Endocytosis Resumes during Late Mitosis and Is Required for Cytokinesis*

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Recent work has underscored the importance of membrane trafficking events during cytokinesis. For example, targeted membrane secretion occurs at the cleavage furrow in animal cells, and proteins that regulate endocytosis also influence the process of cytokinesis. Nonetheless, the prevailing dogma is that endosomal membrane trafficking ceases during mitosis and resumes after cell division is complete. In this study, we have characterized endocytic membrane trafficking events that occur during mammalian cell cytokinesis. We have found that, although endocytosis ceases during the early stages of mitosis, it resumes during late mitosis in a temporally and spatially regulated pattern as cells progress from anaphase to cytokinesis. Using fixed and live cell imaging, we have found that, during cleavage furrow ingression, vesicles are internalized from the polar region and subsequently trafficked to the midbody area during later stages of cytokinesis. In addition, we have demonstrated that cytokinesis is inhibited when clathrin-mediated endocytosis is blocked using a series of dominant negative mutants. In contrast to previous thought, we conclude that endocytosis resumes during the later stages of mitosis, before cytokinesis is completed. Furthermore, based on our findings, we propose that the proper regulation of endosomal membrane traffic is necessary for the successful completion of cytokinesis.

Cytokinesis completes the process of cell division and gives rise to two new daughter cells, each with a complete array of chromosomes and intracellular organelles as well as an intact plasma membrane and cytoskeleton. Throughout mitosis and cytokinesis, cytoskeletal elements are required to mediate both nuclear and cellular division events. Microtubules reorganize to form the mitotic spindle that facilitates chromosome separation, whereas actin filaments build the contractile ring that physically separates the cytoplasm of the dividing cell (1). Although cytokinesis requires the action of the cytoskeleton, membrane components, such as intracellular membrane vesicles and the plasma membrane, are not simply passive participants in this process. In fact, recent work has highlighted a role for membrane remodeling events during cytokinesis in animal cells (2–7). During cell cleavage in Xenopus and sea urchin embryos, microtubules direct the insertion of Golgi-derived membrane at the furrow (8–10). Furthermore, SNARE (soluble NSF attachment protein receptor) proteins, which mediate membrane fusion events, and annexins, calcium-binding proteins known to be involved in membrane trafficking, are important for cytokinesis in animal cells (11–15).

In addition to secretory membrane traffic, it is clear that endosomal trafficking is also important during cytokinesis (reviewed in Refs. 6 and 16). Previous research has indicated that endocytosis ceases during mitosis and is thought not to resume until cell division is complete (17). However, recent work has shown that proteins known to regulate endocytosis in interphase cells, such as clathrin and dynamin, also influence the process of cytokinesis (18–20). Recent studies have also shown that proteins that govern recycling endosome function (Rab11 and Nuf/FIP3) localize near the furrow and are required during cellularization in Drosophila and cytokinesis in mammalian cells (21, 22). Furthermore, work from our laboratory has shown that the ADP ribosylation factor 6 (ARF6)3 GTPase, a key regulator of endocytosis and endosomal recycling, plays a role during cytokinesis in mammalian cells (23). Nonetheless, endocytosis and endosomal membrane trafficking events during cytokinesis have not been well studied in mammalian cells.

In this study, we have investigated endocytic membrane trafficking during mammalian cell cytokinesis. Consistent with previous studies, we have found that endocytosis ceases during early mitosis. However, we have shown that endocytosis resumes during late mitosis in a spatially and temporally regulated manner, describing for the first time endocytic events that occur during mammalian cell cytokinesis. We have found that endocytosis occurs from the plasma membrane at the polar region of dividing cells during cleavage furrow ingression and from the midbody area during late cytokinesis. In addition, we have found that vesicles endocytosed from the polar region during cleavage furrow ingression are trafficked to the midbody region during late cytokinesis. Finally, we have shown that cytokinesis is inhibited when clathrin-mediated endocytosis is blocked via expression of the GTPase-defective ARF6 mutant or other dominant negative proteins. The latter findings suggest that endocytosis is required for cytokinesis and that ARF6-GTP induces cytokinesis defects, at least in part by its effect on endosomal trafficking during cytokinesis.

