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Multifaceted regulation of asymmetric cell division by the actin cytoskeleton

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Asymmetric cell division (ACD) is essential for generating cell diversity in multicellular eukaryotes, yet the underlying mechanisms remain largely unresolved. Well-established models of ACD, such as microtubule-based spindle displacement in *Caenorhabditis elegans* embryos and preprophase band assembly in plants provide valuable insights but fail to fully explain asymmetry establishment in others. In this article, we discuss how actin-dependent mechanisms govern ACD in model systems, highlighting emerging commonalities and differences. Given its broad impact, the actin cytoskeleton may play a more significant role in ACD than currently recognized, serving as a fundamental component during organismal development across kingdoms.

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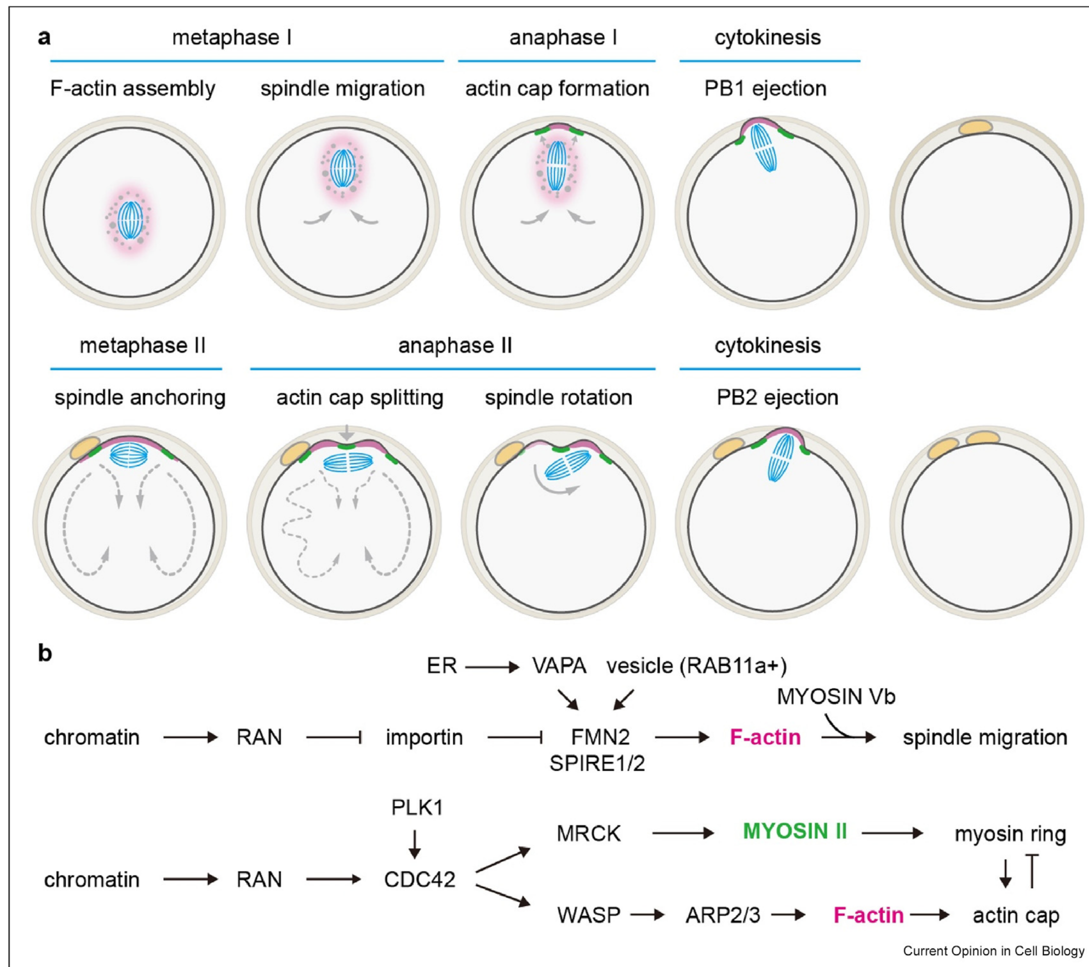
Introduction

