Study offers insights into how cells reverse their decision to divide

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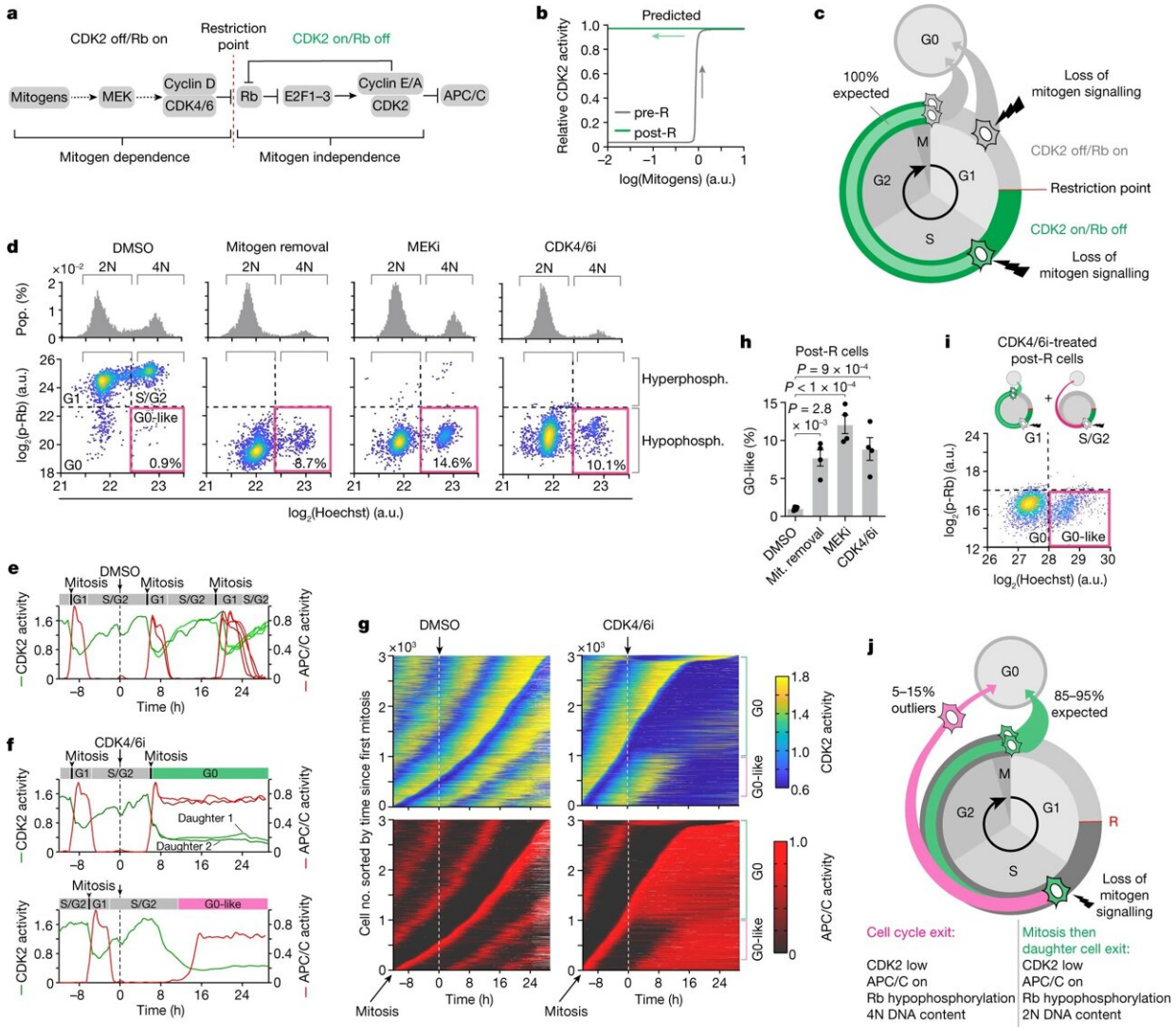