EXPERIMENTAL PROCEDURES

Reagents—Phalloidin conjugates, human transferrin conjugates, and dextran (M, 10,000) were from Molecular Probes (Eugene, OR). Draq5 (a DNA stain) was from Alexis Biochemicals (Carlsbad, CA). Antibodies and Immunofluorescence—Mouse monoclonal antibody against α-tubulin was from Sigma. The rabbit polyclonal antibody against ARF6 has been described elsewhere (23). Mouse monoclonal

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3 The abbreviations used are: ARF6, ADP ribosylation factor 6; FITC, fluorescein isothiocyanate; PBS, phosphate-buffered saline; GFP, green fluorescent protein; EGFP, enhanced green fluorescent protein; AP, assembly protein.
antibody against the transferrin receptor was from Zymed Laboratories Inc. (San Francisco, CA). Secondary antibodies for immunofluorescence were from Amersham Biosciences when conjugated to Cy3, from ICN when conjugated to fluorescein isothiocyanate (FITC), and from Amersham Biosciences when conjugated to Cy5. Procedures for cell fixation, immunofluorescent staining, and microscopy were performed as described previously (24). To label nuclei, cells were incubated with Draq5 (5 μM in phosphate-buffered saline (PBS)) for 3–10 min before fixation. Micrographs were obtained using a Nikon Diaphot 200 fluorescence microscope and a Bio-Rad MRC 1024 confocal system. Images were manipulated using Adobe Photoshop, version 7.0.

**Cell Culture and Plasmid Transfection**—HeLa cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, penicillin, and streptomycin (complete Dulbecco’s modified Eagle’s medium) at 37 °C and 5% CO2. U-2OS cells were maintained in McCoy’s 5A medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, penicillin, and streptomycin. The pIRES-EGFP plasmid containing ARF6(Q67L) has been described elsewhere (23). pEGFP bearing α-tubulin was kindly provided by Dr. Doug Fishkind. A mammalian expression plasmid containing FLAG-tagged assembly protein (AP)180 was kindly provided by Lois Greene (National Institutes of Health), and the GFP-tagged Eps15 constructs were a gift from Alexander Benmerah. The pEYFP-Golgi plasmid (Clontech) encodes a fusion protein consisting of enhanced yellow fluorescent protein (EYFP) and the N-terminal 81 amino acids of human β1-4-galactosyltransferase, which targets the fusion protein to the trans-medial region of the Golgi apparatus. For plasmid transfection, HeLa cells were seeded on 60-mm dishes and transfected with 4 μg of DNA using 12 μl of FuGENE reagent (Roche Applied Science), according to the manufacturer’s instructions.

**Cell Synchronization**—To obtain mitotic cells, cells were synchronized using a single thymidine block followed by nocodazole treatment as described previously (23). For immunofluorescence analysis, collected mitotic cells were seeded on poly-L-lysine-coated coverslips and fixed with 2% paraformaldehyde during cytokinesis. To analyze mitotic cells, isolated mitotic cells were seeded on poly-L-lysine-coated coverslips in serum-free medium. At various times throughout mitosis and cytokinesis, the cells were incubated with fluorescently labeled markers, the cells were washed and fixed them. As expected, we found that transferrin labeling was observed prominently on the polar region of late anaphase cells (Fig. 1C, top row), whereas there is strong labeling at the ingressed cleavage furrow in cells at late telophase/cytokinesis (Fig. 1B, bottom row). Finally, we assessed the localization of the transferrin receptor in dividing cells. Consistent with our transferrin internalization uptake results, we found that transferrin receptor was localized predominantly at the polar region of late anaphase cells (Fig. 1C, top row) but was present at both the polar and equatorial regions in late telophase cells (Fig. 1C, bottom row). We also analyzed transferrin uptake during cytokinesis in the U-2OS cell line and found an identical pattern of endocytosis during cleavage furrow ingression and cytokinesis (supplemental Fig. 1). This finding suggests that endocytosis resumes during cytokinesis in a similar way in mammalian cells in general. During cytokinesis, Golgi fragments also coalesce in two juxtanuclear pools at the polar and equatorial or midbody regions (Fig. 1D, bottom row).

