Cytokinesis in eukaryotes: a mechanistic comparison

Christine Field*, Rong Li* and Karen Oegema†

Cytokinesis is a crucial but poorly understood process of cell proliferation. Recently, molecular genetic analyses of fungal cytokinesis have led to an appreciation of contractile mechanisms in simple eukaryotes, and studies in animal and plant cells have led to new insights into the role of microtubules in the cleavage process. These findings suggest that fundamental mechanisms of cytokinesis may be highly conserved among eukaryotic organisms.

Addresses
*Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, MA 02115, USA
†European Molecular Biology Laboratory, Postfach 10 22 09, Meyerhofstrasse 1, D-69012 Heidelberg, Germany

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Abbreviations

CDK	cyclin-dependent kinase
FH	formin homology
FMA	furrow microtubule array
MT	microtubule
PPB	preprophase band
SBP	spindle pole body

Introduction

Cytokinesis is the process that partitions the cell surface and cytoplasm of one cell to form two cells. Here we compare and contrast the cytokinetic mechanisms in different eukaryotes. Our discussion is organized around three topics: positioning of the cleavage plane; mechanisms of cytokinesis; and temporal coordination of cytokinesis with chromosome segregation. We compare cytokinesis in animal cells, higher plants, invertebrate and amphibian embryos, amoebae and yeasts emphasizing common mechanistic features. For other reviews see [1–5].

Mechanisms for positioning the cleavage plane

To ensure that each daughter cell has a nucleus, the cleavage plane is positioned to bisect the axis of chromosomal segregation. In certain developmentally important cell divisions, the position of the cleavage plane also determines the size and developmental fate of the daughter cells. The fundamental requirement that the cleavage plane bisects the axis of chromosome segregation is achieved in one of two ways: either the cleavage plane is specified prior to mitosis by a mechanism independent of spindle position and, during mitosis, the position of the spindle or cleavage structure is adjusted to correspond to pre-selected division site; or the division plane is specified by the location of the spindle.

The cleavage plane is specified prior to mitosis independently of spindle location

Central to this mechanism is the existence of a landmark established prior to mitosis that dictates the position of the cleavage plane. A much studied organism that employs such a mechanism is the budding yeast *Saccharomyces cerevisiae*, in which the division site (the bud neck) is selected early in the cell cycle prior to spindle assembly (Figure 1). During mitosis, the spindle is positioned in the bud neck by a cytoplasmic dynein-dependent mechanism involving a dynamic interaction of astral microtubules (MTs) with the bud cortex [6–10•]. The position of the bud site is selected according to the site of cell division in the previous cell cycle and is controlled by a small GTPase pathway as well as a number of 'landmark' proteins associated with the previous cell division site (reviewed in [11,12]).

In higher plants, the location of the division plane is also established prior to mitosis but, in this case, it is a specialized cytokinesis assembly — the phragmoplast (see Figure 3) — that conforms to the landmark rather than the metaphase spindle. The site where the new cell plate will fuse with the cell wall is marked by the preprophase band (PPB) — a transient cortical microtubule array that assembles and disassembles prior to formation of the spindle (reviewed in [13,14]; see also Figure 1). Centrifugation studies that shifted the position of the nucleus at different cell cycle stages indicate that the position of the PPB is dictated by the location of the predivision (G_2) nucleus [15]. The PPB is thought to leave a landmark in the cortex that specifies the cleavage plane by inducing rotation and/or translocation of the phragmoplast and associated nuclei during plate formation (reviewed in [3,13]). It will be interesting to see whether the mechanism that reorients the phragmoblast is related to the mechanisms that position the spindle during S/G_2 in budding yeast and during prophase of asymmetric division in nematode eggs (see below and reviewed in [16]), both of which involve capture of MT plus-ends by special cortical sites.

It will also be of interest to determine the molecular mechanisms underlying the function of the PPB. Clues should come from two *Arabidopsis* mutants that fail to make preprophase bands [17,18]. Spindles and phragmoplasts are normal in these mutants, and cell division occurs, but the phragmoplasts do not rotate to the special orientations normally observed during (but apparently not required for) tissue morphogenesis.

In *Schizosaccharomyces pombe*, a medial ring containing actin, myosin II, and other components (Table 1) assembles in the center of the cell early in mitosis (reviewed in [5]; see also