The development of multicellular organisms relies on asymmetric cell division (ACD), a process wherein one cell generates two daughters different in size, cellular contents, and fates [1,2]. How cells generate division asymmetry is an active area of research in cell biology, yet the underpinning mechanism remains incompletely understood. Many pioneering studies have illustrated that polarity-triggered spindle displacement is responsible for ACD in *Caenorhabditis elegans* (*C. elegans*) early embryos, and its conservation has been demonstrated across species [2–6]. However, this mechanism does not apply to acentrosomal cells such as mammalian oocytes and plant cells [7,8]. Instead, the actin cytoskeleton plays a crucial role in these cells. Recently, actin is also found to regulate the asymmetric division of centrosome-carrying cells [9–13], suggesting that actin is widely involved in ACD. Considering that many outstanding reviews have covered the microtubule-based asymmetry establishment and maintenance in *C. elegans* embryos, this review will focus on the contribution of the actin cytoskeleton in ACD. We discuss progress on the function of the actin cytoskeleton and compare the underlying mechanisms in multiple animal and plant models (Supplementary Fig. 1).

Polar assembly of the actin cytoskeleton and its interactions with polarity factors

One important function of actin in ACD is to sense polarity cues and induce symmetry breaking. During mammalian oocyte maturation, the oocyte undergoes two rounds of asymmetric division, generating one large ovum and two small polar bodies (PBs) (Fig. 1a) [14,15]. At the anaphase I (ANI) and metaphase II (MII), an actin cap forms at the cortex, functioning to regulate spindle positioning and PB emission [14,15]. The assembly of actin cap depends on the CDC42/N-WASP/ARP2/3 pathway [16–19] and an upstream RAN GTPase signaling derived from the chromatin (Fig. 1b) [20,21]. Recently, POLO-LIKE KINASE 1 (PLK1) was found to regulate actin cap formation at the metaphase I (MI) and its reassembly at the MII phase upon depletion [22]. This function also depends on CDC42/N-WASP (Fig. 1b). However, PLK1 is not required to maintain actin cap [22]. It is proposed that PLK1 regulates actin cap initiation while RAN GTPase is critical for the maintenance of actin cap [22]. Surrounding the actin cap is a ring composed of NON-MUSCLE MYOSIN II (MYOSIN II, hereafter), which regulates spindle relocation and cytokinesis (Fig. 1a) [15]. The assembly of myosin ring requires RAN GTPase and CDC42 [20,23]. At the MII phase, the MYOTONIC DYSTROPHY KINASE-RELATED CDC42-BINDING

Figure 1



Actin-dependent spindle positioning in mammalian oocytes. (a) The meiotic division of mammalian oocytes. At the metaphase of meiosis I, F-actin (magenta) is assembled around the spindle and its dynamic polymerization moves the spindle toward the cortex. At anaphase I, the chromatin-derived signals induce the assembly of an actin cap and a ring of non-muscle MYOSIN II (green). The actin cap protrudes the membrane and enables the emission of polar body 1 (PB1). The myosin ring functions to assemble the contractile ring during cytokinesis. At metaphase II, the spindle is anchored to the actin cap due to a balanced cytoplasmic flow generated by MYOSIN II and polarized actin polymerization. At anaphase II, the elongation of spindle induces the accumulation of cortical MYOSIN II above the central spindle. MYOSIN II constricts the membrane, leading to the formation of a unilateral furrow and the splitting of the actin cap. Meanwhile, the force that powers the cytoplasmic flow becomes imbalanced. Consequently, the spindle rotates and one spindle pole is randomly selected to be anchored to one of the actin caps. This actin cap protrudes the membrane to facilitate the emission of polar body 2 (PB2) while the other actin cap is disassembled. (b) Pathways that regulate the assembly of F-actin and myosin rings for spindle migration and PB emission.

KINASE (MRCK) activates myosin and ring assembly (Fig. 1b) [24]. An actin flow generated by CDC42/N-WASP/ARP2/3 may transport MRCK from the apical cortex to the ring region, thus enabling spatially controlled myosin activation [21,24].