Next, we examined the uptake of a fluid phase marker, dextran conjugated to AlexaFluor-594, during mitosis. Similar to our transferrin results, we found that early mitotic cells exhibited no dextran uptake, whereas cells at telophase and cytokinesis displayed substantial dextran internalization (Fig. 1D). In anaphase cells, the amount of dextran inter-
nalization was less significant and more variable than what we observed for transferrin uptake. Nonetheless, the general pattern of uptake was the same for both ligands. When late mitotic cells were incubated with dextran and transferrin simultaneously, we observed a similar pattern of internalization for both ligands as well as partially overlapping cytoplasmic vesicles (Fig. 1E). In sum, these results demonstrate that endocytosis of both receptor-mediated and fluid phase markers resumes during cytokinesis in a spatially and temporally regulated manner.

**Endocytosed Vesicles Are Trafficked to the Midbody Region**—Our results revealed a strong labeling of endocytic markers at the cleavage furrow during late telophase and cytokinesis. However, we questioned whether or not the label at the cleavage furrow resulted exclusively from active endocytosis at the ingressed cleavage furrow or from the traffic of endocytosed vesicles from the polar region to the equatorial region. To answer this question, we “pulsed” mitotic cells with transferrin for 5 min during early cleavage furrow ingression (85–90 min after mitotic entry) and then fixed them after a 30-min “chase” (120 min after mitotic entry). Cells fixed immediately after the 5-min uptake were predominantly in anaphase and early telophase. As shown in Fig. 2A, these cells contained transferrin labeling near the spindle poles (top row; fixed at 90 min), whereas cells at late telophase/ cytokinesis exhibit transferrin labeling along the entire plasma membrane near the ingressed cleavage furrow as well as at the polar regions (bottom row). B, cells were fixed at 105 min after mitotic entry. Cells at anaphase and early telophase exhibit prominent transferrin labeling on the polar region of the plasma membrane (top row), whereas cells at late telophase/ cytokinesis exhibit transferrin labeling along the entire plasma membrane (bottom row). C, cells were fixed at 90 min after mitotic entry and labeled with FITC-phalloidin to visualize actin and immunostained for transferrin receptor (Tfn-R, pseudocolored green in the merged image). D, HeLa cells were transfected with α-tubulin-pEGFP, synchronized, and incubated in serum-free medium after release from nocodazole arrest. During mitosis, cells were incubated with AlexaFluor-594-dextran for 5 min, washed three times with cold PBS, and fixed. Cells at late anaphase and early telophase exhibit dextran internalization predominantly at the spindle pole region (top row; fixed at 95 min), whereas cells at late telophase exhibit prominent dextran uptake at the furrow and spindle poles (bottom row; fixed at 120 min). E, synchronized mitotic HeLa cells were incubated with FITC-transferrin, AlexaFluor-594-dextran, and Draq5 for 7 min and then washed and fixed. The top row depicts an anaphase cell (fixed at 90 min), and the bottom row depicts a late telophase cell (fixed at 100 min). Throughout cytokinesis, cells internalize dextran and transferrin in a similar manner. Each image represents a single confocal plane. Scale bars, 10 μm.
AlexaFluor-546-transferrin for 3 min and then the ligand was washed out. Pictures of the dividing cells were captured before, during, and after transferrin addition. In these experiments, we found that initially transferrin was internalized prominently from the plasma membrane at the periphery of the dividing cell and trafficked to the mitotic spindle pole region. Subsequently, after cleavage furrow ingestion was complete, there was further traffic of transferrin-positive vesicles to the cleavage furrow, flanking each side of the midbody. Images from representative time-lapse videos (supplemental Figs. 5 and 6), showing both transferrin labeling and tubulin-GFP, are shown in Fig. 3A.