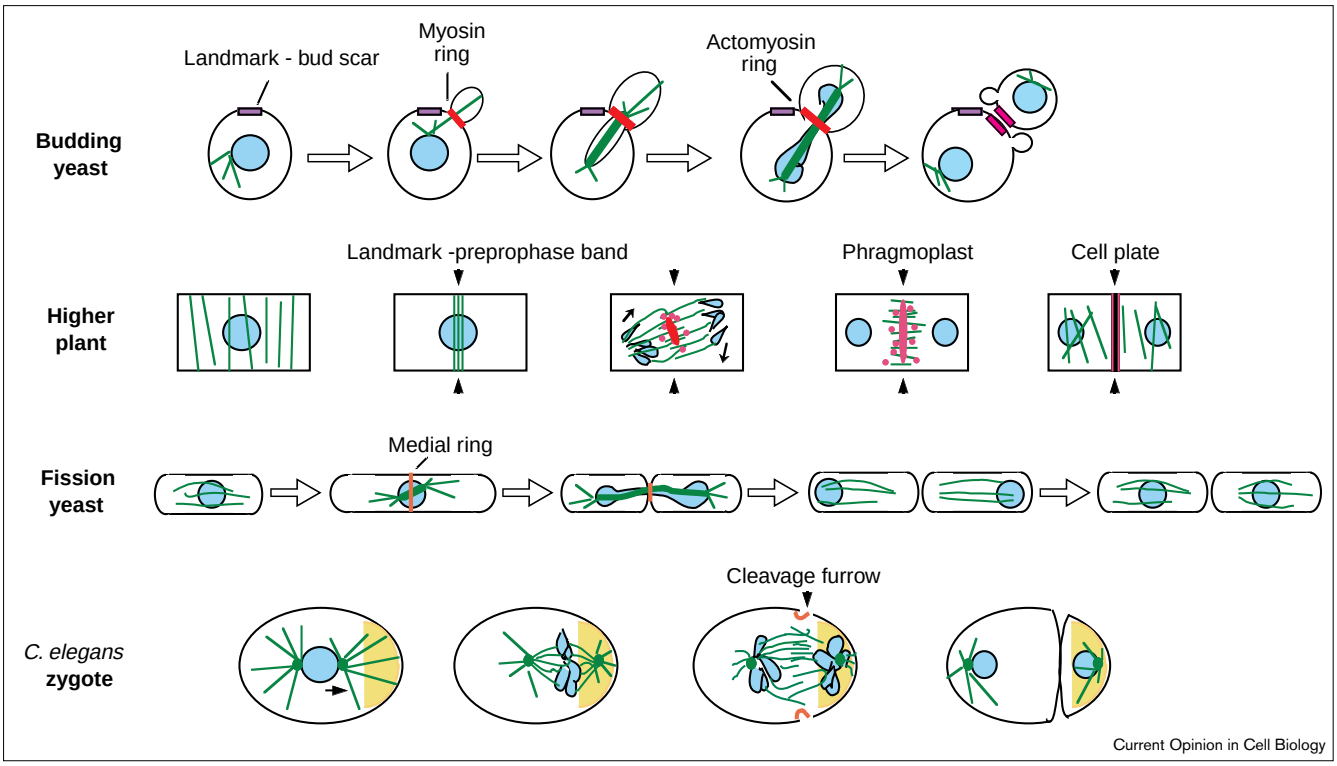
Table 1

Conserved protein families involved in cytokinesis.

Protein family	Protein name	Organism	Localization	Phenotypes of mutant/functional interference
Septins*	Cdc3, 10, 11 and 12	*S. cerevisiae*	Bud neck and base of schmoo tip.	Defects in cytokinesis, bud morphogenesis, and chitin deposition [152].
	Pnut, Sep1, and Sep2	*D. melanogaster*	Cleavage furrow and midbody [53].	Defects in cytokinesis in pnut mutants [53].
	Nedd5, H5, and Diff 6	Murine	Cleavage furrow and midbody [54].	Failure of cytokinesis after injection of Nedd5 antibody [54].
	Spn1–6	*S. pombe*	Septation site (Spn1) [52].	Delay in septum formation or cell separation in the spn1 mutant [52].
Myosin II (non muscle)	Cytoplasmic myosin II	*Dictyostylium*	Actomyosin ring, and cell cortex [49,153].	Cytokinesis failure in cells grown in suspension [154,155].
	Cytoplasmic myosin II	Echinodem embryos	Actomyosin ring [31].	Antibody injection results in cytokinesis failure [156].
	Zipper	*D. melanogaster*	Actomyosin ring [157].	Mutations in regulatory light chain (spaghetti-squash) result in cytokinesis failure [158].
	Myo2	*S. pombe*	Actomyosin ring [38].	Deletion is lethal. Overexpression results in failure to form functional actomyosin ring [38,159].
	Myo3/MYP2	*S. pombe*	Actomyosin ring [161].	Defects in cytokinesis under certain growth conditions [160,161].
	Myo1	*S. cerevisiae*	Actomyosin ring [34,35].	Cytokinesis and cell separation defect [35,76].
Formin	Diaphanous	*D. melanogaster*	Cleavage furrow†.	Null allele is lethal; loss-of-function alleles result in cytokinesis defects in the germline and neuroblasts [61].
	Cappuccino	*D. melanogaster*	Unknown	Defects in nurse-cell cytokinesis and oocyte polarity [162,163].
	Cdc12	*S. pombe*	Actomyosin ring [60].	Defects in actomyosin ring formation and cytokinesis [60].
	Bni1	*S. cerevisiae*	Bud neck and tip; schmoo tip‡ [162,175].	Defects in bipolar bud site selection, cell polarity; synthetic lethality with bnr1 or Cyk2 null mutations [165,176,166].
	Bnr1	*S. cerevisiae*	Bud neck [166].	Synthetic lethality with bnr1 null mutation [166].
	Sepa	*A. nidulans*	Unknown.	Defects in actin ring formation, septum formation, and cell polarity maitenance [62].