During the asymmetric division of *C. elegans* and *Drosophila* neuroblasts, MYOSIN II exhibits polar localization at the smaller pole in anaphase (Supplementary Fig. 1) [25,26]. In *C. elegans*, the localization of MYOSIN II depends on the polarly localized LKB1/PAR4-like kinase PIG-1 (Fig. 2a) [25,27]. Myosin asymmetry in *Drosophila* requires the Gα/PINS/MUD polarity module and is established by the extension of the apical membrane and concurrent myosin clearance at this region (Fig. 2c) [26,28,29]. Evidence suggests that MYOSIN II must be activated by RHOGEF-RHOA to achieve its cortical localization (Fig. 2c) [11]. Subsequently, SCAR/WAVE-ARP2/3-mediated actin polymerization induces a cortical flow, potentially transporting MYOSIN II to the smaller pole (Fig. 2c) [9,30]. Interestingly, during early metaphase, an acto-myosin network flows apically, promoting the polar localization of polarity complexes [30–33], suggesting a

mutual regulation between polarity factors and the actin network. Branched actin-mediated asymmetric membrane expansion has also been reported in other cells. In *C. elegans* one-cell-stage embryo, inhibiting the activity of actin debranching factor POD-1 blocks ARP2/3 motility and disrupts division asymmetry due to a lack of cortical flow [13]. ARP2/3-dependent actin branching and membrane extension are essential for the asymmetric division of *C. elegans* Q neuroblasts and *Drosophila* sensory organ precursors (SOPs) (Fig. 2b and d) [10,12]. In both cases, actin asymmetry is established by WAVE-ARP2/3 but not FORMIN nucleators, and the activity of WAVE-ARP2/3 is controlled by intrinsic and extrinsic signals such as Wnt signaling, PAR polarity complex, and CDC42/RAC GTPases [10,12].

In maize stomata, the asymmetric division of the subsidiary mother cell (SMC) is governed by a polar actin patch facing the adjacent guard mother cell (GMC) (Supplementary Fig. 1) [34,35]. The assembly of actin patch is mediated by receptor-like kinases PANGLOSS 1 (PAN1) and PAN2, RHO OF PLANTS 2/9 (ROP2/9), and BRICK1 (BRK1) [35–40]. ROPs are plant-specific homologs of the CDC42/RHO/RAC family and BRK1 is the HSPC300 subunit of the SCAR/WAVE complex (Fig. 3a and b). These facts suggest that a polarity pathway acts on actin polymerization to shape SMC division. Interestingly, SCAR/WAVE functions genetically upstream rather than downstream of PAN1/2 and ROPs [36]. Recently, two subgroups of the WEAK CHLOROPLAST MOVEMENT UNDER BLUE LIGHT 1 (WEB1)/PLASTID MOVEMENT IMPAIRED 2 (PMI2)-RELATED (WPR) proteins WPRA and WPRB are identified as novel components of the BRK-PAN-ROP module (Fig. 3b) [41]. WPRB not only physically interacts with PAN1/2 and WPRA, but also directly binds F-actin, negatively regulating its stability, although the physiological significance underlying this function is still unknown. The involvement of polarizing factors in organizing the actin cytoskeleton during ACD in plants might be common. In the moss *Physcomitrium patens* (*P. patens*), the asymmetric division of protonemal subapical cells is preceded and regulated by the growth of a polarized bulge (Supplementary Fig. 1 and Fig. 3c). The formation of the bulge depends on a cytoplasmic actin pool and ROPs (Fig. 3d) [42,43]. Thus, actin is an integral component of the polarizing module in plants as it is in animal oocytes and neuroblasts.