We also determined whether or not there was additional endocytosis at the midbody during late cytokinesis. For this experiment, we pulsed mitotic cells with Texas Red-transferrin during early anaphase and telophase as described above, but before fixation at 120 min, we incubated the cells with a second ligand, FITC-transferrin, for 5 min. We reasoned that, if there is new endocytosis at the ingressed cleavage furrow, we would see internalized FITC-transferrin at the midbody in addition to Texas Red-transferrin that was internalized during anaphase and telophase and trafficked to the midbody. As shown in Fig. 2C, cells at late telophase displayed FITC-transferrin at the midbody as well as Texas Red-transferrin that was internalized earlier during anaphase and telophase. This result suggests that, in addition to the traffic of endocytosed vesicles from the polar region of dividing cells to the cleavage furrow, new endocytosis occurs at the ingressed cleavage furrow as well. Furthermore, we found that in the late telophase cells, the Texas Red-transferrin label (added during anaphase and early telophase) was stronger at the spindle poles than at the furrow, whereas the FITC-transferrin label (added after cleavage furrow ingestion) was more intense near the ingressed furrow (Fig. 2C), supporting our contention that endocytosis resumes first at the polar region during cleavage furrow ingestion and then at the midbody region during late cytokinesis.

To further confirm that endocytosis occurs in the midbody region after cleavage furrow ingestion, we performed live cell imaging analysis using cells transiently transfected with tubulin-GFP. Cells at late cytokinesis (that had already undergone cleavage furrow ingestion) were incubated with AlexaFluor-546-transferrin for 3 min and then the ligand was washed out. Pictures of the dividing cells were captured before, during, and after transferrin addition and still images from representative time-lapse videos (supplemental Figs. 5 and 6) are shown in Fig. 3B. In these experiments, we found that internalized transferrin was present in the midbody region immediately after transferrin washout, suggesting that endocytosis occurs at the ingressed cleavage furrow. In addition, we found that several minutes after transferrin washout, there was a further concentration of the internalized transferrin label on either side of the forming midbody. Together, these results indicate that endocytosis occurs in the region of the ingressed furrow and that, even at this late stage of cytokinesis, endosomal vesicles are trafficked at the midbody area in a distinct manner.

Inhibition of Receptor-mediated Endocytosis Induces Cytokinesis Defects—ARF6 is a small GTPase that regulates endocytosis and endosomal recycling as well as actin rearrangements during interphase (26–35). In a previous study, we showed that endogenous ARF6 is transiently activated during cytokinesis. In addition, we found that overexpression of a GTP hydrolysis-defective mutant, ARF6(Q67L), in mitotic cells led to a variety of cytokinesis defects without affecting actin polymerization at the cleavage furrow (23). Thus, we decided to investigate a role for ARF6 in the regulation of endocytic traffic during cytokinesis. For these experiments, we monitored the receptor-mediated endocytosis of transferrin during cytokinesis in cells transfected with ARF6(Q67L)-pIRES-EGFP. As shown in Fig. 4, cells transfected with ARF6(Q67L) displayed little to no transferrin internalization during cleavage furrow ingestion and cytokinesis. When compared with neighboring non-transfected cells, ARF6(Q67L)-transfected cells consistently exhibited dramatically reduced transferrin labeling throughout anaphase to cytokinesis (Fig. 4). Using laser confocal sectioning, we found few to no transferrin-positive vesicles throughout the Z-axis of dividing ARF6(Q67L)-transfected cells (Fig. 4, B and C). Next, we examined the endocytosis of dextran during cytokinesis in ARF6(Q67L)-expressing cells. In general, dividing ARF6(Q67L) cells displayed a low amount of dextran uptake during cytokinesis (data not shown), but the effect was more variable and less conclusive than our findings with transferrin. In sum, our results indicate that ARF6(Q67L) overexpression profoundly inhibits receptor-mediated endocytosis during cytokinesis. Our results are consistent with recent reports that ARF6-GTP inhibits transferrin internalization during interphase (36, 37). These findings suggest that ARF6(Q67L) induces cytokinesis defects, at least in part, via an inhibition of receptor-mediated endocytosis.