IQGAP	Cyk1(Iqg1)	*S. cerevisiae*	Actomyosin ring [34,65].	Defects in actomyosin ring formation, contraction and cytokinesis [34,65].
	Rng2	*S. pombe*	Actomyosin ring [67].	Defects in actomyosin ring formation and cytokinesis [67].
	GAPA	*D. discoideum*	Unknown	Defects in the completion of cytokinesis and the severing of the midbody [70].
	DGAP1	*D. discoideum*	Unknown.	Defects in cytokinesis of cells grown in suspension, cell motility, and development [68,69].
Cdc15	Cdc15	*S. pombe*	Actomyosin ring [167].	Defects in actin ring formation, localization of cortical actin patches to the septum and cytokinesis [167,168].
	Imp2	*S. pombe*	Actomyosin ring [169].	Defects in actin ring disassembly and septum formation [169].
	PSTPIP	Murine	Cleavage furrow and cell cortex [170].	Cytokinesis block when overexpressed in *S. pombe* [170].
	Cyk2(Hof1)	*S. cerevisiae*	Septins and actomyosin ring [81,166].	Defect in actomyosin ring contraction, septin distribution and cytokinesis [81,166].
Kinesin	CHO1/MKLP-1	Mammals	Interzone [171].	Unknown§.
	ZEN-4/MKLP-1	*C. elegans*	Interzone [89,90].	Defects in interzonal microtubules; regression of the cleavage furrow [89,90].
	PAV-MKLP/ (MKLP-1)	*D. melanogaster*	Interzone [91].	Defects in interzonal microtubules and cytokinesis [91].
	KLP-3A	*D. melanogaster* (male meiosis)	Interzone [93].	Defects in interzonal microtubules and cytokinesis [93].
	TKRP125	By-2 Cells (tobacco)	Preprophase band, spindle MT, phragmoplast MT [112].	Antibody inhibits translocation of phragmoplast MTs in membrane-permeabilized cells [112].
	KCBP	*Arabidopsis*	Preprophase band, spindle and phragmoplast [172].	Unknown.
Polo kinase	Polo	*D. melanogaster*	Centrosome, centromere, and interzone [135].	Defects in centrosome organization and spindle formation [135].
	Plk1	Mammals	Centrosome and interzone [173].	Antibody injection causes defects in centrosome maturation and spindle formation; overexpression causes mitotic delay and cytokinesis defect [174,175].
	Plo1	*S. pombe*	Medial ring, spindle and spindle pole body [142].	Defects in spindle formation, actin ring assembly and septum formation; induction of ectopic septa when overexpressed [136].
	Cdc5	*S. cerevisiae*	Nucleus and spindle pole bodies [140].	Cell cycle arrest in anaphase [149].

