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Cytokinesis in Eukaryotes

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INTRODUCTION

Cytokinesis is the final event of the cell cycle and is the process that divides one cell into two daughter cells. Cytokinesis was perhaps the first major cell cycle event observed directly. The use of ingenious micromanipulation experiments in echinoderm embryos led to many early insights into the mechanisms of cytokinesis (211). Unlike other cell cycle events, cytokinesis has been particularly resistant to in vitro biochemical approaches, making progress difficult. However, in recent years, the use of genetically tractable model organisms has been enormously powerful in dissecting out the different steps and molecules involved in cytokinesis.

In general, the goal of cytokinesis is common in all organisms: to physically separate a mother cell into two daughter cells. How different organisms conduct cytokinesis varies, but the major events are universal (Fig. 1). In animal cells, the division site is first chosen, generally at the cell equator, and subsequently the cleavage furrow is assembled at the division site (Fig. 1D). The furrow contains actin, myosin, and other proteins that are organized into a contractile ring called the actomyosin ring. The ring then ingresses or contracts, generating a membrane barrier between the cytoplasmic contents of each daughter cell. The ingressing furrow constricts components of the spindle midzone into a focused structure called the midbody. In the final cytokinetic event, called abscission, the furrow "seals," generating two completely separate cells. The overall approach to division is well conserved between the fission yeast *Schizosaccharomyces pombe* and animals. Fission yeast also positions an actomyosin ring at the cell equator (Fig. 1C). However, unlike animal cells, *S. pombe* cells synthesize a division septum behind the ring as it constricts, generating new

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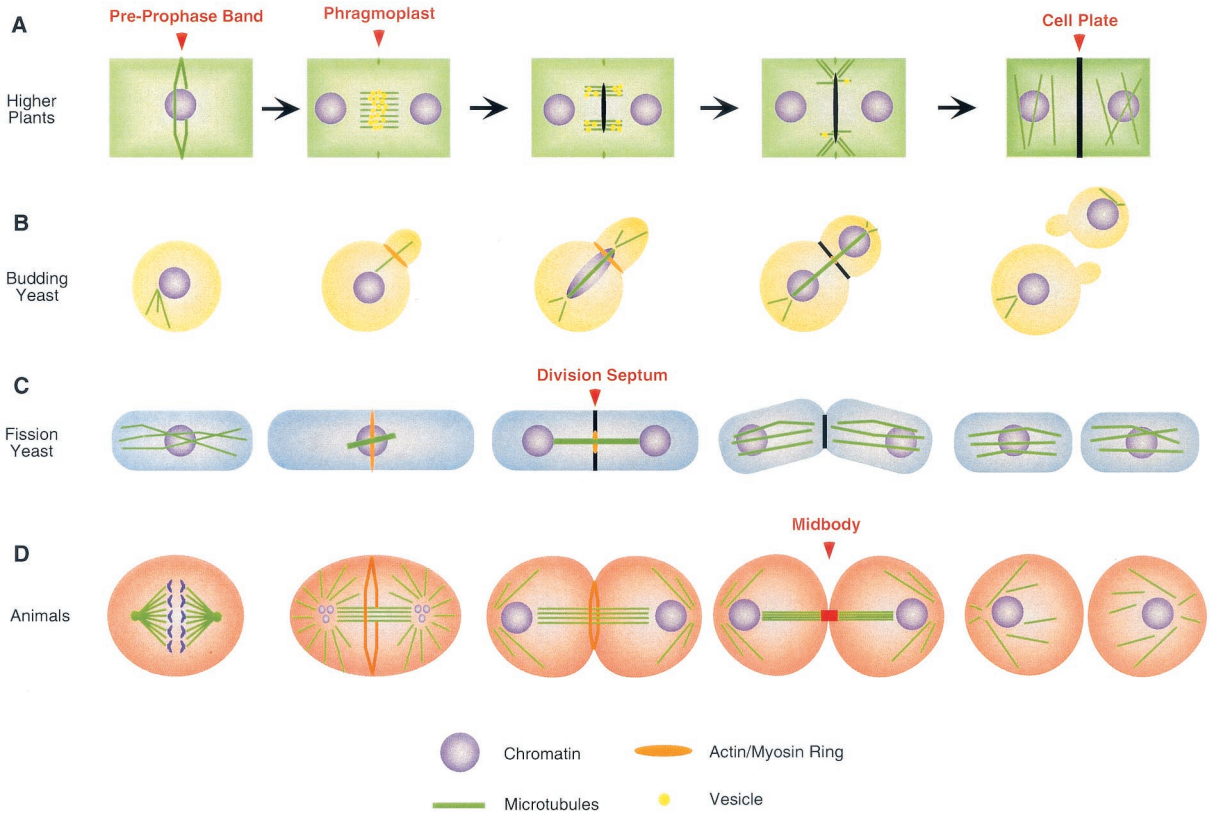

FIG. 1. General mechanisms of cytokinesis in eukaryotes. While the process of cytokinesis results in the physical partition of a mother cell into two daughter cells, the approach to cell division differs between several model organisms. (A) Higher plants, after separating the nuclei, use microtubules to deliver Golgi-derived vesicles to the equatorial region. Vesicles fuse to form the phragmoplast, which, through continued vesicle fusion, grows outward to the cell cortex, ultimately building a physical barrier between daughter cells called the cell plate. (B and C) Yeast and animal cells, unlike plant cells, divide through use of an actomyosin-based contractile ring. (B) In budding yeast cells, the ring is positioned at the interface between the mother cell and daughter bud, termed the bud neck. (C) In fission yeast and animal cells, the contractile ring is centrally placed, as both cell types divide by medial fission. Both budding and fission yeasts synthesize a division septum behind the leading edge of the constricting ring, which is eventually degraded, resulting in physical cell separation. (D) In animals, the ingressing furrow constricts the spindle midzone components into a dense structure called the midbody.

cell wall material between daughter cells. The septum is ultimately degraded by digestive enzymes, physically separating the daughter cells. Unlike animal cells and fission yeast, the yeast *Saccharomyces cerevisiae* divides by budding (Fig. 1B). First the site to bud is marked, and then through polarized cell growth the bud grows outward from the mother cell cortex, gradually increasing in size. The contractile ring is assembled at the bud neck, and similar to fission yeast, a division septum is synthesized behind the constricting ring. Plants significantly differ from yeast and animals in that they do not use a contractile ring to divide (Fig. 1A). In contrast, plants interdigitate microtubules and actin to build a dense structure called the phragmoplast between divided nuclei. Microtubule-directed vesicles containing cell wall material are targeted to the phragmoplast, and fusion of these vesicles causes the phragmoplast to grow outward toward the cell cortex, forming a cell plate. The cell plate fuses to the parent cell wall, dividing the parent cell into two daughters.

A recent area of intense research has focused on the coordination of cytokinesis and the nuclear cycle. It is crucial that cytokinesis only occurs after mitosis to ensure that equal complements of genetic material are transmitted to each future daughter cell. Important signaling mechanisms and checkpoints have recently been uncovered in many model organisms that spatially and temporally coordinate cytokinesis with mitosis, ensuring the integrity of genetic transfer.

In the following sections, we review recent studies using several eukaryotic model organisms to study cytokinesis, focusing on mammalian cells, invertebrates, yeast, and higher plants. The major events contributing to cytokinesis—including determining the division site, building the division apparatus and mechanically dividing, and coordinating cytokinesis with the nuclear division cycle—will be discussed. We conclude with a brief description of variations on the common theme of cytokinesis important for development.

POSITIONING THE SITE OF CELL DIVISION

It is crucial that cytokinesis is tightly coordinated spatially with chromosome segregation. During mitosis, the mitotic spindle directs chromosome segregation. Cytokinesis must only occur between segregated chromosomes to ensure that each daughter cell receives a full set of chromosomes together with a proper complement of cytoplasm and organelles. The

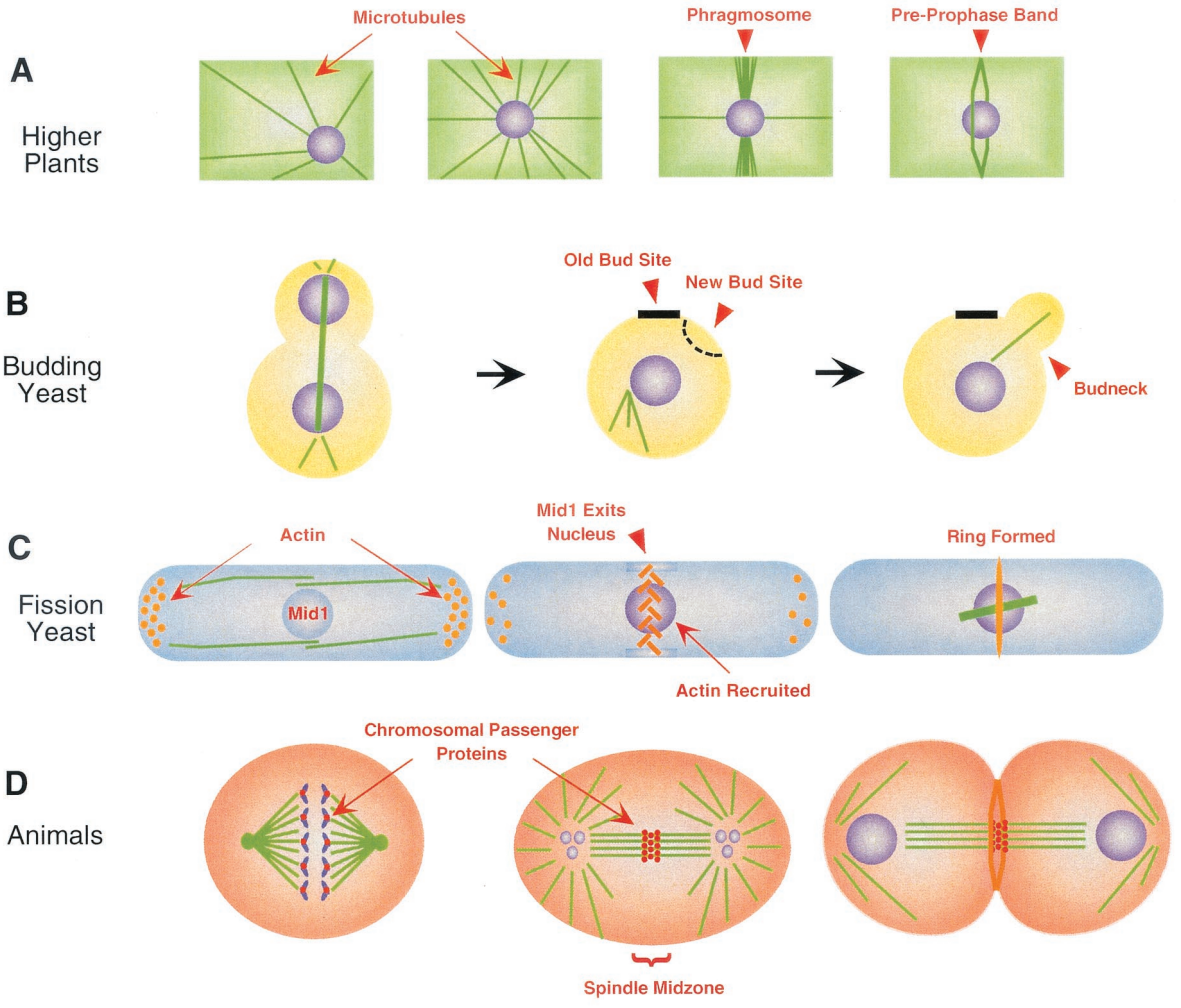

FIG. 2. Positioning the division site. Positioning the division site is one of the least-conserved aspects of cytokinesis. (A) In higher plants, microtubules centrally position the nucleus while condensing in the shortest nucleus-cortex distance to form the phragmosome. Once the nucleus is positioned, the phragmosome appears to mark the position at the cortex for formation of a medial ring structure called the PPB, which marks the division plane. (B) In budding yeast cells, the old or previous bud site is marked on the mother cell cortex by a bud scar. Near the bud scar, a ring containing septins is formed, which marks the site of the new bud. Polarized growth causes the new bud to grow outward from the mother cell cortex. (C) The position of the nucleus in thought to determine the division site in fission yeast. Mid1 protein, which is localized primarily to the nucleus during interphase, exits the nucleus in early mitosis and marks the cortex adjacent to the nucleus. Actin polymers are then recruited to the division site. (D) In animal cells, the spindle midzone determines where the cleavage furrow will form. Many proteins, including the chromosomal passenger proteins, localize to the spindle midzone.

mechanism for determining the cell division plane is one of the least-conserved aspects of cytokinesis in eukaryotic cells. Plants and yeast appear to determine the position of the cleavage furrow independently of the mitotic spindle and subsequently orient the spindle into position with the cleavage plane. In contrast, in animal cells there is growing evidence that the position of the mitotic spindle determines the position of the cleavage furrow.