To further investigate the importance of endocytosis during cytokinesis, we sought to examine how an inhibition of receptor-mediated endocytosis would affect the process of cytokinesis. Eps15 is an accessory protein that is found in clathrin-coated pits, binds AP-2, and is essential for early stages of clathrin-mediated endocytosis. Expression
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of a dominant negative form called Eps15-EH29 blocks clathrin-mediated endocytosis by inhibiting coated pit formation (38, 39). To this end, we transfected cells with GFP-tagged Eps15-EH29 and assessed its impact on cytokinesis. We found that mitotic cells expressing Eps15-EH29 progressed through mitosis at the same pace as non-transfected cells observed in the same experiment (data not shown). However, along with a block in transferrin internalization, we found that, on average, over 95% of mitotic cells expressing Eps15-EH29 exhibited cytokinesis defects, such as excessive cell blebbing throughout the cleavage furrow region and binucleated cell formation (Fig. 5, B and C). We have classified the cell division defects in Eps15-EH29- and AP180-transfected cells as cytokinesis defects, because we did not notice any defective phenotypes in transfected cells during the earlier stages of mitosis. Nonetheless, we cannot rule out the possibility that problems occur during late mitotic stages just prior to cytokinesis that prevent the completion of cytokinesis in Eps15-EH29- and AP180-transfected cells. It is important to note that, in some experiments with mitotic Eps15-EH29- and AP180-transfected cells, we observed chromosome segregation failures in which all the genetic material segregated to one daughter cell. This was a rare phenotype (<2% of the cells) that we only observed in some repetitions of the mitotic experiments. Because AP180 can bind to clathrin and Eps15 to AP-2 (a clathrin-binding protein), this chromosome segregation failure phenotype may be due to a mislocalization of clathrin away from the mitotic spindle poles, as clathrin has recently been shown to have a role in maintaining the integrity of the mitotic spindle (41).

To confirm that each method of inhibiting clathrin-mediated endocytosis effectively blocked transferrin uptake, we monitored the inhibition of transferrin uptake (10-min incubation) in interphase cells co-expressing AP180, Eps15-EH29, or ARF6(Q67L). We found that each method resulted in equivalent inhibition of transferrin uptake as determined by confocal microscopy (supplemental Fig. 7). Taken together, our results support the notion that clathrin-mediated endocytosis is required for the successful completion of cytokinesis and point toward an essential role for endocytosis during the process of cytokinesis.

DISCUSSION

Cytokinesis relies upon the elegant regulation of both cytoskeletal and membrane elements. Although membrane fusion events have been shown to accompany the successful completion of cytokinesis, the involvement of new membrane internalization, or endocytosis, has not
FIGURE 4. ARF6(Q67L) inhibits receptor-mediated endocytosis during cytokinesis. HeLa cells were transfected with ARF6(Q67L)-pIRES-EGFP and then synchronized for mitotic analysis. Mitotic cells in serum-free medium were incubated with Texas Red-transferrin (A) or Texas Red-transferrin plus Draq5, a DNA dye, (B and C) for 7 min during cytokinesis. Thereafter, the cells were washed, fixed, and processed for immunofluorescence. Cells were fixed at 90, 105, or 120 min after mitotic entry, as indicated, and immunolabeled for α-tubulin (pseudocolored green in the merged image). Cells transfected with ARF6(Q67L)-pIRES-EGFP exhibit little to no transferrin internalization during cytokinesis. Scale bars, 15 μm. Each image represents a single confocal plane (A). Cells were fixed at 100 min after mitotic entry and analyzed by confocal microscopy. Confocal sections were acquired every 0.8 μm, and select sections are displayed (B and C). Internalized Texas Red-transferrin is shown in B, and a merged image of Draq5 and GFP is shown in C. In this field of view, a non-transfected cell and an ARF6(Q67L)-transfected cell are shown. ARF6(Q67L)-transfected cells display little to no internalized transferrin at any plane. Scale bars, 10 μm.
been thoroughly examined. In the past, it was thought that endocytosis and endosomal trafficking does not occur during mitosis but instead resumes during the G1 phase (17, 42–44). Previous work asserts that fluid phase endocytosis begins after cells exit cytokinesis, especially because endocytic marker internalization is not observed in early or late mitotic cells (17). In addition, other studies have shown that the mitotic phosphorylation of epsin and Eps15 by CDK1 prevents their efficient interaction with α-adaptin, providing one mechanism by which clathrin-dependent endocytosis is specifically inhibited during mitosis (45). Our current studies revealed that, although endocytosis ceases during early mitosis, it resumes during late mitotic stages and occurs throughout the process of cytokinesis. Our findings support recent reports demonstrating the requirement for endocytic proteins during cytokinesis and the localization of endocytic markers at the cleavage furrow in zebrafish eggs (18–20,46). Altogether, these results point toward an important role for endocytosis and endosomal trafficking during the process of cytokinesis.

