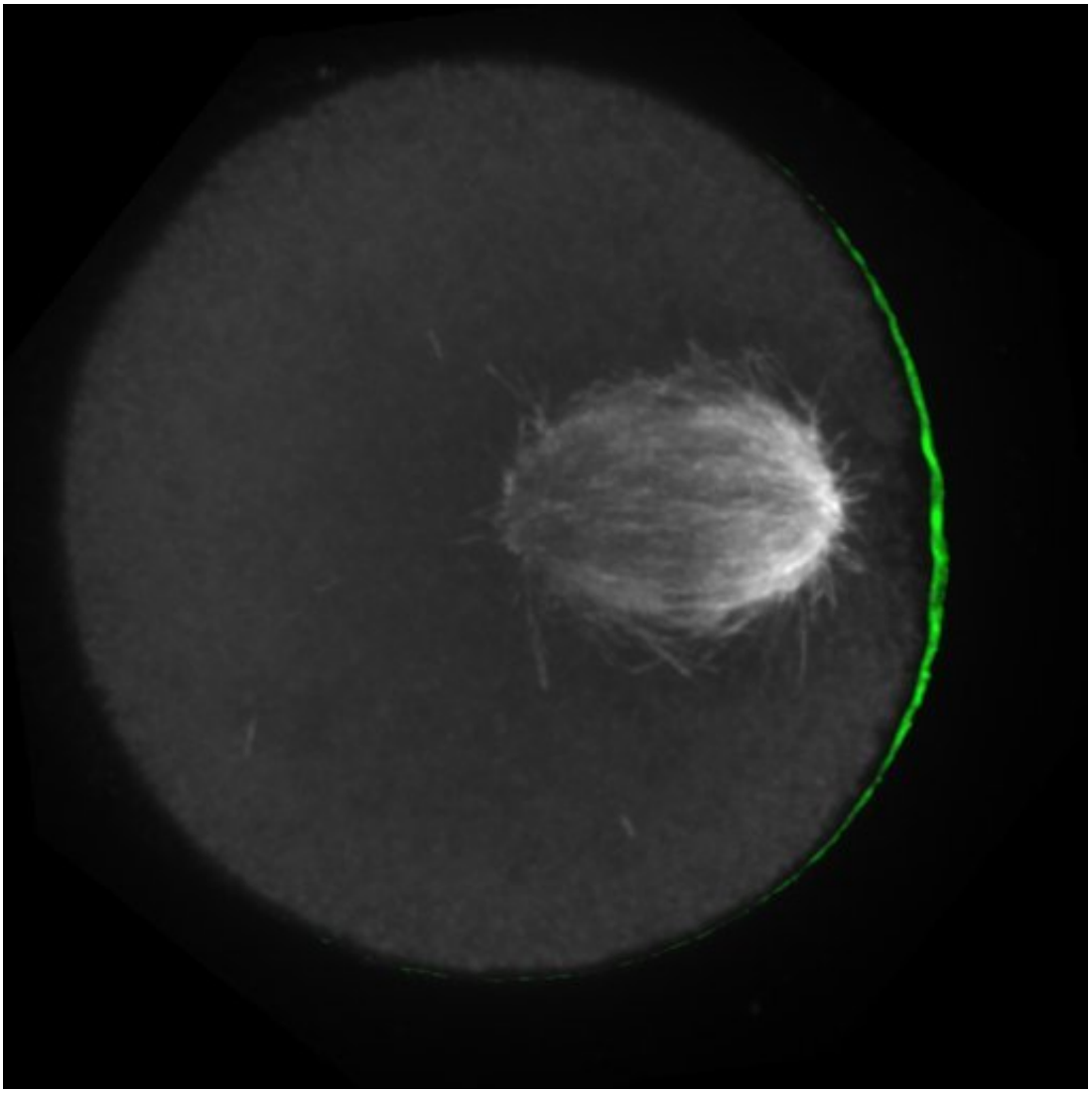

Signals from the polarized cell cortex (in green) in mouse oocytes regulate microtubule tyrosination (white) to generate spindle asymmetry in meiosis I. This asymmetry can be exploited by selfish genetic elements to bias their

transmission to the egg as a form of meiotic drive. Credit: University of Pennsylvania

Each of your cells contains two copies of 23 chromosomes, one inherited from your father and one from your mother. Theoretically, when you create a gamete—a sperm or an egg—each copy has a 50-50 shot at being passed on. But the reality isn't so clearcut.

Scientists have observed that chromosomes can "cheat," biasing the chance that they will make it into a sex cell. Now, a team from the University of Pennsylvania has shown how this bias arises in female cells. With careful observation and experiments with mouse oocytes, the precursors of eggs, they've detected molecular signals that create an asymmetry in the machinery that drives meiosis, the cell-division process that gives rise to gametes. Certain chromosomes, the researchers found, exploit this asymmetry to move themselves over to the "right" side of a cell during division and wind up in the egg.