*For each organism there are more septins than those listed. Some are not involved in cytokinesis. †K Oegema, unpublished data. ‡J Pringle, personal communication. §*In vitro* experiements showed that CHO1 can form cross bridges between antiparallel microtubules and implement microtubule sliding [88].

Figure 1



Comparison of the mechanisms of positioning of the cell division plane in haploid budding yeast, fission yeast and higher plant cells, and in the first division of *Caenorhabditis elegans* zygotes as an example for the spindle-based positioning in animal cells. In budding yeast and higher plant cells, the division site is predetermined by a landmark early in the cell cycle (the bud scar, shown as a purple rectangle, or the preprophase band, shown as vertical green bars); in fission yeast, the site of cell division correlates with the position of the premitotic nucleus; in animal cells, the cleavage furrow is placed on the basis of the position of the mitotic spindle. Red bars indicate the plane of cell division, pink dots indicate membrane vesicles, green lines indicate microtubules.

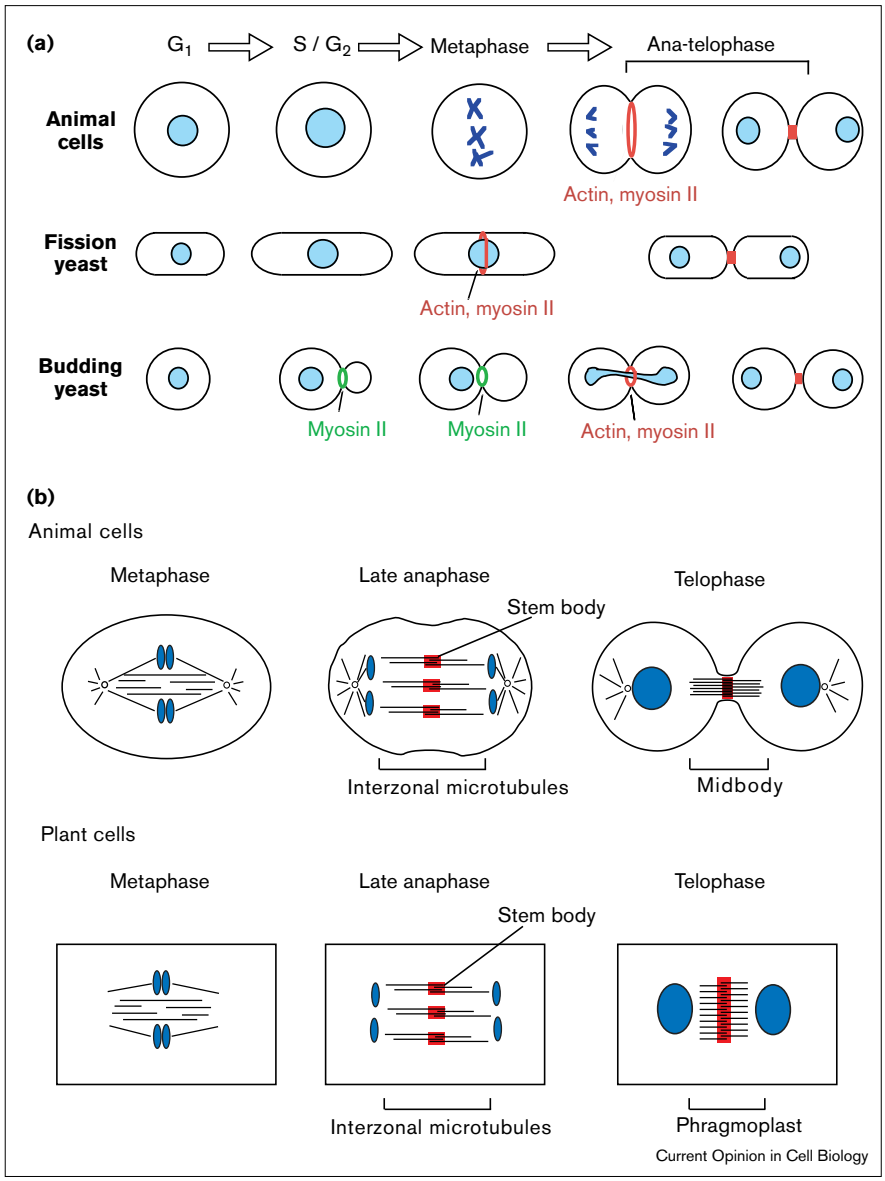
Figure 1). The position of this ring, like the position of the PPB in plants, correlates with that of the nucleus and anticipates the site of septum formation. Medial ring positioning is likely to be independent of the spindle, since it is not affected by a β tubulin mutation that blocks spindle formation [19]. The idea that the nucleus provides the positional stimulus for ring assembly is currently favored [2]. Consistent with this model, the Mid1 protein, which is required for the proper positioning of the septum, is concentrated in the nucleus during interphase and relocates to the site of medial ring formation at mitosis [20]. Several other genes are also required for ring positioning [21,22], including a recently identified protein kinase, Pom1, which has dual roles in polarized cell growth and cytokinesis [22]. The mechanism that positions the nucleus in the center of the cell is not clear. Evidence has suggested the involvement of the spindle pole body, which leads the nucleus during nuclear positioning in a MT-mediated process [23•].

The division plane is specified by the mitotic spindle

This is the classic mechanism for positioning the cleavage furrow in animal cells. There is no landmark that determines the division site prior to mitosis; instead, the spindle dictates where cleavage will occur [24]. In the absence of asymmetric cues, the spindle is 'centered' in the cell. Two plausible centering mechanisms have been postulated: the pulling of astral MTs towards the cortex by a force dependent on MT length [25] and pushing of microtubules away from the cortex by polymerization ([26]; recently reviewed in [27]). Either mechanism would result in centering, and both may operate *in vivo*.

In certain developmentally important divisions the spindle is rotated or positioned asymmetrically prior to cytokinesis in order to generate daughter cells with different fates (reviewed in [28]; see also Figure 1). Positioning of the spindle or nucleus is often achieved by interaction of centrosomal microtubules with specific regions of the cell cortex (for review see [27]). Some examples where this type of mechanism operates include the asymmetric positioning of meiotic spindles in marine invertebrate eggs prior to polar body formation [29], the positioning of nuclei during the development of ascidian embryos [30] and the nuclear rotation during the development of *Caenorhabiditis elegans* (reviewed in [16]). A second mechanism may depend on generating two asters

Figure 2



(a) Comparison of the timing of actomyosin ring assembly in animal cells and yeasts. **(b)** The reorganization of interzonal MTs on animal and plant cells (see text for details).

of different sizes by local regulation of MT polymerization dynamics. In this case, centering forces (discussed above) would result in asymmetric spindle positioning. One example where such a mechanism might operate is during the fourth cleavage of sea urchin embryos [31]. A similar situation can also be brought about experimentally in the normally symmetrical first division by injecting taxol near one pole [32•]. During cell division in animal cells, it is likely that spindles are positioned by the concerted action of the centering forces acting on asymmetric MT arrays and the interactions between spindle MTs and specific cortical sites.

Mechanisms of cytokinesis

In response to cell cycle cues, the cytokinesis machinery is assembled at the division site. Our understanding of the nature of this machinery has benefited from recent progress in two areas. First is an appreciation of contractile mechanisms in fungal cells. Despite the presence of a rigid cell wall, cytokinesis in *Aspergillus* [33•] and both budding [34••,35••] and fission yeasts [36,37,38•] occurs by a centripetal mechanism resembling that of animal cells. In these fungi, contraction of an actomyosin-based ring is at least partially responsible for furrow ingression. This contraction is coupled to mechanisms for the synthesis of a cell wall septum. Second is the realization that the role of MTs in cleavage may extend beyond their well-known signaling role in the positioning of the division plane in animal cells. Recent data has indicated additional requirements for MTs during furrowing and perhaps during the completion of membrane separation of the daughter cells. Specialized MT-based structures may implement these activities. In

this section we review the mechanisms of cleavage furrow assembly with a focus on conserved protein families. We then examine the generation of MT-based structures and their roles during the division process.