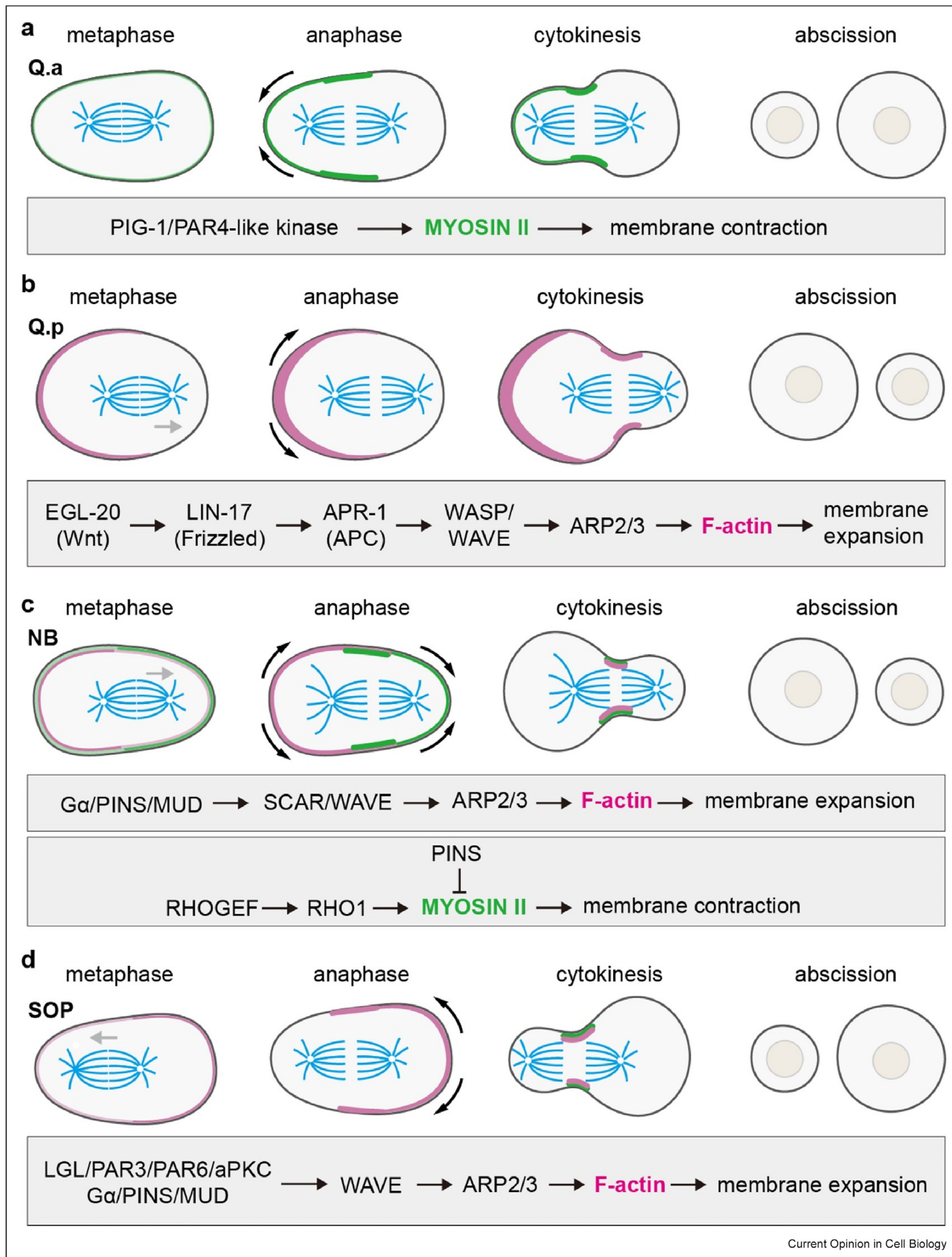
Roles of actin cytoskeleton in spindle migration and positioning

In addition to triggering cell polarization, actin can regulate division plane selection by positioning the spindle. During mammalian oocyte meiosis, the MI spindle migrates a long distance toward the cortex (Fig. 1a). This process depends on a pool of cytoplasmic actin around the spindle [15]. The cytoplasmic actin is nucleated by FORMIN 2 (FMN2) and SPIRE1/2 [44–46]. These nucleators are anchored to RAB11a-positive vesicles [47], where they efficiently nucleate actin polymerization. Aided by the MYOSIN Vb motor, the dynamic actin network generates a pushing force, enabling spindle migration [47]. FMN2 has also been found to be associated with ER-like vesicles [48]. This association allows actin nucleation and the generation of a pushing force against spindle peripheral mitochondria [49]. The activity and recruitment of FMN2 are tightly coupled. A recent study shows that RAN-GTP disrupts FMN2-importin $\alpha 1\beta$ interaction, thus releasing FMN2 and allowing its accumulation around the spindle [50]. FMN2 is then recruited to the ER and activated by the ER-membrane protein VESICLE-ASSOCIATED MEMBRANE PROTEIN-ASSOCIATED PROTEIN A (VAPA) [50]. Two models have been proposed to explain how actin regulates spindle migration. First, FORMIN-mediated actin polymerization generates a force for an initial slow movement [48,51]. A subsequent cytoplasmic stream produced by the decrease of subcortical tension due to ARP2/3-mediated actin thickening and myosin depletion from the cortex triggers a faster spindle migration [48,52,53]. Second, myosin is asymmetrically activated around one of the spindle poles and pulls on F-actin, thus generating forces for migration [47,54].