Division Plane Specification in Plant Cells

Plants determine the division site by use of a "landmark," the placement of which occurs during interphase (Fig. 2A) (14, 238). In general during interphase in plants, microtubules radiate from the nucleus towards the membrane as well as span the cell cortex in an ordered manner. Late in interphase, the nucleus is centrally positioned through microtubule forces (78, 90). Microtubules emanating from the nucleus then accumulate in a transverse plane with the shortest nucleus-cortex distance. This cytoplasmic structure is called the phragmosome. Once the nucleus is positioned, microtubules and actin accumulate in a band on the plasma membrane where the phragmosome network and membrane meet, forming a medial ring called the preprophase band (PPB). The PPB subsequently narrows in early mitosis, marking the future division plane. The PPB disassembles before metaphase; however, the division site remains marked on the cell cortex by an unknown mechanism. This mark eventually guides the fusion of the cell plate with the plasma membrane.

Mutants with defects in the PPB illustrate the importance of

the PPB in division plane selection. In a certain percentage of tobacco BY-2 cells, the PPB is misplaced and the cell plate subsequently fuses at the site where the misplaced PPB localized (91). In *tangled1* mutants in *maize*, the orientation of the PPB is randomized, leading to a misorientation of the division plane (48). Additionally, in *Arabidopsis thaliana fass/tonneau* mutants, the PPB is absent, which leads to a randomization of the division plane (261). Although the PPB is dispensable for cell division in general, it is essential for the spatial orientation of cytokinesis, which is crucial for development.

Division Plane Specification in Yeast Cells

Even between the yeasts *S. cerevisiae* and *S. pombe*, the mechanisms to determine the cell division plane are quite different. In *S. cerevisiae* the cell division site is determined early in the cell cycle, prior to mitosis, by the location of the previous division site (Fig. 2B). In G_1 phase, a small GTPase signaling cascade (see reference 158 for a review) directs formation of a filamentous ring of proteins termed septins at the cell cortex near the previous bud site (149). The septin ring directs formation of a new bud. As the bud grows outward from the septin ring, the bud initiation site, or "bud neck," becomes the future site of cytokinesis. Later in the cell cycle, septins recruit numerous other proteins required for actomyosin ring formation (discussed below). Because the cell division site is determined early in the cell cycle, budding yeasts face a unique challenge to ensure that spindle elongation and chromosome segregation are spatially coordinated with the position of the bud neck. A checkpoint has recently been uncovered that monitors spindle position with respect to the bud, the significance of which is discussed in later sections.

Like most plant and animal cells, *S. pombe* divides by medial fission to generate two equal-size daughter cells (Fig. 2C). *S. pombe* cells do not grow equal amounts from each end; therefore, the position of the cell middle changes during cell cycle progression (172). Thus, the mechanism by which cells specify their middle must be dynamic. In *S. pombe* nuclear position is maintained in the cell middle through opposing pushing forces generated by microtubules (262), leading to a model in which the position of the nucleus determines the division site (38). Consistent with this, the nucleus is frequently mispositioned in tubulin mutants; however, the division site always correlates with the position of the nucleus (38).

How does nuclear position specify the division site? Insight into this has come from analysis of *plo1* and *mid1* mutants, which are defective in positioning the actomyosin ring (15, 38, 240). In interphase, Mid1p resides primarily in the nucleus and can be seen faintly at the medial cell cortex (15, 202, 240). Mid1p appears to shuttle in and out of the nucleus and is thought to continuously mark the cell cortex proximal to the nucleus (202). Upon entry into mitosis, Mid1p becomes phosphorylated and exits the nucleus in a Plo1p-dependent manner. After exiting the nucleus, Mid1p strongly localizes to the cortex overlying the nucleus, recruiting proteins involved in actomyosin ring assembly such as actin and thus marking the cell division site (15, 240). This pathway may be conserved, as Polo kinases and the Mid1p-related protein anillin are required for cytokinesis in *Drosophila melanogaster* and human cells (76, 196). Both Mid1p and anillin cycle from the nucleus in interphase to the contractile ring in mitosis. In addition, the two proteins have some structural similarities, including a proline-rich domain and a carboxy-terminal PH domain (76, 240; D. McCollum, unpublished observations). Other proteins involved in actomyosin ring positioning, such as the Pom1-kinase (16) and products of the *pos* genes (63), have been identified. The mechanism of their action in actomyosin ring positioning is not yet known.

Division Plane Specification in Animal Cells

In animal cells, microtubules specify position of the cleavage furrow (Fig. 2D). Two models have been proposed to account for furrow positioning. The classic model put forward by Rappaport suggests that signals from overlapping astral microtubules determine furrow position (211). This model was proposed based on micromanipulation experiments with marine invertebrate embryos. Although similar results have been reported with cultured cells (212), other convincing studies suggested that the spindle midzone was required for furrow positioning (31, 61, 276).

In late mitosis, after chromosome segregation, the central or interzonal region of the mitotic spindle, which is the region between separated chromosomes, undergoes a reorganization in which microtubules bundle into antiparallel interdigitating arrays. For the purpose of this review we refer to this centralized microtubule bundle as the spindle midzone. During furrow contraction, the spindle midzone is compacted into an electron-dense structure called the midbody. After furrowing completes in animal cells, they remain connected through a structure called the cytoplasmic bridge, which contains the condensed spindle midzone microtubules. This structure persists until the bridge "cuts" during abscission.

The spindle midzone has been shown to directly contribute to signaling actin ring assembly and constriction during later stages of mitosis. In one report, placing an artificial barrier between the spindle midzone and cell cortex in cultured cells during metaphase caused cleavage furrow ingression to be inhibited; however, if the barrier was created in early anaphase, cytokinesis was successful (31). This suggested that transient signals from the spindle midzone were required for cleavage site formation. Wheatley and Wang then examined the relationship between microtubules and cleavage site formation in cultured cells that had been fluorescently labeled for tubulin (276). They confirmed that cleavage furrow formation was linked to microtubules of the spindle midzone as opposed to spindle poles and depolymerization of midzone microtubules with a drug resulted in failed cytokinesis. Consistent with these results, it was observed that during male meiosis in *D. melanogaster KLP3A* mutants (discussed below), mitotic spindles formed normally, but the central spindle midzone failed to form (280) and furrowing was not initiated. Thus, taken at face value, cleavage site positional information seems to be derived from different sources in marine invertebrate embryos compared to cultured cells; however, a closer examination of earlier experiments may reveal more similarities than differences. Since division site selection and furrow ingression occurs virtually simultaneously in animal cells, a more detailed description of the components of the spindle midzone is discussed in the next section.

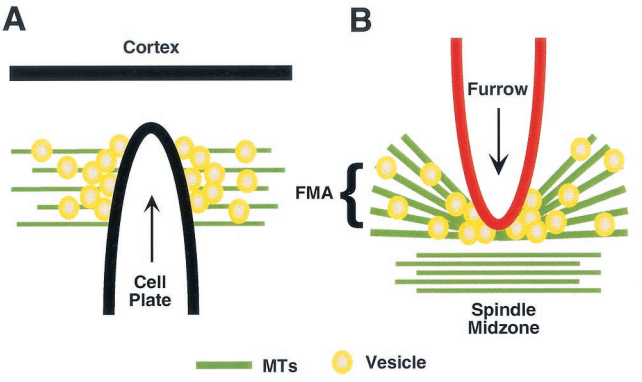

FIG. 3. Vesicle fusion and cytokinesis. (A) In plant cells, Golgi-derived vesicles are targeted by microtubules (MTs) to the cell plate as it grows outward from the cell middle to the cortex. (B) In *Xenopus* and zebra fish embryos, the FMA is an array of microtubules emanating out from just ahead of the advancing cleavage furrow that is thought to deliver membrane-containing vesicles to the division site. It was recently shown that new membrane accumulation at the cleavage site was also associated with dividing early *C. elegans* embryos (see text).

ASSEMBLING DIVISION MACHINERY AND DIVIDING

Construction of the division site is fundamentally different in plant, yeast, and animal cells. Plants, having marked the division site on the cell cortex early in mitosis, build a new cell wall or a "cell plate" outward from the cell center in a process that requires vesicle transport and fusion. Yeast and animal cells, on the other hand, assemble a contractile ring that constricts inward from the cell cortex. In recent years, hints that membrane transport and vesicle fusion events important for cytokinesis in yeast and animal cells have been uncovered. Considerably more is known about the contractile ring in yeast and animal cells, resulting from the ease and availability of a variety of genetic model organisms. In this section we discuss the components and mechanics of the two major modes of division in eukaryotes: the cell plate in plants and the contractile ring in yeasts and animals.

Plants: Constructing the Cell Plate

In plants, the onset of cell division in somatic cells is catalyzed by the creation of the phragmoplast. The phragmoplast forms in the cell middle and is thought to develop from the remains of the mitotic spindle in anaphase. It is composed of interdigitating plus ends of microtubules, actin, and vesicles. The vesicles are transported to the middle of the cell along microtubules (Fig. 3A), as they do not accumulate in the cell middle in cells lacking microtubules (165). A recent study, utilizing high-resolution electron tomography, indicates that kinesins are involved in the transport of vesicles to the division site (200). The cell plate forms through fusion of phragmoplast-associated vesicles. Information on how the cell plate is assembled comes primarily from studies of *A. thaliana*.

Two *A. thaliana* genes, *KNOLLE* and *KEULE*, which encode a cytokinesis-specific syntaxin and a Sec-1 protein, respectively, provide the key links to vesicle fusion and cytokinesis in plants (20). Syntaxins belong to the SNARE family of proteins, which are mediators of vesicle fusion in diverse organisms (44). SNARE proteins are thought to function in concert with members of the Sec-1 family of proteins and small GTPases of the Rab family to regulate membrane docking and fusion. During vesicle fusion, Sec-1 binds to syntaxin and induces a conformational change such that membrane-bound syntaxins are primed to interact with vesicle-associated membrane proteins, and this interaction thus pulls the vesicle into close proximity of the target membrane. KNOLLE was first identified as a cytokinesis-specific syntaxin specifically required for vesicle fusion and not trafficking during cell division (128, 152). Consistent with its role in vesicle fusion, KNOLLE is membrane associated, is expressed during mitosis, and localizes to the division site during cytokinesis (128). KNOLLE functions in concert with and binds to the Sec-1 protein KEULE (13, 270). In both *knolle* and *keule* mutants, vesicles accumulate but do not fuse at the cell plate, resulting in a defective but partially functional cytokinesis (270). These studies suggest that the KNOLLE-KEULE complex functions in targeting and fusing vesicles to form the cell plate.

The cytoskeletal network of the phragmoplast and the cell plate then migrate outward towards the parent cell wall. The expansion of the phragmoplast is somehow directed towards the site in the parent cell wall that was previously marked by the PPB (see above). This directed process seems to be facilitated by the cytoskeletal network (238, 239).

Further clues to how the centrifugal expansion of the cell plate might be facilitated were found with the recent discovery of the mitogen-activated protein kinase (MAPK) kinase kinase NPK1 in tobacco. Expression of a kinase-dead mutant of NPK1 results in multinucleate cells, suggesting that this MAPK kinase kinase regulates cytokinesis but not the cell cycle. Furthermore, NPK1 localizes to the leading edge of the cell plate in mitosis, and biochemical experiments showed an increase in activity in late mitosis. This makes NPK1 a strong candidate for a part of a kinase pathway regulating cytokinesis in plants (188). In alfalfa, a MAPK MMK3 was observed to localize to the phragmoplast with increased activity in mitosis through anaphase. This together with its activity's being dependent on microtubules makes it likely to be involved in the regulation of cytokinesis (27).

This mechanism for cytokinesis is not rigidly adhered to by all cell types. In the *Arabidopsis* endosperm, phragmoplast formation is not dependent on a mitotic spindle remnant. The endosperm arises as a syncytium around the embryo early in development, containing many unseparated nuclei. In this case, to generate distinct cells, the phragmoplast needs to form at more locations than just between a pair of daughter nuclei. To accomplish this, microtubules originating from the nuclear periphery of neighboring nuclei interdigitate, forming several miniphragmoplasts, which then give rise to a tubular network that eventually generates a cell plate (201).