Assembly of the actomyosin-based contractile ring

Studies in mammalian tissue-culture cells have shown that the recruitment and organization of actin and myosin II to the cleavage furrow is dynamic throughout cell division and that the organization of both polymers is likely to be more complicated than predicted by a simple purse string model (reviewed in [39]). The mechanism that leads to the accumulation of actin and myosin filaments in the cleavage furrow is still uncertain. A role for cortical flow (directed transport in the plane of the cortex) has been argued on the basis of imaging data [40–44]. One proposed mechanism for this transport is a contraction of the actin cortex powered by the myosin II ATPase [45]. Studies in myosin II null *Dictyostelium* cells showing normal recruitment to the cleavage furrow of myosin II truncations lacking the ATPase domain or mutants lacking ATPase activity, however, argue against this mechanism [46–48]. Analysis in *Dictyostelium* of mutations of the phosphorylation sites of the myosin II heavy chain suggests that the ability to form bipolar filaments is essential for the recruitment of myosin II to the cleavage furrow [49]. Phosphorylation of the activating site of the myosin regulatory light chain also occurs coincident with the onset of myosin transport to the furrow.

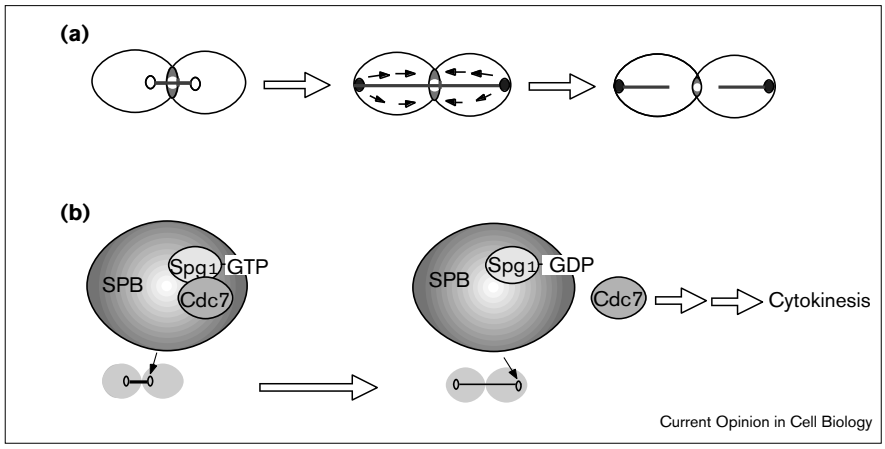
The assembly of the contractile ring in yeast shares both similarities and differences with the process in animal cells (Figure 2a). In animal cells, the accumulation of actin and myosin II to the region of furrow formation occurs simultaneously during late anaphase, concurrent with furrow constriction [51]. In contrast, in the fission yeast, *S. pombe*, the actomyosin ring assembles during early M phase, but cytokinesis does not occur until late anaphase (reviewed in [5]). In the budding yeast, *S. cerevisiae*, the actomyosin ring assembles in a sequential process that occurs during two separate cell cycle stages [34••,35••]: myosin II first assembles into a ring at the site of budding at the $G_1 \rightarrow S$ transition; F-actin is then recruited to the ring during late anaphase just prior to contraction.

In addition to actin and myosin, cytokinesis requires other proteins, many of which are evolutionarily conserved (see Table 1). Assembly of the myosin II ring in *S. cerevisiae* depends on the septins [34••,35••] — a family of proteins required for cytokinesis in budding yeast [52], *Drosophila* [53] and mammalian tissue culture cells [54•]. The septins localize to the bud neck in *S. cerevisiae* (reviewed in [52]) and to cleavage furrows in *Drosophila* [53] and mammalian cells [54•]. In *S. cerevisiae*, the myosin II ring initially appears as a narrow band within the broader septin ring and undergoes a contraction-like size change, that is a reduction in diameter, during cytokinesis [34••,35••]. The role of the septins in cytokinesis remains unclear. Mutations in budding yeast septin genes result in the loss of other proteins (in addition to myosin II) from the bud neck, suggesting that septins might have a scaffold-like function to localize other components (reviewed in [52]). Septins can also bind and hydrolyze GTP [55], and so they may also have some signaling role. Purified septin complexes can form filaments *in vitro* [55–57], but it appears that the filament forming activity is not essential for all aspects of septin function [57].

Several conserved protein families have recently been implicated in regulating the recruitment of actin to the contractile ring (see Table 1). One such family is the formin-homology (FH) proteins (reviewed in [58,59]). In fission yeast, the FH protein Cdc12 is a component of the actomyosin ring required for the recruitment of F-actin to the ring [19]. The fact that *in vitro* Cdc12 binds profilin —a protein that has been implicated in actin polymerization —has contributed to the idea that a Cdc12-containing structure may nucleate the formation of the actin ring [60••]. A requirement for an FH protein in cytokinesis has been shown in *Drosophila* [61] and in *Aspergillus* [62]. SepA is required for actin ring assembly in *Aspergillus*. Recently, however, it was reported that a mutation in the *C. elegans* FH protein, Cyk-1(Iqg1), does not affect the accumulation of actin and myosin II to the cleavage furrow or the initiation of furrowing but prevents the deepening of the furrow [63•]. The localization of Cyk1(Iqg1) also suggests it is involved in a late stage of cleavage furrow progression or maintenance. These results indicate that FH proteins may function at multiple stages in cytokinesis.

