Inactive Actin

Clathrin-mediated endocytosis shuts down during mitosis in eukaryotic cells because all of the required actin is hoarded by the cytoskeleton.

By Anna Azvolinsky | May 1, 2014

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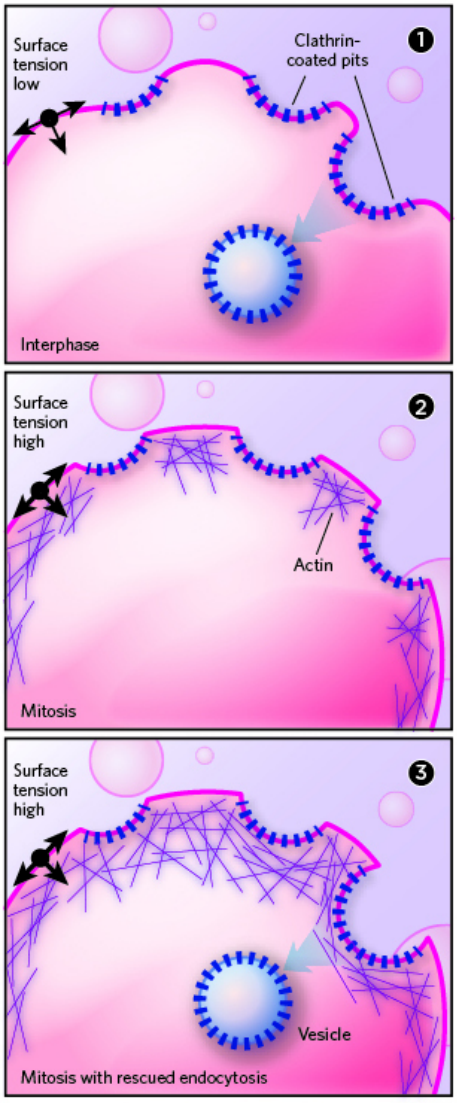

RESTORATION HARDWARE: During interphase, mammalian cells have low membrane tension, and clathrin-mediated endocytosis (CME) proceeds normally with no special need for actin (1). During mitosis, membrane tension is high, the actin (purple) is sequestered at the cell cortex, and CME can't proceed because actin is required to help stretch the clathrin-coated pits to form full vesicles (2). Freeing up some of the actin during mitosis allows the protein to help form clathrin-coated vesicles, restoring CME (3).
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EDITOR'S CHOICE IN CELL BIOLOGY

The paper
S. Kaur et al., "An unmet actin requirement explains the mitotic inhibition of clathrin-mediated endocytosis," *eLife*, 3:e00829, 2014.

For decades, scientists observed clathrin-mediated endocytosis (CME)—the process of forming vesicles to pull protein cargo into a cell—ceasing during mitosis in mammalian cells. But they didn't know why. From prophase to anaphase, shallow clathrin-coated pits form at the plasma membrane, but the cell never internalizes them.

Two main theories have tried to explain how endocytosis is inhibited. After finding that proteins involved in endocytosis are phosphorylated during mitosis, researchers proposed that phosphorylation of crucial components turns off CME. The second theory suggested that elevated tension in the plasma membrane prevents clathrin-coated pits from pinching off into closed vesicles. But scientists had not reached a consensus.

Taking advantage of newer techniques, including proteomics and RNAi, Stephen Royle, a cell biologist at the University of Warwick in the U.K., tackled this question anew. Royle and colleagues first observed that in HeLa cells, cortactin, a protein that activates actin polymerization, was present in clathrin structures during interphase but was greatly reduced during mitosis. This led Royle's team to investigate whether inactive actin was prohibiting endocytosis from occurring.

The researchers showed that, during mitosis, much of the actin is engaged with the cell's rigid cortex, which causes the cells to become round during mitosis, and none is available to help out with endocytosis. Using two different methods that released some of the actin from the cytoskeleton but did not decrease membrane tension, they demonstrated that it is possible to restart endocytosis. This finding nixed the idea that increased membrane tension alone is responsible for the endocytosis shutdown, and instead led the team to propose that actin availability determines whether endocytosis proceeds.

The results make sense in light of previous studies suggesting that when cell membranes are stretched tight there is a greater need for actin to form clathrin-coated vesicles. "It seems that whether actin is required for endocytosis really depends on how much work the endocytic machinery has to do to create a vesicle," says Royle.

"While other researchers were consumed with showing a direct role for actin in the formation of endocytic vesicles, this study shows that if actin is not available, vesicle budding cannot occur," says Linton Traub, a

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cell biologist at the University of Pittsburgh who was not involved in the study. "It's an indirect way to address the question, but an interesting and mechanistically insightful study."

Royle's team also provided evidence against the phosphorylation hypothesis, showing that certain endocytic proteins remained phosphorylated when they restarted endocytosis. Still, Traub suspects that actin unavailability is not the only regulatory mechanism controlling endocytosis.

Royle's team is now addressing how the endocytic machinery is able to sense high membrane tension and recruit actin within cells of tissues undergoing physical stretching or in polarized epithelial cells, which have different tensions at their basolateral and apical membranes. "Understanding what is required for endocytosis may allow for its control," Royle says, "either turning on the process to get mitotic cells to take up drugs or [turning it off] to prevent cells from engulfing molecules or viruses."

Tags

mitosis, clathrin, cell biology, cell & molecular biology and actin

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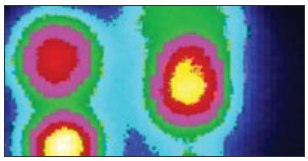

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