Assembly of Actomyosin Ring in Yeast and Animal Cells

Although mechanisms of division site specification are quite diverse in yeast and animal cells, subsequent steps appear more conserved. Both yeast and animal cells divide through use of an actomyosin contractile ring. The ring assembles at the cell cortex, and at the end of anaphase it constricts to bring about partitioning of the cytoplasm. As the name suggests,

TABLE 1. Actomyosin ring proteins[a]

Family	Gene product(s) or name(s)	Organism(s)	Reference(s)
Myosin II heavy chain	Myo2	*D. discoideum*	56, 118
	myo2	*S. pombe*	117, 164
	myo3/*myp3*	*S. pombe*	22, 177
	myosin II	Echinoderm embryos	153
	MYO1	*S. cerevisiae*	23, 140
Myosin RLC	RMLC	*D. discoideum*	42
	rlc1	*S. pombe*	18, 132
	spaghetti squash	*D. melanogaster*	112
Myosin ELC	ELC	*D. discoideum*	53
	cdc4	*S. pombe*	166
	MLC1	*S. cerevisiae*	28, 227
Septin	*CDC3, -10, -11*, and *-12*	*S. cerevisiae*	
	peanut, Sep1, Sep2	*D. melanogaster*	3, 74, 149
	Nedd5, H5, Diff6	Mouse	114, 174, 292
	spn1-6	*S. pombe*	149
	unc-59, unc-61	*C. elegans*	156
Cdc15-like protein	*cdc15*	*S. pombe*	71
	imp2	*S. pombe*	58
	HOF1/*CYK2*	*S. cerevisiae*	111, 141
	PSTPIP, PSTPIP2	Mouse	247, 281
IQGAP	IQGAP	Bovine	126
	IQGAP1	Human	96, 275
	GAPA	*D. discoideum*	1
	rng2	*S. pombe*	64
	CYK1/*IQG1*	*S. cerevisiae*	65, 140, 199
Small GTPase	Rho	*X. laevis*, mouse, echinoderm	60, 115, 173, 189
	Cdc42	*X. laevis*	60
	racE	*D. discoideum*	127
Formin	diaphanous	*D. melanogaster*	34
	BNI1	*S. cerevisiae*	67, 120
	cdc12	*S. pombe*	39
	sepA	*A. nidulans*	95
	cyk-1	*C. elegans*	252

[a] Families of actomyosin ring proteins and selected homologs from different organisms described in the text are shown. In addition, selected key references that are discussed in the text pertaining to these genes are listed. This table is intended to facilitate reading of the text and is not intended to catalog all homologs or list every original reference for each gene.

both actin and myosin are essential components of the actomyosin ring. There is also a considerable degree of conservation in additional components required to assemble the actomyosin contractile ring (Table 1). In the following sections we review conserved families of proteins involved in actomyosin ring formation and discuss how these proteins may function together.

Myosin II. It has long been presumed that myosin motor activity generates the forces necessary for contraction of the actomyosin ring. Type II myosin consists of a dimer of two heavy chains, each having two associated proteins, called the essential light chain (ELC) and regulatory light chain (RLC). Myosin heavy chain has a head domain, which has the motor and actin binding domains, and a long coiled-coiled domain involved in dimerization. In muscle, myosin forms long bipolar filaments which cross-link actin filaments and pull them together to bring about muscle constriction (248). It has been proposed that the actomyosin ring is constructed much like a minimuscle, with arrays of bipolar myosin filaments connected to each other by actin filaments. While this model has not been formally proven, it is clear that in fungus and animal cells, type II myosin is critical for actomyosin ring function. Loss of myosin function leads to cytokinesis failure in starfish blastomeres (153), *Dictyostelium discoideum* (56, 118), *Drosophila* (112), budding yeast (23, 140), and fission yeast (22, 117, 132, 164, 166, 177, 183).

Although actin and myosin probably function together to bring about cytokinesis, recent work suggests that their localization to the furrow is at least partly independent. In budding yeast, the myosin ring assembles at the bud neck early in the cell cycle, well before localization of actin polymers, which localize to the bud neck at the end of anaphase (23, 140). In *S. pombe*, myosin can localize to the cell middle in the absence of filamentous actin polymers but cannot organize into a contractile ring (178, 184). Moreover, in both *S. cerevisiae* and *S. pombe*, myosin ring localization is not affected by actin depolymerization once the actomyosin ring has formed (23, 184). Consistent with myosin localization being somewhat indepen-

dent of actin, the actin binding motor domain of myosin is not essential for myosin localization to the ring (184, 290, 291). In *D. discoideum*, phosphorylation of the Myo2 tail is important for ring localization (56); however, tail binding proteins that mediate ring localization have not been identified.

Some controversy has existed over the years as to the role of the ELC and RLC for myosin function. In *D. discoideum* both myosin light chains are essential (42, 53); however, cells expressing Myo2 in which the RLC binding site has been deleted perform normal cytokinesis (266). One possibility is that the RLC is not important for myosin function but has a separate essential function in cytokinesis. However, recent work with *S. pombe* suggests this is not the case (183). *S. pombe* cells from which the *S. pombe* RLC, Rlc1p, has been deleted have severe cytokinesis defects (132, 183). Expression of a myosin heavy chain in which the Rlc1p binding domain has been deleted rescues the cytokinesis defects of *rlc1* deletion mutants (183). These results suggest that RLCs function to relieve auto-inhibition of Myo2p. Phosphorylation of the RLC may be essential for regulating myosin activity coordinately with progression through mitosis (see below) (218, 254).

Septins. Septins were first discovered in budding yeast, where they localize to the bud neck and are required for cytokinesis, bud morphogenesis, and chitin deposition (3; for a review, see references 74 and 149). Septins contain a GTPase domain, the significance of which is unclear; can form filaments in vitro (75); and may associate with the plasma membrane through binding to phospholipids (292). The *Drosophila* septin peanut localizes to the cleavage furrow, and peanut mutants exhibit cytokinetic defects (185). Also, injection of antibodies against the mammalian septin Nedd5 into cultured cells blocks cytokinesis (114). Despite these results, septins do not appear to be absolutely required for cytokinesis. In *Drosophila* peanut mutants, some cells are able to complete cytokinesis. However, in these mutants, another *Drosophila* septin, Sep2, localized normally, suggesting possible redundancy among septins (2). In *Caenorhabditis elegans* there are only two septin genes, *unc-59* and *unc-61*. Both *unc-59* and *unc-61* are required for normal postembryonic cytokinesis and morphogenesis but have no essential function in embryogenesis (186). Similarly, *S. pombe* septin mutants have only minor defects in cytokinesis (149).

What is the role of septins in cytokinesis? In *S. cerevisiae*, septins seem to function as scaffold proteins for assembly of other ring components (57). Septins have also been identified in complexes with proteins involved in secretion, including the exocyst complex (100) and SNARE proteins (21), suggesting a possible role in directing polarized secretion.

Cdc15-like proteins. Cdc15p was the founding member of a family of SH3-domain containing proteins first identified in *S. pombe* (71). Both Cdc15p and a related *S. pombe* protein, Imp2p, localize to the actomyosin contractile ring (58, 71). *cdc15* mutants can form an actomyosin contractile ring, but the rings are unstable and fail to recruit actin polymers, resulting in cytokinesis failure (18). Two related proteins exist in mammalian cells, PSTPIP and PSTPIP2, both of which localize to the cleavage furrow (247, 281). It is not yet known if these proteins are required for cytokinesis. The Cdc15p-related protein Cyk2/Hof1p in *S. cerevisiae* is also involved in cytokinesis (111, 141). Cyk2p/Hof1p forms a double ring coincidently with septin ring formation early in the cell cycle, and this becomes a single ring colocalizing with the actin ring just prior to contracting (141, 267).

IQGAP. IQGAP family proteins contain a number of different functional domains, including an actin binding domain termed the calponin homology domain, IQ domains, and a GTPase activation (GTPase-activating protein [GAP]) domain (96, 126). The *Dictyostelium* IQGAP-related protein, GAPA, as well as the *S. pombe* and *S. cerevisiae* IQGAP proteins Rng2p and Cyk1p/Iqg1p are required for cytokinesis (1, 64, 65, 140, 199). In *S. pombe*, cells from which the IQGAP homologue rng2 has been deleted form a spot-like structure containing actin in the medial region of the cell but are unable to form actin rings (64). Rng2p localizes to the actomyosin ring and spindle pole body (SPB) of interphase and mitotic cells. Furthermore, Rng2p interacts with calmodulin, a component of the SPB and actomyosin ring. *S. cerevisiae* IQGAP Cyk1/Iqg1 also localizes to the actomyosin ring in late anaphase (65, 140, 199) and is required to recruit actin through its calponin homology domain (140, 226).

Both *S. pombe* and *S. cerevisiae* IQGAP proteins interact with calmodulin, presumably through the IQ motifs. In *S. cerevisiae* the IQ motifs are required for localization of Cyk1p/Iqg1p to the bud neck (64, 226) and bind a calmodulin-related protein, Mlc1p (28, 227). Mlc1p serves as a light chain for the type V myosin Myo2p (249), and the type II myosin Myo1p (28). Mlc1p localizes to the bud neck prior to Cyk1p/Iqg1p and is required to recruit Cyk1p/Iqg1p to the bud neck (28, 227). Mammalian myosin ELC has been shown to bind to IQGAP1, suggesting that light chain binding may be a conserved property of IQGAP proteins (274). Deletion of the carboxyl-terminal GAP-related domain of Cyk1p/Iqg1p does not affect localization or actin recruitment to the ring but prevents actomyosin ring contraction. In vitro binding experiments show that Cyk1p/Iqg1p binds to Tem1p GTPase (226). This result is quite interesting since Tem1p is a component of the mitotic exit network (MEN), which seems to be required for initiation of actin ring constriction at the end of anaphase (see below).

Small GTPases. Several small GTPases of the Rho, Rac, and Cdc42 families are required for cytokinesis in animal cells (207). GTPases are generally considered molecular switches that cycle between active (GTP-bound) and inactive (GDP-bound) states in response to specific cellular cues. GTP-bound GTPases are potent activators of intracellular signaling networks. GDP-GTP cycling is regulated by guanine nucleotide exchange factors (GEFs) and GAPs, which catalyze the activation and deactivation of GTPases, respectively.

Small GTPases of the Rho family are most prominent in carrying out essential functions of cytokinesis. Inactivation of Rho GTPase in animal cells inhibits cytokinesis by disrupting normal assembly of actin filaments and triggering disassembly of the contractile ring (8, 60, 115, 127, 154, 173, 193). Mutants in the *Dictyostelium* rac protein racE are also defective in cytokinesis (127). Rho GTPase is localized to the cleavage furrow and midbody during cytokinesis (60, 189, 253). Regulators of Rho GTPases have also been shown to be important for cytokinesis. Two RhoGEFs required for cytokinesis, human ECT2 and *Drosophila* pebble, have been identified (208, 257). Both localize to the spindle midzone during cytokinesis. A Rho GAP required for cytokinesis, CYK-4, has been iden-

tified in *C. elegans* (102). CYK-4 also localizes to the spindle midzone. CYK-4 and the kinesin-like protein ZEN-4 show a mutual dependence for localization, suggesting these two central spindle midzone proteins may cooperate in executing cytokinesis.

There are several known effectors of Rho GTPases, some of which have been implicated in regulating cytokinesis. Of those required for cytokinesis, three include protein kinases: the *Dictyostelium* p21-activated serine/threonine kinase a (46), bovine Rho-associated kinase (122, 285), and murine citron kinase (157), all of which are implicated in various aspects of assembling and contraction of the actomyosin ring. Rho appears to be crucial for localization of citron kinase to the cleavage furrow and midbody (62).

