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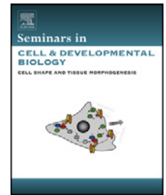

Review

Mechanisms of contractile-ring assembly in fission yeast and beyond

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ABSTRACT

Most eukaryotes including fungi, amoebas, and animal cells assemble an actin/myosin-based contractile ring during cytokinesis. The majority of proteins implied in ring formation, maturation, and constriction are evolutionarily conserved, suggesting that common mechanisms exist among these divergent eukaryotes. Here, we review the recent advances in positioning and assembly of the actomyosin ring in the fission yeast *Schizosaccharomyces pombe*, the budding yeast *Saccharomyces cerevisiae*, and animal cells. In particular, major findings have been made recently in understanding ring formation in genetically tractable *S. pombe*, revealing a dynamic and robust search, capture, pull, and release mechanism.
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1. Introduction

Cytokinesis, the final step of the cell cycle, is the process that divides one cell into two daughter cells containing a full set of chromosomes and other cellular components. Studies in fungi and animal cells have revealed similar steps during cytokinesis in these evolutionarily divergent eukaryotes [1–4]. First, cells define the location for the future cleavage site using positive and negative signaling cues. Then the actin cytoskeleton is drastically reorganized to form an actomyosin-based contractile ring consisting of actin filaments, the motor protein myosin-II, and many actin- and myosin-binding proteins. The subsequent interactions of actin filaments with myosin-II lead to the sliding of actin filaments and constriction of the assembled contractile ring. Lastly, in coordination with ring constriction, targeted secretion delivers membrane fusion machinery to the cleavage furrow, allowing the separation of the two daughter cells.

The fission yeast *Schizosaccharomyces pombe* has emerged as one of the favorite models for cytokinesis studies. Most proteins involved in cytokinesis are evolutionarily conserved from yeast to mammals [1,2,5], so understanding basic cytokinesis mechanisms in *S. pombe* could be applicable to animal cells. More than 130 proteins implied in cytokinesis have been identified and characterized in fission yeast [1,3,6–8], the current challenge is to piece these proteins together to elucidate the molecular mechanisms for cytokinesis. Besides this large inventory, the ability to integrate green fluorescent protein (GFP) and its variants into the genome by homologous recombination has been critical for microscopic

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studies of cytokinesis proteins expressed at their endogenous levels in live cells. Using high-resolution live cell imaging, many key cytokinesis proteins are now temporally and spatially localized, and their global and local concentrations are determined [9]. Combining numerical simulation and microscopy, contractile-ring assembly was mathematically described [10], providing a testable model for the field. Despite significant advances, several open questions remain regarding how cells are able to position, assemble, and contract the actomyosin ring during cytokinesis. This review aims to highlight the mechanism relating to contractile-ring assembly in fission yeast and other organisms.

2. Specification of the division site

Mechanisms that determine the position of the division plane vary depending on species. In *S. pombe*, the division-site selection is finalized at early mitosis and depends on both the nucleus and anillin-like protein Mid1p/Dmf1p. In the budding yeast *Saccharomyces cerevisiae*, the division plane is determined at late G1 phase by the budding site. In animal cells, the division site is dictated by the position of the mitotic apparatus at metaphase/anaphase. In each case, precise location of the division site ensures correct segregation of the nucleus and other components to daughter cells.

2.1. Division-site selection in fission yeast

In the fission yeast *S. pombe*, placement of the contractile ring (4 μm in diameter) and division site always occurs at the cell center, resulting in two daughter cells with equal size. Because *S. pombe* cells do not grow equally from each end after cell separation, the position of the medial cortex changes during cell-cycle progression. Thus, the mechanism by which cells specify their middle must be dynamic. Nuclear position is maintained in the cell middle through opposing pushing forces generated by the interactions between microtubules and cell cortex [11], which determines the localization of the anillin-like protein Mid1p.