Upon spindle migration to the cell cortex, the RAN GTPase signaling triggers the activation of CDC42, and the assembly of the actin cap and myosin ring as mentioned earlier (Fig. 1a) [17,20,21,24]. After meiosis I, the MII spindle is quickly assembled and anchored laterally to the cortex underneath a newly formed actin cap (Fig. 1a). The anchorage of the MII spindle depends on the RAN-CDC42/N-WASP/ARP2/3 pathway and RAC/WAVE2 [55,56]. Mechanistically, ARP2/3-mediated actin polymerization drives a cytoplasmic flow away from the cap and generates a balanced pushing force underneath the spindle [21]. During ANII, two actin caps form surrounding the segregated chromosomes and the membrane between them invaginates (Fig. 1a). Subsequently, the ANII spindle rotates and becomes radially positioned. The rotation of the ANII spindle is powered by antagonistic cytoplasmic streaming forces generated by ARP2/3-dependent actin polymerization and MYOSIN II (Fig. 1a) [57]. These two forces are initially balanced but become imbalanced as the unilateral membrane furrowing proceeds [23,57].

Actin-triggered spindle positioning may not be oocyte-specific. In mosses, the disruption of TPX2, a key MT polymerization-promoting factor, causes a basal shift of the mitotic spindle in gametophore initials [58]. This phenotype can be rescued by depolymerizing actin filaments. Although the underlying mechanism is still unclear, these results suggest potential roles of actin in

Figure 2



Actin induces asymmetric membrane expansion and contraction in neuroblasts. (a) Asymmetric division of *C. elegans* Q.a cell. Q.a division uses a spindle-independent membrane contraction mechanism (black arrows). At anaphase, MYOSIN II accumulates on the anterior cortical membrane and is supposed to generate a contractile force that pushes the cytoplasm to the opposite site. MYOSIN II localization is controlled by the PAR4-like kinase PIG-1. (b) Asymmetric division of *C. elegans* Q.p cell. Q.a division depends on the spindle displacement mechanism (grey arrow) and the membrane expansion mechanism (black arrows). In the membrane expansion mechanism, branched F-actin is preferentially assembled at the anterior cortex during metaphase and anaphase. This causes asymmetric membrane expansion and enables the generation of a 2~3-fold size difference in daughter cells. The polar assembly of F-actin is controlled by Wnt signaling and WAVE/WASP/ARP2/3. (c) Asymmetric division of *Drosophila* brain neuroblasts. The division of neuroblast (NB) depends on the spindle displacement mechanism (grey arrow), the membrane expansion mechanism (black arrows, left), and the membrane contraction mechanism (black arrows, right). At anaphase, branched F-actin is preferentially polymerized at the apical cortex, enabling

spindle positioning in other acentrosomal cells. More importantly, actin seems to antagonize MT-dependent force. A similar effect is critical for spindle positioning in mouse oocytes [59].

Actomyosin-mediated asymmetric membrane expansion and contraction

In neuroblasts of *C. elegans* and *Drosophila*, the cortical actomyosin exhibits asymmetric distribution with branched actin enriched at the larger pole and MYOSIN II at the smaller pole (Fig. 2) [9,10,12,25,26,30,31]. Collective data indicate that this asymmetry allows enhanced membrane expansion, namely the increase of cell surface, at the actin-rich pole, thus leading to asymmetric positioning of the cleavage furrow. Two models have been proposed to explain how actomyosin generates membrane asymmetry. First, MYOSIN II at the smaller pole constricts the membrane and causes a pushing force in the cytoplasm [25,28,60]. Second, active polymerization of branched actin at the larger pole generates a cortical flow and/or locally remodels the membrane, resulting in asymmetric membrane expansion [9,10,12,13,30–33]. These two mechanisms are mutually non-exclusive but could be differentially employed for ACD (Fig. 2). For example, the division of Q.a neuroblast in *C. elegans* requires the myosin contraction mechanism while its sister cell Q.p relies on actin-driven membrane expansion [12,25]. The division asymmetry of *Drosophila* SOP cell requires actin polymerization but likely does not involve MYOSIN II [10]. However, in *Drosophila* neuroblasts, both mechanisms are functional [9,26,30]. How actomyosin produces biased forces is not fully answered. One promising model is that polarity proteins at the larger pole selectively activate actin polymerization and those at the smaller pole recruit MYOSIN II [9,10,25,26,30]. This triggers differential assemblies of actomyosin networks at each pole with one being highly dynamic and the other being relatively stable. Such a difference allows the generation of asymmetric pushing and contractile forces, leading to the shift of cytokinetic furrow.