Formins. The most compelling evidence for a downstream effector of Rho GTPases is that for formin homology (FH) proteins. Formins comprise a large family of proteins—including diaphanous of *Drosophila* (34), Bni1p of *S. cerevisiae* (67, 120), Cdc12p of *S. pombe* (39), and sepA of *Aspergillus* spp. (95)—and are involved in cell polarity and cytokinesis. Formins bind the small GTPases Rho and Cdc42 but also numerous other proteins, including actin; the actin-associated proteins profilin, Bud6p (Aip3p), and Spa2p; and the Cdc15-like protein Hof1p (39, 67, 82, 101, 111, 120, 273). Because of their ability to bind numerous components of the actomyosin contractile ring, it has been proposed that formins serve as scaffolds to organize macromolecular protein complexes involved in actomyosin ring formation (39). Consistent with a role in cytokinesis, formins localize to the actomyosin contractile ring (7, 39, 111). Moreover, *S. pombe* Cdc12p is essential for actomyosin ring formation. In *C. elegans*, the *cyk-1* gene encodes an FH protein required for a late step in cytokinesis, as cleavage furrows ingress normally in *cyk-1* mutant embryos and regress once mitosis completes (252). CYK-1 localizes to the cleavage furrow subsequent to initiation of furrow ingression, supportive of a role in latter stages of cytokinesis. *S. cerevisiae bni1* mutants have a mild cytokinesis defect (67, 120); however, Bni1p also appears to be involved in spindle orientation (83, 130, 169, 286), which helps ensure that cytokinesis is spatially coordinated with mitosis.

Order of assembly. The study of cleavage furrow formation has consisted largely of characterization of new proteins that either localize to the furrow and/or are required for assembly of the furrow. Because an enormous number of proteins localize to the cleavage furrow simultaneously, determining their order of function and interdependence has been a daunting task. A number of factors have made *S. cerevisiae* a useful organism for these types of studies. First, this yeast is useful because the bud neck forms early and assembly of actomyosin ring components is spread over much of the cell cycle. Second, unlike in other organisms, the actomyosin ring is not essential, allowing easier study of ring mutants. Recent studies indicate that myosin ring formation depends on septins (23, 140) and that the myosin ring can form without filamentous actin but does not constrict without actin (23). The multifunctional myosin light chain Mlc1p depends on septins for localization to the bud neck, and it in turn is required for recruitment of the IQGAP protein Iqg1p/Cyk1p (28, 227). Iqg1p/Cyk1p is essential for formation of the actin ring (140, 226). Although these types of studies are still at an early stage they appear quite promising. It will be of interest to see if the dependency relationships in ring formation identified in *S. cerevisiae* are conserved in other organisms.

Furrow Formation and Spindle Midzone Signals in Animals

During animal cell cytokinesis, signals to assemble the actomyosin ring originate from the spindle midzone. Positioning and assembly of the ring occur virtually simultaneously. What constitutes the signals from the spindle midzone, and how do they promote actomyosin ring assembly? Genetic studies are beginning to reveal some factors and mechanisms involved. Elegant studies in cultured cells, *C. elegans*, and *D. melanogaster* have uncovered many diverse proteins that localize to and function at the spindle midzone in directing furrow formation and completion of cytokinesis. Two major classes of proteins appear important (Table 2): chromosomal passenger proteins, which localize initially to chromosomes and centromeres and subsequently to the midzone and furrow, and motor and associated proteins, which are required to maintain the spindle midzone.

Chromosomal passenger proteins. An interesting group of spindle midzone-associated proteins required for cytokinesis are the so-called chromosomal passenger proteins. These molecules are so called because they translocate from centromeres to the spindle midzone at anaphase onset (4). Passenger proteins are implicated in regulating a number of mitotic processes, including chromosome alignment in metaphase, chromosome segregation, and cytokinesis. The major chromosomal passengers include the inner centromere protein (INCENP), the Aurora-B/Ipl1 kinase, Bir1/Survivin, and the telophase-disk 60 (TD-60) protein. TD-60 has not been cloned and will not be discussed further.

The first chromosomal passenger protein identified was INCENP (49). Because of its localization to metaphase centromeres and then to the central spindle and midbody, it was initially thought that such passenger proteins marked the cleavage furrow position so that it would bisect segregated chromosomes. A role for INCENP in cytokinesis eluded researchers for some time until dominant negative forms of INCENP which caused cells to fail cytokinesis were identified (61, 156). Additionally, both RNA interference experiments with flies and worms and knockout experiments with mice have revealed that INCENP is essential for cytokinesis (4, 110, 156).

A second chromosomal passenger protein involved in cytokinesis is the Aurora-B/Ipl1 kinase. Aurora-B/Ipl1-related kinases are part of a large family of serine/threonine kinases important for regulating chromosome segregation and cytokinesis (24). Aurora-B/Ipl1 proteins in *C. elegans* (AIR-2), *Drosophila* (Aurora-B), and humans (AIM-1) are all required for cytokinesis (88, 162, 221, 256, 265). Importantly, however, the target(s) of Aurora kinases at the spindle midzone is unknown.

A third family of chromosomal passenger proteins implicated in cytokinesis is the family of Survivin-like proteins (233). Survivin was originally identified in baculovirus as an inhibitor of apoptosis protein that associates with mitotic spindles (10, 135). Later work showed that a *C. elegans* Survivin-like protein, BIR-1, was required for cytokinesis (80). This defect could partially be rescued by transgenic expression of a mammalian homolog. In addition, mouse null embryos indicated that Sur-

TABLE 2. Spindle midzone-associated proteins[a]

Family and protein group	Gene or product name(s)	Organism or cell type	Reference(s)
Chromosomal passenger proteins			
INCENP	INCENP	Human	49
	INCENP	Mouse	53
	DmINCENP	*D. melanogaster*	4
	ICP-1	*C. elegans*	110
Aurora	AIM-1	Human	256, 258
	XAIRK2	*X. laevis*	5
	Aurora-B	*D. melanogaster*	88
	Air-2	*C. elegans*	221
	Ip11	*S. cerevisiae*	37
Survivin	Survivin	Human	10, 135
	Survivin	Mouse	264
	BIR1	*C. elegans*	80
	bir1/pbh1/cut17	*S. pombe*	
	BIR1	*S. cerevisiae*	175, 210, 265
Microtubule motor proteins			
CHO1/MKLP1	CHO1	Chinese hampster ovary	191, 192, 224
	pavarotti	*D. melanogaster*	6
	ZEN-4	*C. elegans*	206, 209
KLP3A	KLP3A	*D. melanogaster*	280
Polo kinase	Plk	Mouse	129
	Polo	*D. melanogaster*	146
	plo1	*S. pombe*	198
	CDC5	*S. cerevisiae*	116

[a] Families of spindle midzone-associated proteins and selected homologs from different organisms described in the text are shown. In addition, selected key references that are discussed in the text pertaining to these genes are listed. This table is intended to facilitate reading of the text and is not intended to catalog all homologs or list every original reference for each gene.

vivin was required for mitosis during development, further suggesting that Survivin function is conserved (264). More recently, Survivin localization was shown to mirror that of chromosomal passenger proteins (237, 246, 264).

Based on the similar localization and mutant phenotypes of the chromosomal passenger proteins, it was hypothesized that these proteins may function as part of a complex (Fig. 4). Recent reports have now uncovered that chromosomal passengers do appear to function as a complex in cells. INCENP directly interacts with Aurora-related kinases from *Xenopus laevis* (XAIRK2), *C. elegans* (AIR-2), and humans (AIRK2) (5, 110). In addition, a dominant negative INCENP mutant disrupted AIRK2 localization during mitosis in HeLa cells, further suggesting that this interaction is conserved and essential in vivo (5). In *C. elegans*, inactivation of Survivin protein prevented the proper localization of the aurora kinase AIR-2 (246). In a recent report, human Survivin was shown to interact directly with both Aurora-B and INCENP by yeast two-hybrid and in vitro pull down assays, and loss of INCENP localization disrupted the ability of Survivin to properly localize (277). Thus, to date, there is biochemical evidence for at least a tripartite chromosomal passenger complex at the spindle midzone.

What is the function of the passenger proteins in cytokinesis? It was found that depleting Aurora-B from cultured *Drosophila* cells resulted in mislocalization of the microtubule motor protein pavarotti/MKLP (88). Since pavarotti/MKLP is required for spindle midzone formation, this suggests that passenger proteins are required for midzone formation (see below). In contrast, RNAi depletion of *Drosophila* INCENP did not disrupt pavarotti localization or spindle midzone formation but did block cytokinesis, suggesting that chromosomal passenger proteins are involved not only in spindle midzone formation (4). In *C. elegans*, INCENP, BIR-1/survivin, and AIR-2 are all required for localization of ZEN-4/MKLP (225, 246). Thus, the best-defined role for the chromosomal passenger complex in cytokinesis is to localize the MKLP-1/ZEN-4/pav family of motor proteins to promote formation of the central spindle.

Microtubule motor proteins. The major motor proteins associated with the spindle midzone are the microtubule motor protein kinesins, specifically, those of the CHO1/MKLP1 and KLP3A families. Both are required for mitotic progression, localize along spindles during metaphase, and concentrate in the spindle midzone region during anaphase (191, 192, 224, 280). Bacterially expressed CHO1 can bundle antiparallel microtubules in vitro and, in the presence of Mg-ATP, can cause sliding of antiparallel microtubules (192). Mutants in the *Drosophila* CHO1/MKLP1 homolog, pavarotti, or Klp3A resulted in normal anaphase but cytokinesis failure due to disruption in the structure of the spindle midzone and contractile ring assembly (6, 280). The furrow proteins peanut, actin, and anillin do not localize in *pavarotti* mutants. The failure in contractile ring formation when the spindle midzone is disrupted indicates

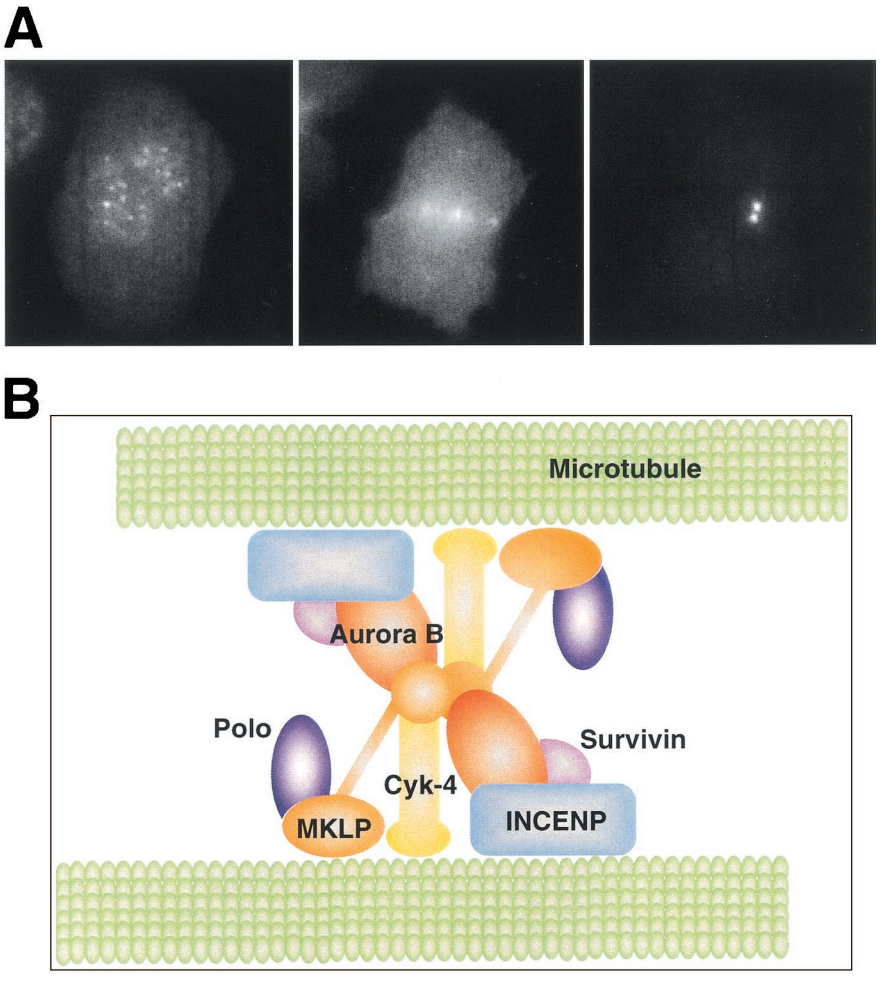

FIG. 4. Chromosomal passenger proteins. Chromosomal passenger proteins are so called because they translocate from centromeres to the spindle midzone in anaphase. (A) Aurora-B is localized to centromeres in metaphase in rat NRK cells. During anaphase, Aurora-B translocates to the spindle midzone and subsequently is condensed into the midbody during furrow ingression. (Images courtesy of Maki Murata-Hori and Yu-li Wang.) (B) INCENP, Aurora-B, and Survivin are thought to function as a tripartite chromosomal passenger complex at the spindle midzone. A speculative model suggests that the chromosomal passenger complex interacts with the kinesin MKLP, Polo kinase, and the Rho GAP Cyk-4 to maintain the spindle midzone and promote cytokinesis (see text).

that the midzone plays a key role in furrow assembly in *Drosophila*. This may result from a failure to transport furrow components along microtubules to the cleavage site. Consistent with this, it has been shown that in mammalian cells, preexisting actin filaments get transported to the furrow (32).

