Cellular sentinel prevents cell division when the right machinery is not in place

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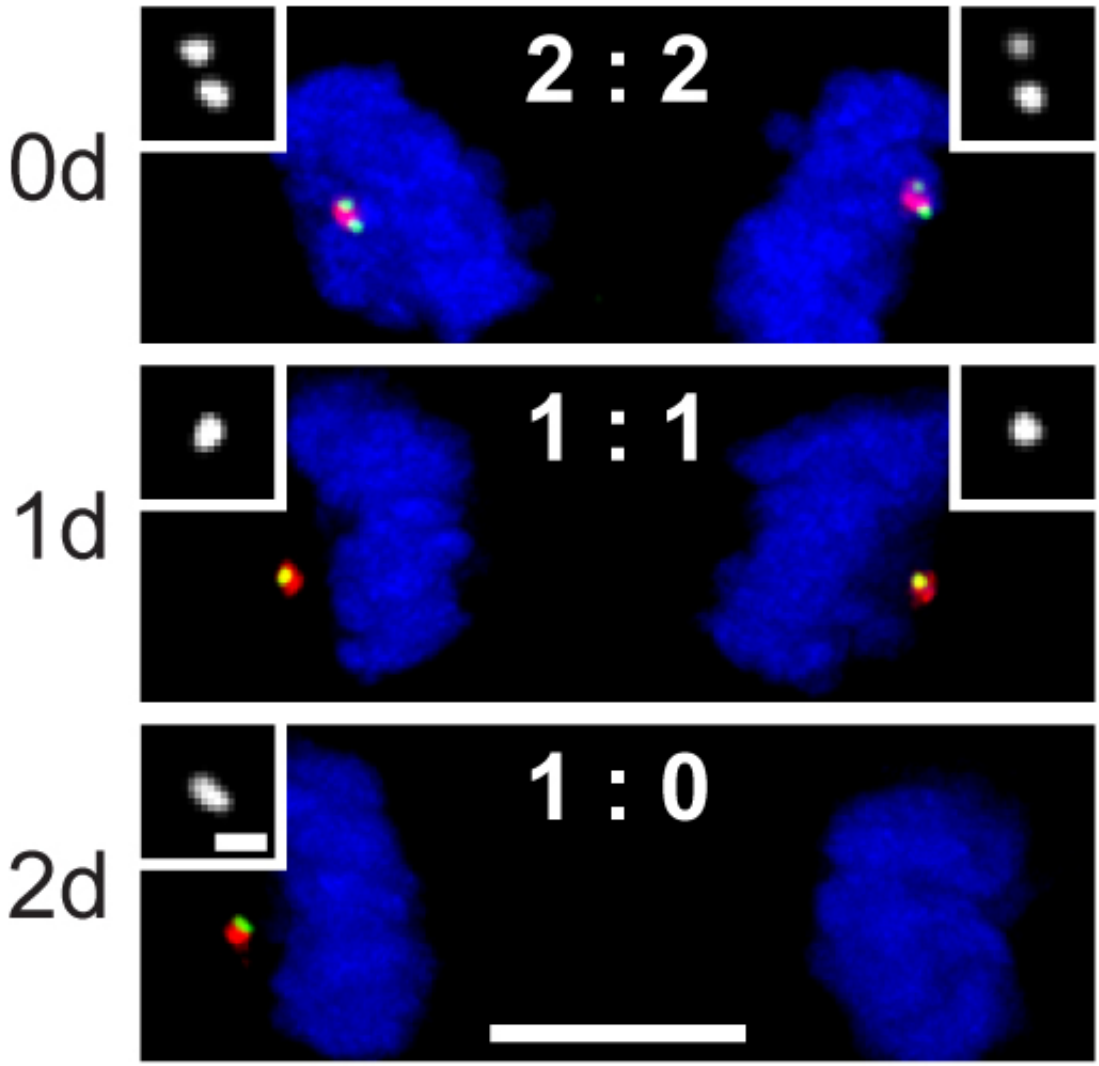

After cells are treated with auxin to prevent centriole duplication, the number of centrioles (green dots) per cell is halved with each cell division. The number of days of auxin treatment is shown at left. DNA shown in blue. Credit: *Journal of Cell Biology*

For cell division to be successful, pairs of chromosomes have to line up just right before being swept into their new cells, like the opening of a theater curtain. They accomplish this feat in part thanks to structures called centrioles that provide an anchor for the curtain's ropes. Researchers at Johns Hopkins recently learned that most cells will not divide without centrioles, and they found out why: A protein called p53, already known to prevent cell division for other reasons, also monitors centriole numbers to prevent potentially disastrous cell divisions.