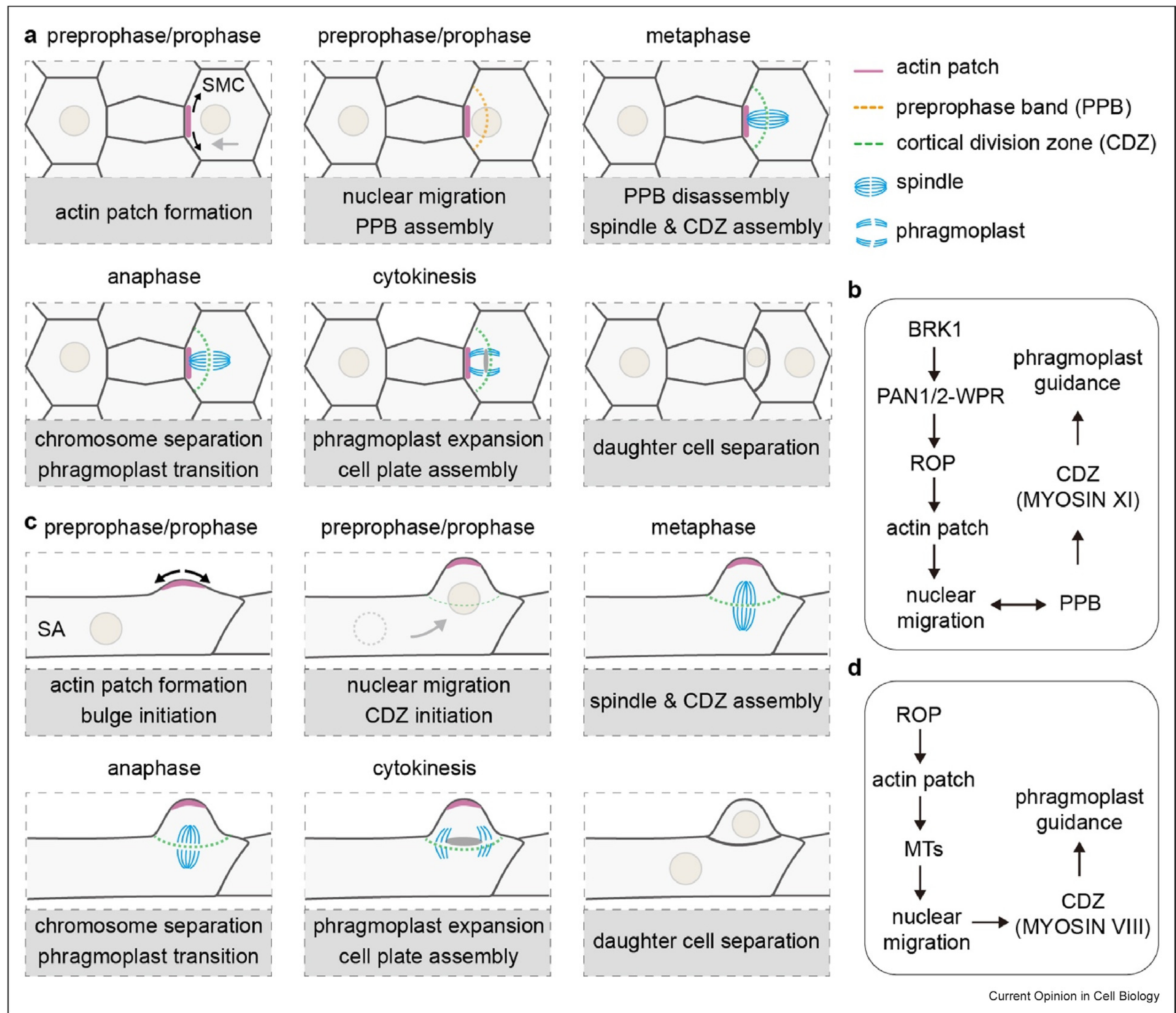
Actin-dependent phragmoplast guidance and nuclear positioning in plants