Cytokinesis is also defective in *Drosophila polo* mutants, where Polo is required for the correct localization of pavarotti (which is mutually required for Polo localization) and the septin peanut and for normal formation of the actomyosin ring (6, 33). Polo is a protein kinase localized to interzone microtubules during anaphase and to the midbody during late cytokinesis, where it colocalizes with the kinesin-like protein CHO1/MKLP1 (129). In *S. pombe*, disruption of the Polo homolog Plo1 results in a population of cells defective in actocyosin ring formation, suggesting that Polo kinase may play a direct role in this process (198).

In *C. elegans* embryos lacking the CHO1/MKLP1 homolog ZEN-4, cells continue through mitosis but fail to undergo normal cytokinesis, resulting in multinucleate embryos (206, 209). Close inspection of these cells revealed that furrow ingression initiates normally but fails and regresses prior to completion and is preceded by disruption of spindle midzone microtubules. Thus, in *C. elegans*, the spindle midzone is required not for furrow formation but for completion of cytokinesis, suggesting a second function for the spindle midzone.

What then is the function of spindle midzone motor proteins? One possibility is that they provide structural support for interdigitating microtubules at the midzone region, which may provide a platform to localize furrow components to the cell middle. Another alternative is that motors help deliver the necessary molecules to build the cleavage furrow. Along these lines, the spindle midzone may be necessary for vesicle delivery required to complete cytokinesis, much like the phragmoplast in plants. These models are probably not mutually exclusive; however, proof awaits future studies.

Interplay between the spindle midzone and contractile ring. Is there a mutual dependency between the spindle midzone and contractile ring formation? Two models have emerged from genetic experiments with *C. elegans* and *Drosophila*.

Work with *Drosophila* suggests that a mutual dependent relationship may exist, while studies with *C. elegans* argue that they are genetically separable entities.

In *Drosophila*, a cooperative interdependence may exist in which if either the spindle midzone or contractile ring is disrupted, the other fails to form properly (85). The *Drosophila* mutants *chickadee* (*chic*), *diaphanous* (*dia*), *spaghetti squash* (*sqh*), *KLP3A*, and *polo* (33, 86, 97, 280) all have defects in formation of both the spindle midzone and contractile ring. The *chic* gene encodes the actin binding protein profilin, *dia* encodes a formin homology protein (discussed above), and *squ* encodes a myosin II RLC (34, 50, 86, 112). Since they are all furrow components, mutants in these genes probably lead to defects in the contractile ring. As described above, the products of the *KLP3A* and *polo* genes localize and appear to function at the spindle midzone. Therefore, mutants in these genes probably lead to defects in midzone formation. The fact that all cytokinetic mutants identified in *Drosophila* to date are either defective for both spindle midzone and contractile ring formation, or for neither, has led to a model in which a cooperative interdependence exists between these two structures. One speculative idea is that the spindle midzone may promote assembly of furrow components, and in turn, the furrow may stabilize bundled ends of midzone microtubules. In support of such a model, KLP3A was found to bind both actin and mitcrotubules (235).

Using *C. elegans* as a genetic model, Severson et al. observed that ZEN-4/MKLP localization was normal in CYK-1 mutant embryos (CYK-1 is a formin which localizes to the cleavage furrow and is required for cytokinesis [see above]), and CYK-1 localization to the leading edge of the furrow was normal in ZEN-4 mutant embryos (225). In addition, genetic experiments indicated that *air-2 zen-4* double mutants were equally as defective as single mutants, in that cleavage furrows ingressed and then failed. In contrast, *air-2* or *zen-4* mutants in combination with a *cyk-1* mutation were more defective, in that furrows even failed to ingress. These data suggest that the spindle midzone proteins AIR-2 and ZEN-4 are genetically separable from the ring protein CYK-1 and may function in separate pathways required for cytokinesis. Moreover, it appears that formation of the contractile ring in *C. elegans* does not require an intact central spindle and organization of the central spindle does not require an intact contractile ring. Functionally, one model is that CYK-1 contributes to contractile ring dynamics, while AIR-2 and ZEN-4 may be involved in membrane secretion.

Finishing Cytokinesis in Yeast and Animal Cells

Models for ring constriction. Numerous models have been proposed to explain the mechanism of actomyosin ring constriction in animal cells. In the classical model of cytokinesis, myosin-driven constriction at the cell equator is sufficient to cause furrowing (56, 118, 153). In contrast, the polar relaxation theory supposes that it is global contraction combined with relaxation of the cortex at cell poles which leads to medial constriction (279).

Recent experiments have begun to reveal the mechanics behind cytokinesis (214). Using atomic force microscopy, Matzke et al. were able to record mechanical measurements of the cell cortex during the cell cycle and cytokinesis in mammalian cell cultures (163). It was observed that global "stiffness" of the cell cortex was higher in metaphase compared to interphase. Global stiffness increased until anaphase onset, and then the equatorial region where the cleavage furrow was to form began to show a higher degree of stiffness than background global stiffness. During furrowing, equatorial stiffness reached up to 10-fold higher than background stiffness, probably as a result of cytoskeletal and associated components concentrating and contracting at the cleavage site. Such an observation indicates that forces generated by cytokinesis are not distributed across the entire cell cortex, perhaps ensuring that furrowing remains concentrated at the cell middle.

In another approach to understanding how cortical regions of cells contribute to cytokinesis, O'Connell et al. applied localized cytochalasin D treatment to disrupt actin-based cellular functions in mammalian cells (194). When applied to the equatorial region, cytokinesis seemed to be facilitated, probably as a result of weakening the equatorial stiffness. In contrast, when applied between the spindle pole and distal end of cells, cytokinesis was inhibited, indicating that polar cortices somehow "communicate" with the equatorial cortex during cytokinesis. In a reciprocal experiment, cells were treated with the drug jasplakinolide, which stabilizes actin filaments. When this drug was applied to the equatorial region, cytokinesis was inhibited; however, cytokinesis was unaffected when it was applied to polar regions. While Matzke et al. indicate that the cortex is not elastic and focuses cortical stiffness to the cleavage furrow, O'Connell et al. emphasize that the equatorial region alone is not sufficient to complete cytokinesis, but rather division involves coordination of the entire cell cortex. Future studies comparing such high-resolution mechanical measuring with genetic and biochemical studies will be crucial in fully characterizing the interface between the mechanical forces of cleavage and the molecules that generate them.

Yeast cell and cells of the filamentous fungus *Aspergillus nidulans* are different from animal cells in that a septum forms centripetally through the deposition of cell wall material behind the constricting actomyosin ring. Studies with *S. pombe* suggest that the actomyosin ring requires septum formation for its ability to constrict (107, 145). One explanation for the difference between yeast and animal cells is that in yeast, the contractile force of the ring may not be sufficient to counteract the turgor pressure of the cell without cell wall formation. Perhaps the primary purpose of the ring is to localize and guide septum formation. This is consistent with the fact that the actomyosin ring is not essential in *S. cerevisiae*, possibly because the bud neck is quite narrow and an actomyosin ring is not essential to guide septum formation.

Membranes, vesicles, and cytokinesis. Based on early morphological studies of plants, it seemed clear that vesicle fusion and secretion might play a role in plant cytokinesis; however, the idea that cytokinesis in animal cells might also require secretion has only recently gained wide acceptance. It was thought that actomyosin-based constriction of the ring is sufficient to pinch a cell in two and there is no need to add new membrane to get the process to work. Nonetheless, it seems reasonable to suggest that membrane addition could contribute to cytokinesis. First, addition of new membrane to the furrow may facilitate constriction of the ring by reducing the

force necessary for ring constriction. The ring would be required not simply to pull in the plasma membrane but to guide the direction of furrowing, as in yeast cells. Second, secretion to the furrow could be important for delivery of membrane proteins specifically to the furrow to facilitate cytokinesis. Third, vesicle delivery could play a role in the final stage of membrane fusion at the end of cytokinesis, as in plant cells.

Early evidence of a role for secretion in animal cell cytokinesis came from pioneering work using cleaving *Xenopus* embryos. These early studies suggested that the cleavage furrow is formed by fusion of new Golgi-derived membrane near the leading edge of the furrow (26, 30, 234). Later studies suggested that this vesicle delivery depended on a specialized array of microtubules at the cleavage furrow termed the furrow microtubule array (FMA) (Fig. 3B). Using confocal microscopy on dividing *Xenopus* eggs, Danilchik et al. observed the FMA as a V-shaped array of microtubules emanating from a point just ahead of the advancing furrow that seems to form from spindle midzone microtubules (54). Appearance of this array is coincident with furrow ingression and new membrane insertion and is suggestive of an active role for microtubules in membrane insertion during furrowing. In fact, using depolymerizing drugs, it was shown that disrupting the microtubule cytoskeleton blocked new membrane insertion and cytokinesis while disrupting the actin cytoskeleton neither blocked new membrane assembly nor displaced the FMA but did block furrow ingression (54, 219). It also should be noted that once these embryos reached the midblastula stage, FMAs disappeared and were replaced by midbody-like structures similar to those found in somatic cells, suggesting this specialized structure for membrane delivery may only be needed for cytokinesis in large cells.

FMAs are also found associated with furrows in dividing blastomere stage zebra fish embryos (105). These studies indicated that secretion to the furrow may be important for delivery of membrane proteins specifically to the furrow (after cytokinesis in early embryonic cells, daughter cells do not move apart but rather tightly adhere in a cadherin-dependent process called cohesion). These data suggest that during furrowing, FMAs deliver specific cargoes to the cleavage site, probably as membrane vesicles. In support of this, labeling of membranes in dividing blastomeres indicated that new membrane accumulates near furrows in a microtubule-dependent manner (105). Genetic evidence is also consistent with this hypothesis. In a mutant screen for zebra fish maternal effect mutations, the gene *nebel* was identified as having cell adhesion defects (203). *nebel* mutants have a defective FMA and do not effectively localize β-catenin or concanavalin A (another cleavage plane marker) to the cleavage site; however, other microtubule structures appear normal. Initiation of furrowing occurs in *nebel* mutants, but blastomeres fail to adhere, and in some cases the furrows regress. This suggests that target delivery of cell adhesion molecules may allow for dividing cells to be adhered behind the constricting furrow, lessening the force required for constriction and thereby promoting cytokinesis. This mechanism seems similar to the targeted delivery of cell wall-synthesizing enzymes in yeast, without which the actomyosin ring is unable to constrict (145).

Several motor proteins, both plus and minus end directed, localize to the spindle midzone region (discussed above). It will be interesting in future studies to determine what motors use these specialized FMAs and what cargoes they transport. It is also not clear whether FMAs are a universal feature of dividing cells or specific to early embryos. Recently Skop et al. inhibited secretion in early *C. elegans* embryos with a drug and found that the spindle midzone appeared intact and furrow ingression initiated normally, but furrows soon regressed, resulting in failed cytokinesis (236). Using a membrane probe, it was also observed that membrane accumulation occurred at the apices of late cleavage furrows, which form the intracellular bridge (236). The authors propose that the final stage of cell separation in animal cells may be quite similar to cytokinesis in plants, with the spindle midzone or midbody serving a function similar to that of the phragmoplast in plants.

One thing is clear: microtubule networks are important for targeted vesicle delivery to the furrow. Once there, vesicles need to be directed to fuse to appropriate membranes. The first definitive hint that targeted vesicle fusion machinery contributed to cytokinesis came from the identification and characterization of the SNARE family member KNOLLE (*syntaxin*) and KEULE (*s-1*) genes in plants (discussed above). Recently, genetic studies have suggested a role for vesicle fusion proteins in cytokinesis in animal cells. In *Drosophila*, *syntaxin1* is required for a specialized form of cell division in the early embryo called cellularization (29). In the *Drosophila* early blastoderm, a syncytium of about 6,000 nuclei is located in the peripheral cytoplasm. During interphase of cycle 14, membrane vesicles that were concentrated in the periplasm are redistributed to align between the nuclei (148). These vesicles fuse to form double membranes, which continue to recruit additional vesicles, ultimately building a membrane that encircles each nucleus. During cellularization, syntaxin1 protein is localized to newly forming cell surface and cleavage furrows, and lack of syntaxin1 causes cellularization to fail, generating large acellular patches (29). Also in *C. elegans* it was discovered that disruption of the syntaxin *syn-4* (103) or *rab-11* (236) caused defects in early embryonic cleavage divisions.