By casting light on a common yet poorly understood facet of meiosis, the findings may lead to a better general understanding of meiosis, including how and why mistakes can arise. Errors in how chromosomes segregate to gametes during meiosis are the root cause of some miscarriages and conditions such as Down's syndrome.

"If we understand how these selfish elements are exploiting the mechanics of meiosis, then we'll understand more deeply how that process works in the first place," said Michael Lampson, associate professor of biology in Penn's School of Arts and Sciences and senior author on the study.

Lampson teamed with lab members Takashi Akera, Lukáš Chmátal,

Emily Trimm and Karren Yang, as well as Richard M. Schultz, the Charles and William L. Day Distinguished Professor of Biology; David Chenoweth, associate professor in the Department of Chemistry; Chenoweth lab member Chanat Aonbangkhen; and Carsten Janke of France's Institut Curie. Their study appears in the journal *Science*.

For decades, scientists have been aware that genetic elements seemed to engage in competition during meiosis, as some were transmitted to the gametes at a rate consistently higher than chance would dictate. The term for this biased transmission is "meiotic drive."

"Usually we think about selfish genes at the level of natural selection and selection of the fittest," Lampson said. "That might mean a gene that makes you live longer or reproduce more or kill your enemies is more likely to be passed on. But we can also think about selfishness at the level of the gene itself. In that context, genes are competing with each other to get into the gamete. And while we had evidence that this could happen, we didn't really understand how it did happen."

For biased transmission to occur, the Penn team reasoned, something about the physical machinery of cell division must enable it. In the case of females, the final stage of meiosis leads to the creation of one cell that becomes the viable egg and another cell called a polar body, which is typically degraded.

The researchers chose to focus on the cell-division machinery, studying the meiotic spindle, the structure comprised of microtubules that attaches to chromosomes, pulling them to opposite sides of a cell before it divides.

Looking at microtubules in mouse oocytes, they found a lopsided distribution of a modification called tyrosination: The egg side of the cell had less of this modification than the other side, closer to what is

called the cortex. This asymmetry was only present at the stage of meiosis when the spindle moves toward the cortex from the middle of the cell.

"That told us that whatever signal is setting up the tyrosine modification is coming from the cortex," Lampson said. "The next question is, What is that signal?"

The researchers already had some information about molecules that increase in expression on the cortical side of the cell, including one called CDC42. To test whether this molecule contributed to the asymmetrical tyrosination, the researchers used an experimental system that Lampson and Chenoweth had devised previously that uses a light-sensitive assay to selectively enrich CDC42 on one side of the pole. Their results suggested that CDC42 was responsible, at least in part, for inducing the tyrosination asymmetry and thus the asymmetry of the spindle in the dividing cell.

Having established that asymmetry exists and how it arises, the Penn researchers set out to show that this asymmetry enables chromosomes to cheat. They did so by focusing on centromeres, the region of a chromosome that attaches to the spindle. Crossing two strains of mice, they wound up with animals that possessed two types of centromeres in each of their cells, one bigger and one smaller.

From earlier work by the group, they knew that the larger centromeres were known to transmit preferentially to the gametes. In the current work, they confirmed that the bigger, "stronger" centromeres were indeed more likely to go toward the pole of the cell that would become the egg.

When the researchers abolished the spindle asymmetry by mutating CDC42 and other targets, the bias in centromere orientation

disappeared.

"That connects the spindle asymmetry to the idea of chromosomes or centromeres actually cheating," Lampson said.

But this result also raised the question of when the centromeres became biased in their orientation, as the spindle starts out in the middle of the cell, at which point centromeres are already attached in an unbiased fashion. The asymmetry and biased centromere attachment occur later.

Enter the flipping centromere. Using live imaging of mouse oocytes, the researchers found that the "stronger" centromeres were more likely to detach from the spindle than weaker centromeres and were especially likely to detach if they were oriented to the cortical side of the cell, presumably in order to flip and reorient themselves to the egg pole of the cell. The weaker centromeres only rarely detached and showed no preference for one side of the cell or the other.

"If you're a selfish centromere and you're facing the wrong way, you need to let go so you can face the other way," Lampson said. "That's how you 'win.'"

In future work, Lampson and his team hope to further explore what characteristics of the centromeres make them strong or weak.

"This work gave us some good information about biased transmission of centromeres, but it also brings up a ton of other questions," Lampson said. "Why do our centromeres look the way they do, and how do they evolve to win these competitions? These are fundamental biological questions that we still don't know a lot about."

More information: "Spindle asymmetry drives non-Mendelian chromosome segregation" *Science* (2017).

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