The IQGAP proteins are another conserved family involved in cytokinesis. IQGAPs contain domains that interact directly with F-actin, calmodulin, and small GTPases, making them candidates for proteins that link signaling pathways to actin remodeling (reviewed in [64]). In budding yeast, the recruitment of actin filaments to the contractile ring requires Cyk1(Iqg1). A direct role for Cyk1(Iqg1) in actin ring assembly is suggested by its localization to the myosin ring slightly before and independently of actin during anaphase [34••,65], and by the inability of the actin ring to form when a portion of Cyk1(lqg1) containing the F-actin binding domain was deleted [66]. The fission yeast IQGAP-like protein, Rng2, is also an actomyosin ring component required for cytokinesis [67•]. In *rng2* mutants, actin filaments accumulate in the medial region of the cell but fail to organize into the tight ring seen in wild-type cells. *Dictyostelium* has two IQGAP-related proteins, DGAP1 and GAPA, both involved in cytokinesis [68,69,70•]. GAPA-null cells grown in suspension can initiate a cleavage furrow but frequently fail to complete cleavage, suggesting that GAPA is unlikely to be required for the establishment of the contractile ring [70•]. This functional difference between *Dictyostelium* and yeast IQGAP-like proteins could be due to the lack of the F-actin binding domain in DGAP1 and GAPA. In mammalian cells, IQGAP1 was found to concentrate in actin-rich areas such as the membrane ruffles [71] and sites of cell–cell contact [72], but its involvement in cytokinesis has yet to be determined.

Figure 3



Spindle pole body signaling of cytokinesis. **(a)** A change in spindle pole body (SPB) biochemistry occurs at the end of spindle elongation, releasing a signal (arrows) that activates actomyosin ring maturation (F-actin recruitment) or contraction. **(b)** A model for the role of Spg1 and Cdc7 in coordinating cytokinesis with spindle elongation. GTP hydrolysis by Spg1 occurs at the end of anaphase, releasing Cdc7 from one of the spindle poles and providing a positive signal for cytokinesis.

Existence of myosin-II-independent mechanisms for cleavage furrow formation

Although *Dictyostelium* cells lacking myosin II fail to divide in suspension, relatively normal-looking cytokinesis can occur when the cells grow attached to a substrate [73•,74,75]. This process has been termed attachment-assisted mitotic cleavage or cytokinesis B. Similarly, budding yeast cells lacking myosin II can also carry out cytokinesis with varied efficiency depending on the strain background [35••,76]. These results indicate the existence of an alternative, possibly redundant, cleavage mechanism. The nature of this mechanism is unknown. For *Dictyostelium* it might involve other myosins, addition of new membrane, or possibly a weakening of the cortex in the region of furrowing. The last could be accomplished by changes in actin cross-linking, or locally increased severing or depolymerization of actin filaments. Candidates for proteins involved in cytokinesis B in *Dictyostelium* include the actin-binding proteins cortexillins I and II [77]. Cortexillins bundle and cross-link actin filaments *in vitro* and are enriched in the cell cortex. Elimination of cortexillins results in defects in cell shape and cytokinesis.

The generation of new cell surface during cytokinesis

In higher plants, cytokinesis does not appear to involve a contractile apparatus but is accomplished solely by the *de novo* formation of a membrane/cell-wall separation between the daughters. Even in systems where the contractile ring-dependent furrowing mechanism operates, however, there are reasons to believe that the completion of cytokinesis requires the generation of new cell surface membrane. First, if the volume of a cell stays constant, new surface area must be added when it divides into two cells of a similar shape. Second, furrow ingression alone only narrows the passage connecting the two daughter cells but is not sufficient to create two topologically distinct cell surfaces. The final closure of the passage must therefore be accomplished either by homotypic fusion of the plasma membrane at the leading edge of the furrow or by plugging the hole with internal membranes, generated perhaps by local delivery and fusion of vesicles.

The extent to which new membrane generation contributes to cell division is likely to vary between systems. In the first cleavages of *Xenopus* embryos — possibly because of their large size — the majority of the new cell surface is generated during furrow ingression by vesicle fusion with the plasma membrane behind the leading edge of the furrow [78,79]. A similar coupling of new surface generation and actomyosin ring contraction may occur in fission yeast (reviewed in [5]). In budding yeast, the generation of septum membrane and cell wall may occur after the completion of furrowing, because cortical actin patches, structures specialized in cell surface growth (reviewed in [80]), accumulate at the division site after actomyosin ring contraction [81]. The exocytic machinery also accumulates at the bud neck during cytokinesis [82], but the exact timing of this event relative to contractile-ring activity has not been determined. The mechanism by which the exocytic machinery is targeted to the site of cell division in coordination with furrow progression is not understood in any system. As discussed in the next section, MTs may be involved in membrane deposition during cell division.

Old and new roles for microtubules in cytokinesis

A mechanical role for MTs during cytokinesis in plants is well established. In plants, cytokinesis is achieved by the centrifugal formation of a cell plate that divides the cell into two (Figure 1). Vesicle fusion to assemble the cell plate is directed by an ordered dynamic array of interzonal MTs and actin filaments called the phragmoplast (reviewed in [3]). MTs have also long been known to play a signaling role in cytokinesis in animal cells by positioning the furrow. In recent years evidence has accumulated that MTs also play a mechanical role in animal cells. Here we critically compare assembly and function of MT arrays specialized in cytokinesis in animals (interzonal arrays) and plants (phragmoplast).