Mitogen signaling maintains CDK2 activity in S/G2. **a**, Textbook signaling pathway indicating that the R point marks the switch from mitogen dependence to independence. **b**, Mathematical model adapted from Yao et al.[8] showing

bistability and hysteresis in CDK2 activity with respect to mitogen signaling. **c**, Predicted fates for pre- and post-R cells made by the R-point model. **d**, Histograms show DNA content (upper panels). Scatterplots of Rb phosphorylation versus DNA content (lower panels). Pink boxes mark the G0-like state (hypophosphorylated Rb and 4N DNA content). The percentage of G0-like cells is indicated. $N = 2{,}000$ cells per condition. **e**, CDK2 and APC/C activity from an example MCF-10A cell treated with DMSO at the indicated time. The cell divides multiple times, giving rise to four granddaughter cells (Supplementary Video 1). **f**, CDK2 and APC/C activity from two example MCF-10A cells treated with CDK4/6i at the indicated time. In the upper panel, the cell divides, and its daughters arrest in G0. In the lower panel, the cell exits the cell cycle to a G0-like state without dividing (Supplementary Videos 2 and 3). **g**, Heat maps show CDK2 and APC/C activity sorted by time of mitosis for cells treated with DMSO (left panels) or a CDK4/6i (right panels). Extended Data Fig. 2b demonstrates how CDK2 and APC/C activities are converted to the heat map. **h**, Percentages of post-R cells that exit to the G0-like state after mitogen (Mit.) removal, MEKi or CDK4/6i. Error bars represent s.e.m. from $n = 4$ independent experiments. *P* values were calculated using a one-way analysis of variance. *P* values from top to bottom are 9×10^{-4}, less than 1×10^{-4} and 2.8×10^{-3}. **i**, Scatterplot of Rb phosphorylation versus DNA content for CDK4/6i-treated post-R cells from **g** showing two distinct cell cycle trajectories for post-R cells after loss of mitogen signaling. The pink box indicates the G0-like state, and cartoons (upper panel) show cell cycle trajectories. $N = 3{,}621$ cells. **j**, Schematic showing observed fate outcomes for post-R cells after loss of mitogen signaling. a.u., arbitrary unit. phosph., phosphorylation. Credit: *Nature* (2023). DOI: 10.1038/s41586-023-06274-3

A new study suggests that cells preparing to divide can reverse this process and return to a resting state, challenging long-held beliefs about cell division. If interrupted early in their preparation to divide, cells were able to halt the division process, known as mitosis.

The finding, led by researchers at the National Cancer Institute (NCI),

part of the National Institutes of Health, and reported July 5, 2023, in *Nature*, could point toward more effective treatments to interrupt the process by which cancer cells divide quickly and spread.

When cells receive growth-promoting signals, called mitogens, they enter the cell cycle—synthesize new copies of their DNA in a series of steps that culminate in cell division. Scientists have long thought that the preparatory stage of this cycle includes a point after which cells cannot halt the process. Researchers believed that after this "point of no return," growth signals are no longer needed to drive cells to divide.

In the new study, scientists at NCI's Center for Cancer Research captured videos of thousands of cells undergoing mitosis and watched what happened to those cells when mitogens were withdrawn. About 15% of the cells exited the cell cycle and returned to a resting state.

What those cells had in common was that they hadn't been as far along as others in the cycle when they stopped receiving growth-promoting signals. In experiments with many different kinds of cells, researchers found that all types of cells were capable of exiting the cell cycle if it was early enough.

Drugs that inhibit the cell cycle regulators CDK4 and CDK6, such as the breast cancer drug palbociclib (Ibrance), likely interrupt cells' progression through the cell cycle differently than previously thought, the researchers said. They are now looking at whether they can take advantage of this new molecular mechanism to design a more durable therapy by combining CDK4 and CDK6 inhibitors with traditional chemotherapy drugs that induce DNA damage.

More information: Steven Cappell, Loss of CDK4/6 activity in S/G2 phase leads to cell cycle reversal, *Nature* (2023). DOI: 10.1038/s41586-023-06274-3.

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