In this study, we showed that, during late mitosis, endocytosis begins again in a distinct manner, first from the polar region of a dividing cell as cleavage furrow ingression commences and then from the equatorial region after furrow ingression is complete (Fig. 6). We propose that there are at least two different ways in which endocytosis and endosomal traffic may participate in the process of cytokinesis. First, we find that vesicles endocytosed from the polar region during cleavage furrow ingression are trafficked to the midbody region during late cytokinesis.

![Figure 5](image_url)

**FIGURE 5.** Inhibition of clathrin-mediated endocytosis induces cytokinesis defects. HeLa cells were transfected with Eps15-EH29-pEGFP (dominant negative Eps15) or FLAG-tagged AP180, synchronized for mitotic analysis, and fixed during cytokinesis. Mitotic cells in serum-free medium were incubated with Draq5, a DNA dye (A) or Draq5 plus FITC-transferrin (B) for 6 min before fixation. Thereafter, cells were washed, fixed, and immunolabeled for α-tubulin (red in A) or FLAG (red in B). Along with endocytic defects, cells transfected with Eps15-EH29-pEGFP or AP180 display defects during cytokinesis, including excessive blebbing at cleavage furrow and throughout dividing cell (A and B) as well as binucleated cell formation. Scale bars, 10 μm. Each image represents a single confocal plane. Cells transfected with Eps15-EH29-pEGFP or AP180 were scored for their cytokinesis phenotype (“normal,” “binucleated,” or “blebbed”) 115 min after mitotic entry (C) (see “Results” for further phenotypic description). Results were averaged from three independent experiments. Over 100 transfected cells were counted in each experiment. Standard error bars are included.

**FIGURE 6.** Model for endocytic traffic during cytokinesis. During the early stages of mitosis, no endocytosis of extracellular ligands is detected. During anaphase and early telophase, internalized ligand is observed in the polar regions of the dividing cell but not in the region of the cleavage furrow. Our results suggest that, as cells begin cleavage furrow ingression, endocytosis resumes first at the polar regions of the dividing cell. After cleavage furrow ingression, internalized ligand is found at the polar region and near the ingressed furrow. From our fixed and live cell studies, we know that vesicles endocytosed during cleavage furrow ingression are trafficked to the cleavage furrow during late cytokinesis and that endocytosis also occurs at the ingressed cleavage furrow. Endocytosed vesicles trafficked from the polar region to the ingressed cleavage furrow may help to complete the final stages of cytokinesis and to balance membrane addition and retrieval in the midbody region.
The traffic of endocytosed vesicles and their cargo to the cleavage furrow may represent a mechanism by which membrane or protein components needed for cytokinesis can be moved to the cleavage furrow. Second, we find that endocytosis occurs at the ingressed cleavage furrow, perhaps providing a means for terminating cytokinesis through the internalization of cytokinesis components that are no longer needed. In addition, endocytosis at the ingressed cleavage furrow may help to physically seal off daughter cell membranes, facilitating the final completion of cytokinesis. It is also likely that endocytosis at the midbody helps to balance membrane delivery and retrieval and thereby maintain proper plasma membrane surface area.

Previously we have shown that the ARF6 GTPase, which regulates endosomal traffic during cytokinesis and how ARF6 regulates endosomal traffic during cytokinesis and how its interaction with SMAP1, an ARF6-GAP that is essential for clathrin-dependent endocytosis, and its dominant negative Eps15 or AP180 also leads to pronounced cytokinesis defects. Taken together, our findings strongly suggest that clathrin-mediated endocytosis is a critical step in cytokinesis.

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