Another family of proteins that may be important for vesicle fusion during cytokinesis is the septin family (74, 113). As described earlier, septins are conserved in most eukaryotic organisms with the exception of plants and function in regulating cell morphological changes. How might septins function in vesicle fusion during cytokinesis? Two reports of septin-interacting proteins have shed light on this question. Using coimmunoprecipitation experiments, Hsu et al. found that septins associated with the exocyst complex, which is required in yeast for transport of Golgi-derived vesicles (77, 94, 100). The exocyst is a large complex that functions in vesicle fusion and is thought to help target vesicles to specific sites at the plasma membrane (100). A second septin-interacting protein was identified as the SNARE protein syntaxin. Two septins, CDCrel-1 and Nedd5, were found to physically associate with syntaxin in a complex (21). Overexpression of CDCrel-1 inhibits exocytosis, while overexpression of a dominant negative mutant can enhance exocytosis, an effect that can be alleviated by coincidently preventing SNARE complex formation. These reports suggest that septins may function in both targeting of membrane vesicles through interactions with the exocyst complex and mediating membrane fusion in conjunction with SNARE proteins.

COORDINATION OF CYTOKINESIS WITH NUCLEAR CYCLE

One crucial aspect of cytokinesis in eukaryotes is that it is absolutely essential that cytokinesis not occur prior to segregation of chromosomes. Failure to delay cytokinesis until after mitosis can result in aneuploidy and polyploidy. Thus, it is not hard to imagine that cells have evolved multiple ways to inhibit cytokinesis until chromosomes have been segregated. The best-known regulators of cell cycle progression are the cyclin dependent kinases (CDKs); however, Polo kinase has recently acquired status perhaps on par with CDKs with respect to controlling mitosis and cytokinesis. We are also now aware, at least in yeast, of complex signal transduction networks that coordinate mitotic exit and cytokinesis with progression through mitosis; however, there are hints that some aspects of these regulatory networks are conserved.

CDK

Cytokinesis is carefully regulated so that it is precisely coordinated with other events of the cell cycle and does not occur until chromosomes have been segregated. In eukaryotic cells, transitions between different phases of the cell cycle are driven by CDKs consisting of protein kinase and cyclin subunits. Cytokinesis normally depends on prior entry into mitosis, which requires the CDK Cdk1 and its cyclin partner cyclin B. Activation of Cdk1 is regulated by phosphorylation, and inhibition occurs through cyclin destruction, which initiates at anaphase onset (197). Expression of a stable nondestructible cyclin causes cells to become blocked in anaphase and to fail to undergo cytokinesis (251, 278, 284). Mammalian cells injected with nondestructible cyclin B undergo anaphase and chromosome segregation but do not form a spindle midzone and fail cytokinesis (278). Interestingly, in these cells, the passenger protein TD-60 does not redistribute from the centromeres to the spindle midzone, perhaps explaining the failure of these cells to form a spindle midzone. Coupling cytokinesis to CDK inactivation is one key mechanism for cells to ensure that division is not initiated until chromosomes have been separated. However, the exact mechanism by which CDK activity inhibits cytokinesis is not known.

Another potential role for CDK activity is to inhibit myosin through inhibitory phosphorylation of the myosin RLC (171, 217, 259). Myosin RLC can be phosphorylated by Cdk1, which inhibits its actin-activated ATPase activity in vitro. Phosphorylation of the RLC at a different site by myosin light chain kinase promotes actin-activated ATPase activity in vitro (223). It has been shown that inhibitory phosphorylation increases early in mitosis and subsequently decreases, coincidently with Cdk1 inactivation in anaphase. Simultaneously, activating phosphorylation of RLC increases (283). It is not entirely clear which kinases perform these phosphorylation events in vivo. For example, although myosin light chain kinase is thought to be responsible for activating phosphorylation of RLC, AIM-1 (182) and Rho-kinase (122) are also capable of this phosphorylation. Moreover, activating phosphorylation of RLC seems to be important for cytokinesis in vivo (109, 121), but it is not clear how significant Cdk1 phosphorylation of RLC is for regulating cytokinesis (232). It seems likely that CDK phosphorylation inhibits cytokinesis through numerous mechanisms.

Polo Kinase

Polo kinase, like Cdk1, has numerous functions in mitosis. Polo kinase is required for centrosome maturation, spindle formation, Cdk1 activation and inactivation, and cytokinesis (187). Polo may function in cytokinesis by promoting cyclin B destruction and CDK inactivation (59, 123, 124, 228). Polo kinase also seems to play a more direct role in regulating cytokinesis. Polo kinase associates with the CHO-1/MKLP-1 kinesin (59) and is required for spindle midzone and cleavage furrow formation in *Drosophila* (6, 33). In addition, *S. pombe* and *S. cerevisiae* polo kinase homologs, Plo1p and Cdc5p, respectively, appear to have several functions during cytokinesis (15, 198, 243, 255). Consistent with a direct role in cytokinesis, Polo kinase localizes in animal cells to kinetechores and then to the spindle midzone and the midbody (12, 89, 129, 147, 179), and in *S. pombe* and *S. cerevisiae* it localizes to the actomyosin ring (15, 181, 244).

Signal Transduction Pathways and Timing Cytokinesis

SIN. In yeast cells, signal transduction pathways have been identified that function to coordinate late mitotic events with cytokinesis. One such pathway in fission yeast is the septation initiation network (SIN) (17, 167). SIN mutants can form actomyosin rings but fail to initiate constriction of the ring and become multinucleate (18, 71). The SIN is a GAP kinase cascade consisting of three protein kinases (Cdc7p, Sid1p, and Sid2p) (68, 93, 245) and one small GTPase, Spg1p (220). Additionally, the Cdc14p (69) and Mob1p (99, 216) proteins function as subunits of the Sid1p and Sid2p kinases, respectively. All SIN components localize to the SPB (Fig. 5A). Sid4p and Cdc11p form a complex which localizes constitutively to the SPB and seems to function as a scaffold required for localization all known SIN components to the SPB (40, 93, 99, 125, 134, 245). While eight of the SIN genes are required for septation, mutations in two (*cdc16* and *byr4*) lead to continuous septation in the absence of nuclear division cycles, indicating that they act antagonistically to the others (179, 242). Cdc16p and Byr4p function as part of a two-component GAP for Spg1p (84). A GEF for Spg1p has not been identified; however, it is thought that Plo1p kinase may promote the formation of Spg1p-GTP (255).

In interphase Cdc16p-Byr4p localize to the SPB (36, 134), and consistent with this, Spg1p is at the pole but in the inactive GDP-bound state (241). As the mitotic spindle forms during metaphase, Spg1p becomes activated at both SPBs (GTP-bound form), and Cdc16p-Byr4p leave both SPBs (36, 134). Cdc7p is recruited to the SPB by the GTP-bound form of Spg1p, to which it binds directly (241). During anaphase B Cdc16p-Byr4p returns to one SPB (36, 134). Spg1p is inactivated and Cdc7p becomes delocalized at that SPB, giving rise to a poorly understood asymmetric state. Cdc7p activity remains constant throughout the cell cycle, but it presumably finds its substrate(s) only when targeted to an SPB. Cdc7p is then required for recruitment of Sid1p-Cdc14p to the single Cdc7p containing SPB in anaphase (93). Sid1p-Cdc14p are

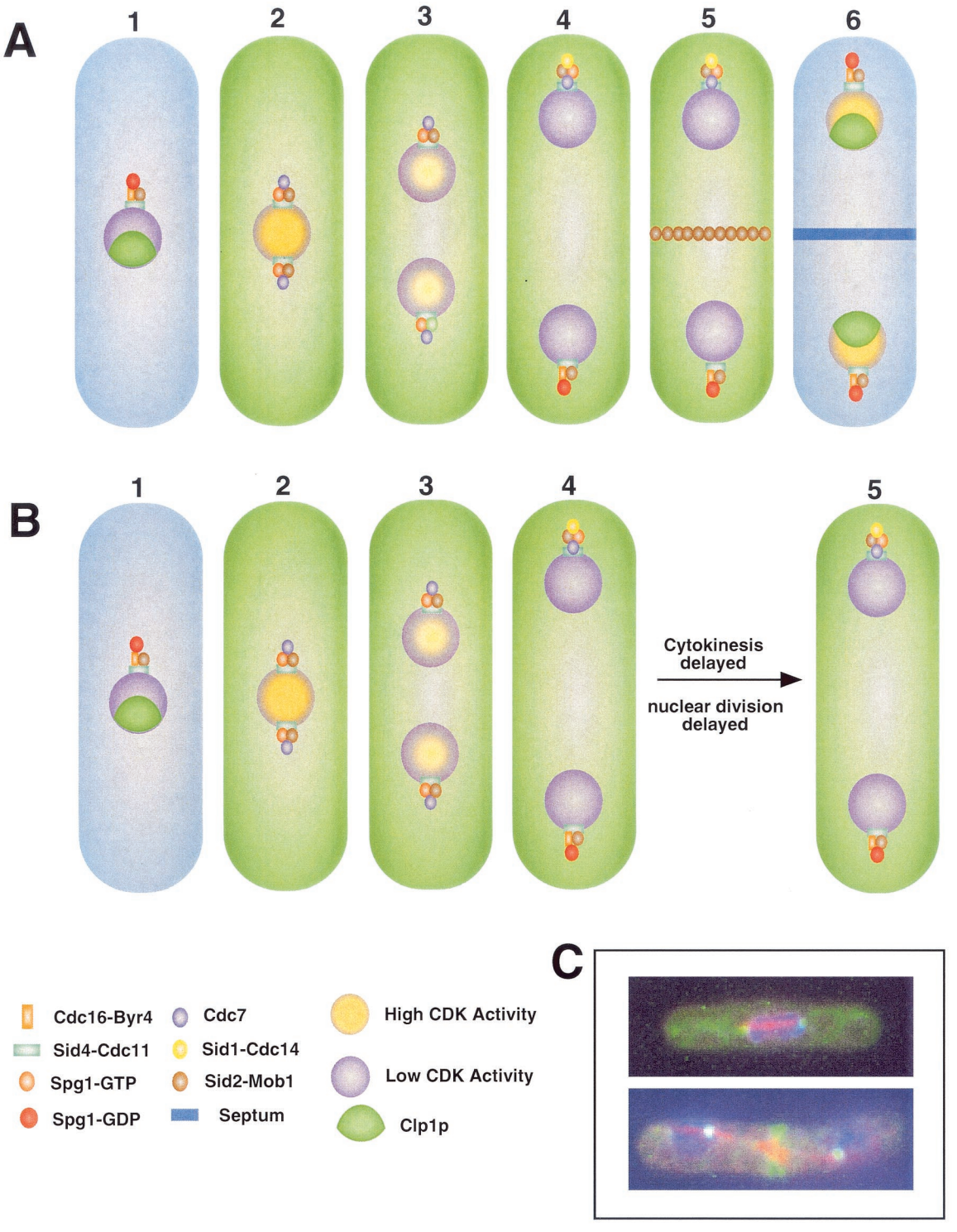

FIG. 5. Model for localization of the SIN proteins in fission yeast. (A) The SPB is a regulatory headquarters for the organization and activation of the SIN pathway. (Panel 1) In interphase Clp1p is in the nucleolus, CDK activity is low, and Sid4p-Cdc11p, Cdc16p-Byr4p, and Spg1-GDP localize to the SPB. (Panel 2) Upon entry into mitosis, CDK activity becomes high, Clp1p leaves the nucleolus, Cdc16p-Byr4p leave both SPBs, and Spg1p converts to the GTP-bound form, which recruits Cdc7p to the SPB. Note that Clp1p also localizes to the SPB, spindle, and actomyosin ring; however, this has been omitted for simplicity. Upon anaphase onset, CDK activity begins to drop (panel 3), and then Cdc16-Byr4p return to one SPB, which results in conversion of Spg1-GTP to Spg1-GDP and loss of Cdc7p from that SPB (panel 4). In addition, Sid1p-Cdc14p are recruited to the Cdc7p-containing SPB. (Panel 5) Just prior to initiation of cytokinesis, the Sid2p-Mob1p complex localizes to the division site and is thought to deliver the signal to divide to the actomyosin ring. (Panel 6) Once the septum has fully formed, the cell returns to the interphase state. (See text for references.) (B and C) SIN proteins and the cytokinesis checkpoint. (B) In cells that have defects in actomyosin ring formation, SIN pathway activation proceeds normally; however, cells undergo a prolonged delay with the SIN "on," Clp1p out of the nucleus, and CDK activity low, which blocks further nuclear division cycles until cytokinesis is complete. (See text for references.) (C) Sid2p-green fluorescent protein (green) localization in early anaphase (above) and in telophase (below). DNA (blue) and tubulin (red) are also shown.

then presumed to function to activate Sid2p-Mob1p and cause them to translocate to the actomyosin ring to trigger ring constriction and septation (Fig. 5C) (93, 245).