Assembly of cytokinesis-associated microtubule arrays

Both animal and higher plant cells reorganize their interzonal MTs — those in the interzone after chromosome separation — between late anaphase and telophase, to generate similar dynamic arrays specialized to function during cytokinesis (Figure 2b). In animal cells, the first step in this reorganization is the formation of bundles of 10–30 antiparallel MTs [83,84]. The central regions of these bundles, where MTs of opposite polarities overlap, are associated with an electron-dense matrix [83,85,86]. In the older literature, these regions of MT overlap are referred as stem bodies. In the later stages of cytokinesis, the interzonal MT bundles are compacted to form the midbody with the stem body matrix concentrated at its midline [83,85] (Figure 2b).

A number of proteins are associated with stem bodies, including: INCENP [87]; the kinesins CHO-1/MKLP-1 [88–91], CENP-E [92], KLP-3A [93], members of the Polo [94,95] and aurora kinase families [90,96], and an as yet uncloned antigen called TD-60 [97]. Many of these proteins have been implicated in cytokinesis [89–91,93,95,96,98]. Three of the stem body components, TD60, INCENP, and AIM-1, have also been localized to an equatorial disc that extends outwards from the interzonal MT bundles to the cortex [99]. A role for this somewhat more controversial structure, the 'telophase disc' [97,100], has been proposed in the communication between the spindle and the cortex in positioning the cleavage furrow [100]. It is not clear, however, to what extent the telophase disc is a structural entity independent of the aligned stem bodies.

The plant phragmoplast, like the interzonal microtubule array in animal cells, arises at least in part from the microtubules in the interzonal region of the anaphase spindle [101,102] (Figure 2b). Ultrastructural analysis of the phragmoplast reveals that it has a similar organization to animal midbodies. Each half of the phragmoplast/midbody is composed of MTs of the same polarity with their plus ends embedded in a phase-dense matrix associated with the region of MT overlap [101,103–105].

The formation of interzonal MTs and their dynamics is not well understood. γ-tubulin is associated with the MTs in both animal [106,107] and plant structures [108]. Disruption of γ-tubulin during anaphase by injection of either antibodies or antisense RNA leads to a failure in midbody formation and consequently a failure in cytokinesis in animal cells [106,107], indicating that the nucleation of new MTs may be important for the formation or maintenance of the midbody. Antiparallel sliding — generating a 'flux' of the MT lattice away from the midline — may occur in the interzonal arrays of both animal and plants cells [109–111]. In plant cells this translocation might be mediated by a BimC family kinesin [112]. In animal cells, the CHO1(MKLP1) family [88] (Table 1) are candidates for this activity and elimination of family members results in defects in interzonal MT arrays and cytokinesis [89–91].

Functions for cytokinesis associated microtubule arrays

Role in the specification of the cleavage plane in animal cells

Classic experiments in marine invertebrates demonstrated that two juxtaposed asters lacking intervening chromosomes are sufficient to induce furrow formation. Astral MTs were proposed to be the source of the signal [24,113,114]. More recent experiments in mammalian tissue culture cells have led to the idea that the interzonal MT array signals the cortex to position the furrow (reviewed in [4,115]). In this model, two juxtaposed asters might signal to the cortex indirectly via the formation of antiparallel MT bundles, analogous to interzonal MT bundles. Consistent with this idea, a recent study by Savoian and co-workers [116] demonstrates that formation of ectopic furrows in mammalian cells correlates with the formation of interzonal MT bundles and the accumulation of the stem body components, CHO1 and INCENP. It is now important to re-examine the classic Rappaport experiment in sea urchins using molecular markers to determine whether stem body components also assembled on overlapping MTs between asters in this system.

Role during furrowing

MTs have been thought to be dispensable during furrow ingression after establishment of the cleavage plane. This view came from elegant experiments by Hiramoto showing that neither the removal nor the displacement of the mitotic apparatus affected furrow ingression (reviewed in [24]). One of the most significant developments in cytokinesis research in the last few years has been the recognition of a continuing requirement for interzonal MTs during furrow ingression in a number of animal systems. In mammalian cells, the position of MT bundles near the cortex correlates with cortical ingression and the accumulation of F-actin and myosin II [117,118••]. In *Drosophila* [91,93,119•] and *C. elegans* [89,90•], mutations that specifically remove or disrupt the interzonal microtubule array result in the failure of cytokinesis.

What might be the role of interzonal MTs during furrow ingression in animal cells? One possibility, suggested by the similarity between the organization of microtubules in stem bodies and in those in the plant phragmoplast, is that microtubules are required for vesicle accumulation and membrane deposition during furrowing. This possibility is supported by the identification of a microtubule structure called the FMA (furrow microtubule array) in *Xenopus* eggs.

Depolymerization of FMA MTs prevents the addition of new plasma membrane and causes the cleavage furrow to recede [120••]. Perhaps in smaller cells, interzonal MT bundles play a similar role either during the furrowing process or during completion. Analysis of the role of microtubules in cytokinesis both as signaling structures and tracks for vesicle transport is likely to be a major research topic in the next few years.