Mid1p is crucial to position the division plane [12] and to assemble the contractile ring normally [13,14]. Before mitosis, Mid1p exits the nucleus and binds to the plasma membrane close to the nucleus in a band of ~65 cortical dots, called nodes, by interacting with kinase Cdr2p [12,15–17]. How Mid1p is positioned at the cell equator has attracted more and more attention in recent years. Mid1p localization is regulated by both positive and negative cues. Nuclear position determines Mid1p plasma membrane localization and the division plane [18]. Thus, changing the nuclear position affects the localization of cortical Mid1p nodes [19]. The polo kinase Plo1p interacts with Mid1p and is essential for Mid1p nuclear exit as observed in *plo1-1* mutant [12]. Conversely, Plo1p overexpression induces premature Mid1p cortical accumulation mainly in the hyperphosphorylated form normally found in mitotic cells [12]. Thus, the interaction between Plo1p and Mid1p provides the positive signaling cue for Mid1p localization. However, it is not known whether Plo1p directly phosphorylates Mid1p or which residues are phosphorylated. Negative cues also regulate Mid1p localization: Pom1p (DYRK-family kinase) and other unknown protein(s) inhibit Mid1p localization at the cell poles [20,55]. The balance of the signaling cues restricts Mid1p to the cell equator, allowing the cell to localize the division plane precisely at the center. Then Mid1p acts as a scaffolding protein to recruit other proteins for contractile-ring assembly.

2.2. Division-site selection in budding yeast and animal cells

In the budding yeast *S. cerevisiae*, the 1-μm diameter bud neck bridging the mother cell and the bud is the future cell-division site. Thus, the division site is determined at late G1 phase by the bud-site selection genes [21,22]. Because the mother cell is always bigger than the bud at division, cytokinesis is asymmetric in budding yeast. Five members of the septin family (Cdc3p, Cdc10p, Cdc11p, Cdc12p, and Shs1p/Sep7p) interact with each other to form a collar-like structure at the bud neck serving to anchor the assembly of the actomyosin ring. Type II myosin Myo1p fails to localize to the bud neck in septin mutants [23–25]. By contrast, *myo1* mutation does not affect septin recruitment to the division site, consistent with the model that septins are the scaffolding proteins at the division site in budding yeast.

In animal cells, the position of the mitotic apparatus at metaphase/anaphase dictates the division site. Spindle midzone or astral microtubules, or both are involved in the division-site selection [2], though recent findings reveal that astral microtubules are not necessary for delivering the cytokinesis signals in sea urchin and frog embryos [26]. Accumulating evidence suggests that anillins might act as scaffolding proteins to recruit other proteins to the division site [27,28]. The spatial-temporal regulation of the division plane positioning is covered in more detail elsewhere in this series, and will not be elaborated here.

3. Assembly of an actomyosin-based contractile ring

Fission yeast, budding yeast, and animal cells all establish an actomyosin-based contractile ring during mitosis. Interestingly, although the majority of proteins implied in ring assembly are conserved among different species (Table 1), their temporal and spatial regulation and order of assembly are less conserved, probably reflecting the coordination of ring assembly with some species-specific features like cell size and cell shape. We know more about the stepwise assembly of the contractile ring in fission yeast than in other model systems. Thus, we consider three stages in the assembly process in fission yeast. The stages in budding yeast and animal cells are less distinct and so the assembly of the contractile ring is discussed as a whole.

3.1. Contractile-ring assembly in fission yeast

3.1.1. Formation of cytokinesis nodes

As discussed in Section 2.1, Mid1p is highly regulated to position the contractile ring correctly. However, it is still obscure how cells recognize the Mid1p positioning signal to initiate ring assembly. Mid1p-dependent equatorial nodes have been proposed to be the precursors of the contractile ring in wild-type cells [12,29–32]. The assembly and integrity of nodes are independent of actin filaments. More than 90 min before spindle pole body (SPB) separation, a fraction of Mid1p localizes in a broad band of ~65 nodes on the plasma membrane around the cell center [18]. Between 10 min before and 2 min after SPB separation, this broad band of Mid1p nodes is joined by conventional myosin-II (heavy chain Myo2p and its light chains Cdc4p and Rlc1p), IQGAP Rng2p, F-BAR protein Cdc15p, and the formin Cdc12p [29–32]. These studies find that Mid1p precedes other node proteins and nodes cannot form without Mid1p, reinforcing the idea that Mid1p initiates the formation of cytokinesis nodes. Of note, in absence of Mid1p, an actomyosin ring can still form, suggesting that nodes are not the only way for contractile-ring formation. However, the timing and efficiency of contractile-ring assembly and its orientation are seriously affected without nodes [33,34].

Actually, our knowledge of the node-assembly pathway is still limited, mainly due to limited information on protein interactions and localization dependence. It has been shown that the IQ domains of Myo2p interact with Cdc4p and Rlc1p [35,36]. Cdc4p also interacts with IQGAP Rng2p, probably via its IQ domains [35]. In one study, Myo2p immunoprecipitated with Mid1p when both proteins

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