Inactivation of Cdc16p or Byr4p in G_1 phase, when CDK activity is normally low, or in cells blocked in G_2 phase by inactivation of Cdc2p, leads to inappropriate septation. However, inactivation of Cdc16p in G_2 phase when CDK activity has not been inhibited does not lead to uncontrolled septation (36). Thus, Cdc16p-Byr4p seems to function to ensure that cells do not initiate cytokinesis during interphase when CDK activity is low (36, 134). These results indicated that, in *S. pombe*, CDK inhibition of cytokinesis seems to function through inhibition of the SIN. This effect appears to be mediated, at least in part, through the Sid1p kinase, whose localization is inhibited by Cdc2p kinase (41, 93). Interestingly, cells expressing a nondestructible cyclin arrest in anaphase B with Cdc7p at both poles, indicating that CDK inactivation is also important for asymmetric activation of Spg1p; however, the functional significance of this is unclear (41).

Since Cdc2p inactivation occurs coincidently with chromosome segregation, coupling initiation of cytokinesis to Cdc2p inactivation ensures that cell division does not initiate before chromosomes have been segregated. However, this mechanism renders cytokinesis sensitive to Cdc2p activity, which begins to rise as the next cell cycle initiates around the time of septation (160). If cytokinesis is delayed, the rising Cdc2p activity could inhibit the SIN and cytokinesis unless the cell has a way to inhibit CDK activity until cytokinesis is complete. Evidence for a cytokinesis checkpoint to ensure that cytokinesis is complete before initiation of the next nuclear division cycle was revealed through characterization of cytokinesis mutants defective for either actomyosin ring formation or septum synthesis (Fig. 5B) (133, 144, 145, 263). These mutants complete mitosis and then arrest the cell cycle after failing cytokinesis with two interphase nuclei. The block in nuclear division is relieved by inactivation of either the CDK inhibitory kinase Wee1p; the SIN (133, 144, 145); or Clp1p/Flp1p, the *S. pombe* homolog of the *S. cerevisiae* Cdc14p phosphatase (51, 263). Clp1p/Flp1p localizes to the nucleolus and SPB in interphase, and then in mitosis it exits the nucleolus and localizes to the mitotic spindle and actomyosin ring. Once cytokinesis is complete Clp1p/Flp1p relocalizes to the nucleolus. It appears that Clp1p/Flp1p functions to keep CDK activity low by promoting inhibitory tyrosine phosphorylation of the *S. pombe* CDK, Cdc2p (263). This lets the SIN stay on until cytokinesis is complete. When cytokinesis fails or is delayed, the SIN keeps Clp1p out of the nucleolus until cytokinesis can be completed. This complex feedback loop helps keep cells from becoming multinucleate and thus polyploid when cytokinesis is delayed.

MEN. In *S. cerevisiae* the pathway analogous to the SIN is termed the MEN (see Table 3 for a comparison of SIN and MEN genes). Like the SIN, the MEN appears to be a GAP kinase cascade, whose components localize to both the SPB and the bud neck (167). At present, the MEN consists of four protein kinases (Cdc5p, Cdc15p, Dbf2p, and Dbf20p), a GTPase (Tem1p), an exchange factor (Lte1p), a protein phosphatase (Cdc14p), and a Dbf2p binding protein (Mob1p) (108, 116, 151, 220, 229, 230, 260, 271). Additionally the SPB component Nud1p seems to function to anchor MEN proteins at the cytoplasmic face of the SPB (92). Lte1p is presumed to activate Tem1p, which then recruits Cdc15p to the SPB(s) (19, 204). Cdc15p is thought to activate Dbf2-Mob1 (131, 159). The MEN functions in anaphase to inhibit CDK activity and cause mitotic exit by promoting release of the Cdc14p phosphatase from the nucleolus by an unknown mechanism (231, 268). Cdc14p then dephosphorylates a number of CDK substrates, including Cdh1p/Hct1p and the CDK inhibitor Sic1p (269). Dephosphorylation by Cdc14p stabilizes Sic1p and also causes activation of Cdh1p/Hct1p, which promotes cyclin B proteolysis. Together, these events result in CDK inactivation and exit from mitosis.

TABLE 3. SIN and MEN components

S. pombe gene	Protein function	*S. cerevisiae* homolog
plo1	Kinase	*CDC5*
sid4	SPB scaffold?	Unknown
cdc11	SPB scaffold?	*NUD1*
spg1	GTPase	*TEM1*
cdc7	Kinase	*CDC15*
sid1	Kinase	Unknown
cdc14	Sid1 binding	Unknown
sid2	Kinase	*DBF2*
mob1	Sid2/Dbf2 binding	*MOB1*
clp1	Phosphatase	*CDC14*
cdc16	Part of GAP	*BUB2*
byr4	Part of GAP	*BFA1/BYR4*

The key function of the MEN appears to be in promoting mitotic exit. How then does the MEN become activated in anaphase? As described in *S. pombe*, Cdc16p-Byr4p function to inhibit signaling through the SIN (70, 84, 242). Following this up, several groups showed that budding yeast Bub2p and Bfa1p, the *S. pombe* Cdc16p and Byr4p homologs, respectively, function in a separate branch of the spindle checkpoint to inhibit mitotic exit through inhibiting the MEN (9, 73, 79, 138). It was unclear, however, what cellular event this branch of the spindle checkpoint monitored. A clue came from study of the timing of cell division in mutants with defects in orienting their mitotic spindle along the axis between the mother cell and bud (66, 139, 287), which causes anaphase to initiate with the spindle confined to the mother cell. Yeh and colleagues discovered that cells containing anaphase spindles within the mother cell delay exit from mitosis and cytokinesis until the spindle becomes properly oriented (287). This checkpoint was subsequently shown to require the microtubule end binding protein EB1/Bim1p (180). Recently, several laboratories have shown that this checkpoint also requires Bub2p and Bfa1p (19, 25, 55, 204, 272).

How is this spatial information integrated with the mitotic exit machinery? Major insight into this question has come from localization studies (Fig. 6). Two laboratories have demonstrated that Lte1p, the putative exchange factor for the Tem1p GTPase, localizes specifically to the bud (19, 204). Bub2p, Bfa1p, Tem1p, and Cdc15p localize to the cytoplasmic face of the SPB in anaphase (19, 35, 55, 204, 282). Although not all reports are in agreement, the MEN components Bub2p and Tem1p seem to preferentially localize to the SPB that enters the bud (19, 204). These data suggest a model by which passage of one end of the spindle through the bud neck allows Lte1p to activate Tem1p, which then binds to Cdc15p (19, 204). The

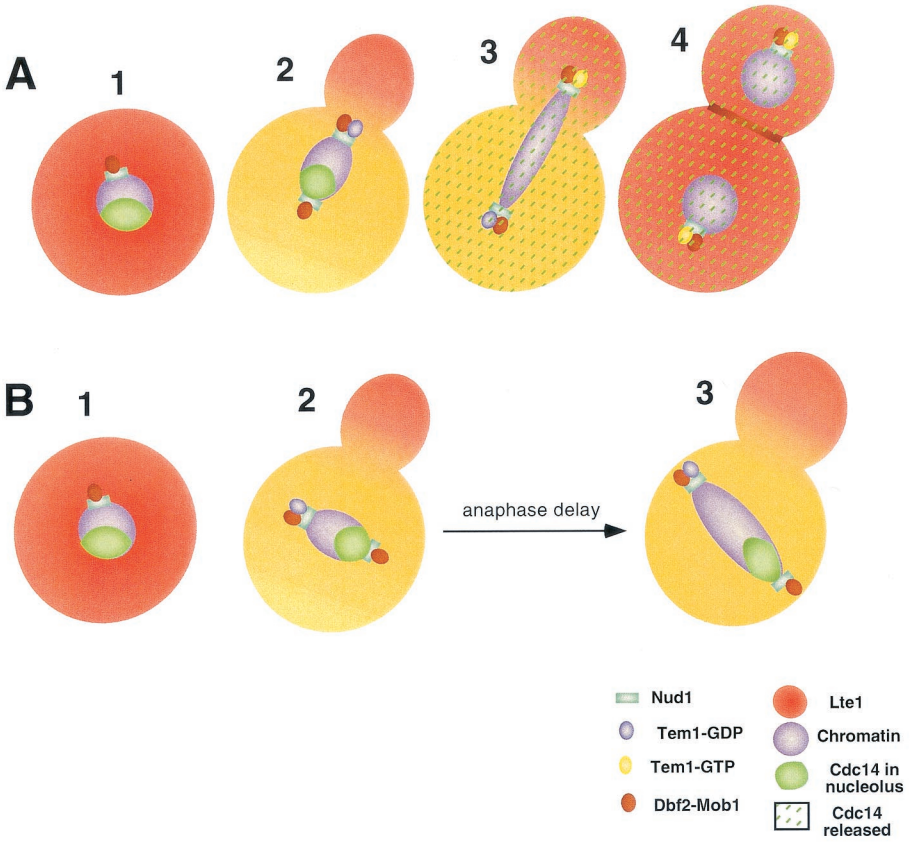

FIG. 6. Model for activation of the MEN in budding yeast. (A) (Panel 1) In G_1 phase Cdc14p localizes to the nucleolus, Lte1p is diffuse, and Nud1p is at the SPB, as is Dbf2p-Mob1p (reports differ [see text] about whether Dbf2p-Mob1p localizes to the SPB in interphase). Also note that because there is no consensus for the Cdc15p localization pattern, it is not shown. (Panel 2) After bud emergence, the nucleolus migrates to the bud neck, Tem1p localizes to the SPB closest to the bud neck, and Lte1p localizes to the bud. (Panel 3) Upon anaphase onset, the spindle elongates into the bud, bringing Tem1p close to its activator, Lte1, causing it to be activated. This leads to activation of the MEN and release of Cdc14p from the nucleolus. (Panel 4) In telophase Cdc14p promotes mitotic exit, localization of Dbf2p-Mob1p to the bud neck, and cytokinesis. (B) The MEN and the spindle orientation checkpoint. Mutants that have defects orienting the mitotic spindle behave normally in G_1 (panel 1) but have defects in orienting the mitotic spindle after bud emergence (panel 2). This causes Tem1p not to be brought into contact with its activator Lte1p (panel 3), keeping it in the inactive state, which causes a delay in Cdc14p release from the nucleolus. Thus, cells delay mitotic exit and cytokinesis until the spindle becomes properly oriented.

kinase activity of Cdc15p does not appear to be regulated (104), so it seems likely that its recruitment to the SPB (35, 282) by Tem1p allows access to its substrates, possibly including Dbf2p. Dbf2p is not required for localization of Cdc15p (35); however, Dbf2p does require Cdc15p to become activated (80, 159), suggesting that Dbf2 functions downstream of Cdc15p.

Recent evidence suggests that the MEN, like the SIN, also plays a more direct role in cytokinesis, although this function does not appear essential. Cells in which the requirement for the MEN in mitotic exit has been relieved are viable but still have defects in cytokinesis (142, 150, 168). Moreover, certain alleles of *cdc15* have been identified that are specifically defective for cytokinesis (106, 168). The intracellular localization of some MEN components is also consistent with a role in cytokinesis, as Cdc15p (282), Cdc5p (45, 244), and Dbf2p-Mob1p (81, 289) have been observed to localize at the bud neck. The MEN is required to promote splitting of the septin ring and constriction of the actomyosin ring in telophase (47, 142); however, as with the SIN, it is not yet clear at a molecular level how the MEN triggers cytokinesis.