Coordination of cytokinesis with the cell cycle

Successful cell division requires the temporal coordination of cell cycle events. In particular, cytokinesis must not

occur before spindle assembly and chromosome segregation. In this section, we discuss two specific mechanisms for achieving this coordination, one involving cell cycle kinases, and the other relying on a signaling function of the spindle pole body.

Regulation of cytokinesis by cell cycle kinases

Cell cycle kinases, such as cyclin-dependent kinases (CDKs) and Polo, are known to play major regulatory roles in cell cycle progression. In all systems studied, including *Xenopus* eggs [121,122], mammalian tissue culture cells [123], *Drosophila* [124,125], *S. cerevisiae* [126] and *S. pombe* [127], the initiation of cytokinesis correlates with and normally requires the inactivation of the kinase activity of CDK1. When the behavior of cells expressing a nondegradable form of cyclin B (and thus preventing CDK1 inactivation) was observed in real time, the chromosomes disjoined normally and anaphase-like movement of the chromosomes occurred, but the interzonal microtubule bundles that normally form in the midzone of the anaphase spindle were absent and neither actin nor myosin II were recruited to the cell equator [123]. In *Xenopus* eggs, CDK1 inactivation is also coincident with a cortical contraction wave that may represent activation of the cortex required for furrowing [128,129]. CDK1 has been shown to affect microtubule dynamics [130–132] and the phosphorylation state of the regulatory light chain of myosin II [133,134] *in vitro*, but the *in vivo* relevance of these interactions in cytokinesis has not been demonstrated directly.

Another cell cycle kinase implicated in cytokinesis is Polo, first identified in *Drosophila* [135]. Overexpression of a Polo-like kinase (Plo1) in *S. pombe* can induce the formation of ectopic septa even in interphase [136] which has lead to the idea that Polo-like kinases are master regulators of cytokinesis. Recently, Polo-like kinases have been implicated in the activation of CDK1 during entry to mitosis [137] and in activation of the anaphase promoting complex and CDK1 inactivation during the exit from mitosis [138,140,141]. These results raise the possibility that the main role of Polo-like kinases in the initiation of cytokinesis is to promote CDK1 inactivation; however, other new data still support a direct role for Polo-like kinases during cytokinesis. A recent study in *S. pombe* showed that Plo1 interacts physically with Mid1, a contractile ring component required for the organization and positioning of the ring [142•]. Plo1 is required for the translocation of Mid1 from the nucleus to the contractile ring and, and like Mid1, localizes to the ring during its formation.

In human [94] and *Drosophila* [143] cells, Polo-like kinases localize to the interzonal microtubule bundles in the telophase disc. In addition, Plk (mammalian Polo) co-immunoprecipitates and phosphorylates CHO1/MPLK1, a stem body component [144]. A similar interaction has been demonstrated for the *Drosophila* Polo and the CHO1 homologue PAV-KLP [91]. In support of the idea that Polo may function directly in the formation of the stem bodies, characterization of alleles of *Drosophila* Polo during spermatogenesis detected a failure to form correct interzonal microtubule structures [95]. In budding yeast, the Polo-like kinase, Cdc5, localizes to the nucleus and spindle pole bodies [140]. Interestingly, a high-level expression of mammalian Plk can complement a *cdc5* mutation and the expressed Plk localizes to the spindle pole bodies and to the septin rings in the bud neck [145]. This result suggests that there may be a structural similarity between the *S. cerevisiae* bud neck and the stem bodies found in plant and animal cells.

A potential role for the spindle pole bodies in the temporal regulation of cytokinesis

Although chromosome segregation and cytokinesis both occur after the anaphase-to- metaphase transition, the appearance of the cleavage furrow always coincides with the completion of anaphase B spindle movement [51]. Recent studies in fission yeast have raised the possibility that spindle pole bodies (SPB) might play a role in the coordination of anaphase with the initiation of cytokinesis (Figure 3a). Spg1 and Cdc7, two proteins required for cytokinesis but not chromosome segregation [146,147•], both localize to the SPB [148••]. Perhaps these proteins function at the SPB to monitor the progression of anaphase and signal the initiation of cytokinesis. Supporting a signaling function, Spg1 is a small GTP-binding protein belonging to the Ras superfamily and Cdc7 is a novel protein kinase.

Interestingly, an interaction between Cdc7 and the GTP-bound form of Spg1 is required for the localization of Cdc7 to the SPB [148]. In cells where spindle elongation has occurred, GTP hydrolysis by Spg1 at one of the SPBs correlates with a local loss of Cdc7. Figure 3b illustrates a model in which GTP hydrolysis by Spg1 triggers the release of a positive signal for cytokinesis. Spg1 GTPase activity could be stimulated by an interaction of the polar cortex with the SPBs of the elongated spindle, or possibly by a change in the force applied to the SPBs at the end of anaphase movement. In *S. cerevisiae*, mutations in Tem1 and Cdc15, homologs of Spg1 and Cdc7, respectively, result in cell cycle arrest in anaphase with an elongated spindle and a high level of mitotic kinase activity [149–151], making it unclear whether these proteins are directly required for cytokinesis. Although direct homologs of Spg1/Tem1 and Cdc7/Cdc15 have not yet been identified in animal cells, a role for spindle pole proteins in regulating cytokinesis in yeast is reminiscent of Rappaport's conclusions from the micromanipulation experiments [24], and this will be a fascinating area to watch for future developments.

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