Details of the findings will be published online in the *Journal of Cell Biology* on July 6. The new information, plus new tools for centriole manipulation, should help researchers figure out how p53 helps safeguard cells—and how it causes cancers when it doesn't.

"P53 was already known to monitor many things, like DNA damage and having the wrong number of chromosomes, that make division dangerous for cells," says Andrew Holland, Ph.D., an assistant professor of molecular biology and genetics at the Johns Hopkins University School of Medicine. "We've discovered one more item on its checklist: centriole number."

Cells normally have two centrioles that work together as a unit to anchor and organize microtubules, the molecular rods that form the cell's backbone. As a cell prepares for division, one new centriole forms alongside each existing centriole. Then, each pair goes to opposite sides of the cell. Before dividing, pairs of identical chromosomes line up in the middle of the elongated cell, and the microtubules, emanating out from the centrioles on either side, help pull the chromosomes in opposite directions so that each new cell receives one member of each chromosome pair.

"If cells don't segregate their chromosomes properly, there can be dire consequences," says Bramwell Lambrus, a graduate student in Holland's laboratory. "Down syndrome, for example, results from an embryo inheriting an extra copy of chromosome 21. What's fascinating is that the cells that divide to create a woman's egg cells do not have centrioles, so we know that they're not absolutely necessary but very helpful."

To better understand the role of centrioles in cell division, the team needed to see how cells behaved without them. However, fully wiping out a cell's centrioles for long enough to study the results posed a serious challenge because, when a cell senses its centrioles are gone, it makes new ones from scratch. To overcome this hurdle, Holland's team went after the protein Plk4, which is required for centriole formation. Instead of permanently deleting the Plk4 gene from the cells, they used a trick from plant biology to toggle its presence in the cells—one that had never before been applied to an animal cell's proteins.

Working with human retina cells, the researchers tweaked Plk4 so that it would be sent to cellular trash cans whenever they gave the cells a plant hormone called auxin. As long as it was present, auxin prevented new centrioles from forming, so each cell division halved the number of centrioles per cell. By the fourth cell division, most of the cells had no centrioles, and none of them divided again. But even after auxin was removed and Plk4 was restored, the cells refused to divide or make more centrioles.

"The cells were permanently stuck," explains Holland. "It was a Catch-22. They couldn't divide again without making new centrioles, but they couldn't make new centrioles without starting the process of division. It was clear that something was telling the cells not to divide."

After testing a few different hypotheses to explain why the cells were stuck, the team turned to p53, a protein known for preventing cell

division when things aren't right. When they halted p53 production in cells with no centrioles, they began to divide again. As expected, the newly formed cells had many chromosome abnormalities.

In a final experiment, the scientists restored Plk4 to cells lacking both centrioles and p53 to see if the cells would make new centrioles. Since p53 wasn't there to prevent their division, the return of Plk4 was all that was necessary for the cells to start centriole formation again from scratch. "Since centriole formation without an existing centriole template only occurs when cells lack all of their centrioles, it's a rare occurrence, and it was exciting to watch it happen under the microscope," says Lambrus.

The team plans to continue analyzing the formation of new centrioles, and how p53 detects centrioles and prevents cells from dividing without them. "Ninety percent of human tumors have chromosome abnormalities, and we know that many of these are made possible by mutations in p53," says Holland. "If centrioles aren't there to aid proper chromosome segregation, p53 acts as backup to prevent making abnormal cells. It's an important safeguard that we'd like to understand more."

Provided by Johns Hopkins University School of Medicine

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