There is also evidence that MEN function in cytokinesis is inhibited by CDK activity, similar to the SIN in *S. pombe*. For instance, the MEN promotes release of Cdc14p from the nucleolus; however, Cdc14p seems to also promote the cytokinesis function of the MEN. In early mitosis, Cdc15p is phosphorylated by Cdk1, and in late mitosis as CDK activity drops, Cdc15p becomes dephosphorylated by Cdc14p (168, 282). Dephosphorylation of Cdc15p seems to be important for its ability to promote cytokinesis but not mitotic exit (168). Cdc14p may also be important for regulating Dbf2p-Mob1p localization, since Dbf2p becomes activated in *cdc14* mutants (131, 159) but does not localize to the bud neck (81, 289). This is reminiscent of observations of *S. pombe* showing that the SIN is inhibited by CDK activity to ensure that cytokinesis does not occur until exit from mitosis is complete.

Signaling cytokinesis in higher eukaryotes. It is worth asking whether animal cells would need regulatory networks similar to

the SIN and MEN. Budding yeasts face a unique challenge in having to orient the mitotic spindle such that it can elongate through the narrow bud neck. Because of this, it is unclear whether the spindle orientation checkpoint functioning through a MEN-like pathway would be conserved in other species. However, it has been observed that mammalian cells with misoriented mitotic spindles delay exit from mitosis until the proper orientation is established, suggesting that animal cells may also have a checkpoint analogous to the *S. cerevisiae* spindle orientation checkpoint (195). Additionally, it has been observed that similar to *S. pombe* cells, mammalian cells in which cytokinesis has been blocked delay the following nuclear cycle (11, 161).

At present it is not clear if signaling pathways exist in mammalian cells analogous to the SIN and MEN; however, evidence suggests that many SIN- or MEN-related proteins are conserved in higher eukaryotes. There are a number of kinases related to Sid2p/Dbf2p in animal cells (our unpublished observations). Interestingly, the Sid2p/Dbf2p-related kinase human Warts has a localization pattern similar to that of Sid2p/Dbf2p. Human Warts localizes to centrosomes and then the spindle midzone and midbody and functions in cell division control (98, 190). Moreover, the Sid2p/Dbf2p binding protein Mob1p is highly conserved from yeast to human cells, suggesting the possibility that Mob1p may be a conserved regulator of these types of kinases (151). A GAP, human GAPCenA, which is related to Cdc16p-Bub2p, also localizes to centrosomes (52). Two human homologs of Clp1p/Flp1p/Cdc14p phosphatase called CDC14A and CDC14B have also been identified (137) and seem to be involved in antagonizing CDK activity as in yeasts (143). Thus, while there are some tantalizing hints that the SIN and MEN may be conserved in animal cells, there is as yet no definitive proof.

A key aspect of the SIN and MEN is that the SPB serves as a regulatory site or signaling "headquarters" to organize the pathway. A recent study has shown human centrosomes, which are analogous to yeast SPBs, play a key role in completion of cytokinesis (205). It was observed in a human cell line that after furrow ingression completes, daughter cells remain linked for a few to several hours by a structure termed a cytoplasmic bridge. Separation of this bridge, termed abscission, completes cytokinesis. Using time-lapse video microscopy of cells stably expressing the centrosomal protein centrin fused to green fluorescent protein as a centrosomal marker, Piel et al. observed that immediately before abscission, the mother centriole transiently and quickly migrates to the intracellular bridge near the midbody (205). Each centrosome is comprised of two distinguishable centrioles, a mother and daughter. Only when the mother centriole moved back from the bridge to the center of the cell did cytokinesis (abscission) finish. This is reminiscent of previous observations in which centrosomes, in association with the Golgi complex, appear to shift localization from poles to the intracellular bridge and back at the end of mitosis (155, 176). These observations suggest that centrosomes and associated organelles must temporally and spatially come in close contact with the midbody for completion of cytokinesis to occur. In fact, observations of cell division in BSC1 cells in which the centrosome was surgically removed, or in an acentriolar *Drosophila* cell line, showed that a high frequency of these cells specifically failed cytokinesis (205). What function might this centrosome repositioning serve? Since Golgi complex associates with migrating centrosomes, this transient movement may deliver membrane and secretory vesicles required for complete cell separation. However, another exciting possibility is that centrosomes harbor regulatory components required for mitotic exit and cytokinesis, as in budding and fission yeasts.

CYTOKINESIS AND DEVELOPMENT: VARIATIONS ON THE COMMON THEME

Throughout this review we have generalized cytokinesis as an event that routinely occurs at the cell equator and inevitably results in physical partitioning of a mother cell into two equal daughters. Nature, however, has provided us with some beautiful examples of how multicellular organisms have modified traditional cytokinesis to aide the developmental process.

Asymmetric Division

In most cases, cell division is symmetric in that cytokinesis results in two equal daughter cells. However, in many developing organisms, asymmetric cell division provides an important mechanism for determining the fate of cells (Fig. 7A) (119). During asymmetric division, an axis of polarity is established in the mother cell, and the mitotic spindle reorients along this axis. Cell fate determinants are then asymmetrically segregated in the cell such that cytokinesis produces unequal daughter cells containing different concentrations of fate-determining molecules. Different concentrations of determinants induce different developmental outcomes for each daughter cell. The bulk of our knowledge of asymmetric cell division has come from experiments in the *C. elegans* zygote and *Drosophila* neuroblast. Several conserved proteins, including the Par proteins (for "partitioning defective") have been identified that are required for asymmetric divisions; however, the mechanism of how the spindle orients and subsequently triggers cytokinesis is not known. One recent report which analyzed the role of centrosomes and astral microtubules in *Drosophila* neuroblast divisions concluded that astral microtubules are not required for signaling or positioning cytokinesis (87), consistent with the spindle midzone being required for positioning the cleavage furrow.

Incomplete Cytokinesis

During *Drosophila* oogenesis, the ability to arrest cytokinesis is fundamental in oocyte maturation (213). Drosophila oogenesis begins with the asymmetric division of a stem cell into a daughter stem cell and a cystoblast. The cystoblast undergoes four rounds of mitosis in the absence of intervening cytokinesis, producing a 16-germ-cell syncytium. At each would-be cleavage site, cytokinesis is arrested and specialized cytoskeletal structures called ring canals are formed at cleavage furrows. Ring canals (Fig. 7B)—which are composed of actin, anillin, and other proteins similar to traditional cleavage furrows—form intracellular bridges between germ line cell chambers. These bridges are important for allowing transport of cytoplasm and organelles into the developing oocyte.

Pseudocleavage

During syncytial divisions (mitosis in the absence of cytokinesis) in the developing *Drosophila* embryo, actin is observed

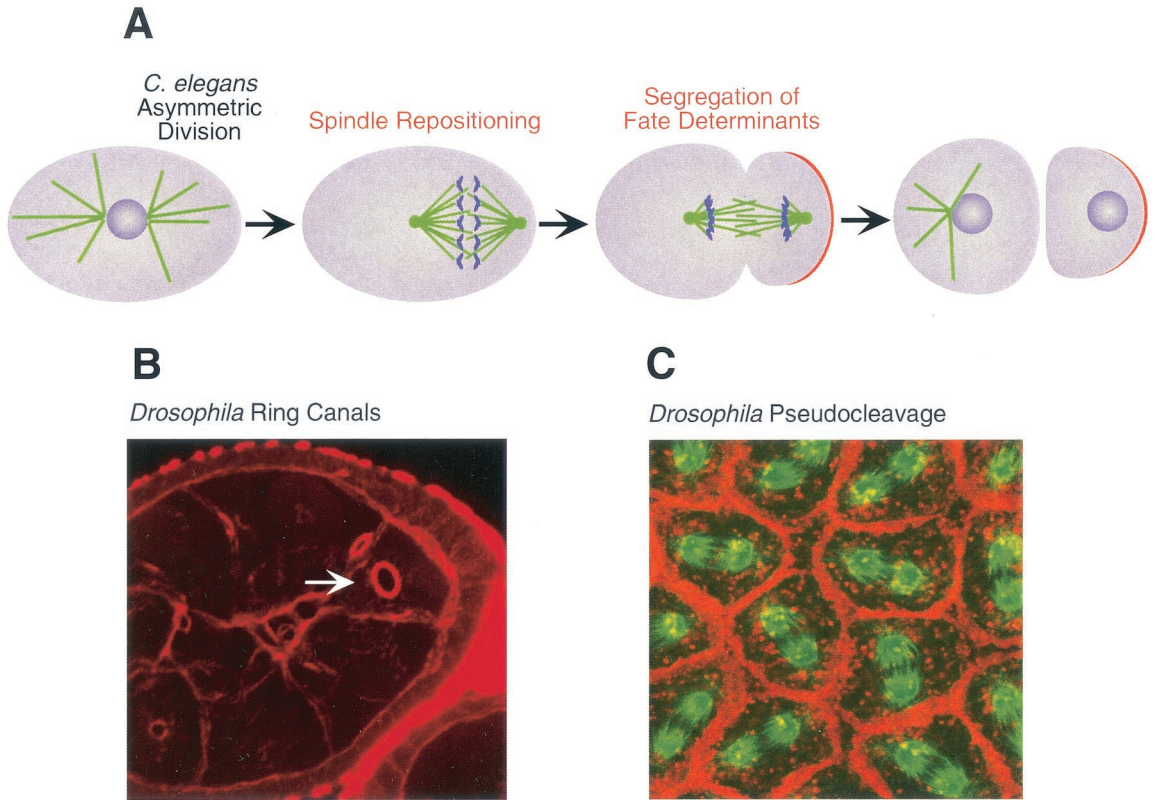

FIG. 7. Variations of traditional cytokinesis important for development. (A) Many organisms, including *C. elegans*, reposition the spindle such that cytokinesis will result in unequal-size daughter cell's. By segregating specific fate determinants (red) into the daughters, an asymmetry is established that is important for determining a cell's developmental outcome. (B) In *Drosophila* embryogenesis, incomplete cytokinesis produces a specialized structure called the ring canal. Ring canals (arrow) serve as intracellular bridges in which cytoplasm is shared between adjacent cells and the oocyte. (C) During syncytial divisions in the developing *Drosophila* embryo, actin (red) ingresses into a pseudocleavage furrow around nuclei during mitosis and is thought to prevent aberrant interactions between adjacent spindles (green). Once mitosis completes, pseudocleavage furrows disassemble and actin is organized into caps between the plasma membrane and centrosomes (see text).

surrounding nuclei during interphase and mitosis. In interphase, actin is organized into "caps" between the plasma membrane and centrosomes. During late interphase and mitosis, actin reorganizes into a structure called the pseudocleavage furrow that ingresses from the plasma membrane and surrounds each nucleus (Fig. 7C). Pseudocleavage furrows persist until late anaphase, when they regress and reform actin caps. In *scrambled* mutants, the normal assembly of the pseudocleavage furrow is disrupted (250). In the absence of pseudocleavage furrows, chromosomes can interact with adjacent spindles and do not segregate properly, suggesting that the function of the pseudocleavage furrow is to prevent the inappropriate segregation of chromosomes during syncytial divisions. Interestingly, many components of traditional cleavage furrows in addition to actin are found in the pseudocleavage furrow, including myosin II, anillin, septins, and formins. Moreover, these actin rearrangements are tightly linked to the nuclear cycle, making this an attractive model for studying the coordination between cytoskeletal reorganizations and the nuclear cycle.

CONCLUDING REMARKS

The process of cytokinesis is a remarkable example of the force and flexibility of the cytoskeleton. While tremendous advances in cell biology and genetics over the past few years have answered many of our questions regarding how cells divide, there are many mysteries that still challenge researchers. Although many of the molecular components of the division machinery have been identified, and hints as to how some of the parts are put together have been borne out through biochemical studies, how the machine is built and how the different parts work together are not known. In animals, the cleavage furrow is a complex yet dynamic organization of diverse molecules, undermining its precise characterization. The same is surely true for the division machinery in plants. Cytokinesis is not an event that can be easily recapitulated in the test tube. Nor does the initiation of cytokinesis simply follow chromosome segregation in a linear plan of events during cell cycle progression. Rather, it is regulated at multiple points during the cell cycle by a variety of signals, many of which are organism specific. Describing cytokinesis will be a fruitful area of research for some time.

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