Since plant cells lack centrosomes and MYOSIN II, the spindle displacement and myosin contraction mechanisms are not operative in plants. Instead, a specialized structure phragmoplast, transformed from the anaphase spindle, is essential for division site selection [61]. The phragmoplast contains abundant MTs and F-actin. During cytokinesis, it expands centrifugally and delivers vesicles for cell plate assembly, leading the cell plate edge to a predefined cortical division zone (CDZ), a process known as phragmoplast guidance. Although the assembly and orientation of phragmoplast are predominantly controlled by MTs, increasing evidence indicates that actin also plays an inevitable role (Fig. 3). For example, in the moss *P. patens*, MYOSIN VIII localizes at the phragmoplast and CDZ [62]. MYOSIN VIII can directly associate with phragmoplast MTs and regulate phragmoplast orientation. In *Arabidopsis* and maize *Zea mays* (*Z. mays*), a similar localization pattern and function are found for MYOSIN XI [41,63]. The function of MYOSIN XI depends on intact actin filaments and direct interactions with the PHRAGMOPLAST ORIENTING KINESINs (POKs). The assembly of CDZ is triggered by multiple MT-interacting proteins including POKs whose localization is instructed by a transient MT structure preprophase band (PPB) formed at early prophase [61]. As MYOSIN XI is present in discrete cortical foci with CDZ and PPB proteins, it is proposed that MYOSIN XI functions as a component of cytoskeleton-associated motor assemblies that translate the PPB into the phragmoplast fusion site [63].

In addition to phragmoplast guidance, the approximate division site of cells that generate daughter cells with extreme size difference is largely predefined by the nuclear position as has been found in the maize SMC and moss protonemal cells (Fig. 3) [8]. The actin cytoskeleton may specify the nuclear position in several ways. First, it senses polarity signals and drives local membrane expansion to influence nuclear positioning [36,39,40,43,64]. Second, it serves as a track to facilitate motor-dependent nuclear transport [65,66]. The direct involvement of myosin motors in pre-mitotic nuclear transport during ACD has not been reported. However, given that myosin rather than kinesin plays a prominent role in organelle transport in flowering plants [67], and a subunit of the nuclear membrane LINKER OF NUCLEOSKELETON AND CYTOSKELETON (LINC) complex, which interacts with cytoskeletons and regulates nuclear positioning, controls nuclear migration during SMC division [68], actin-dependent

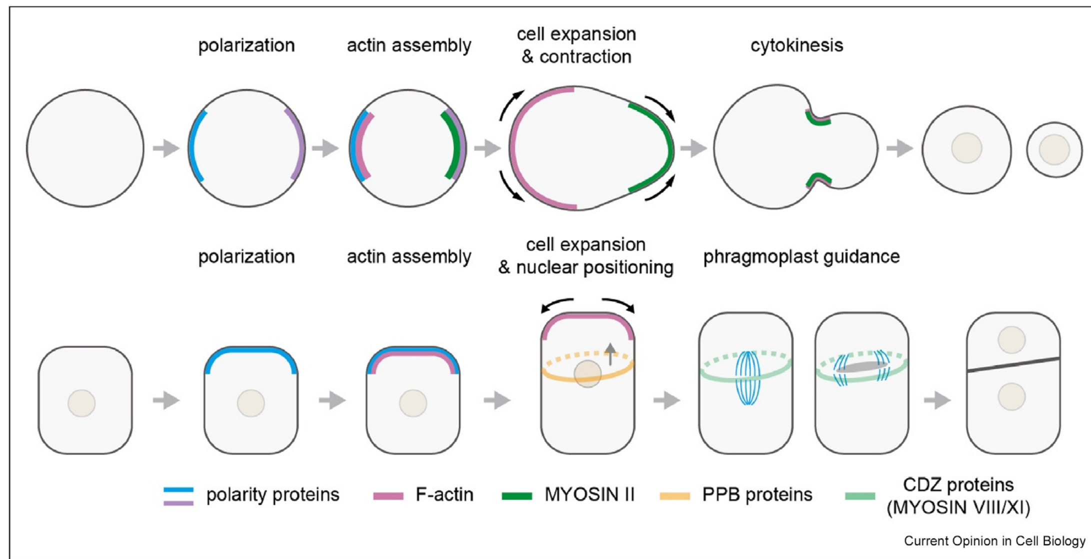
asymmetric membrane expansion. Meanwhile, MYOSIN II accumulates at the basal cortex and generates a contractile force which further enhances membrane asymmetry. During cytokinesis, F-actin and MYOSIN II are depleted from the cortex and participate in contractile ring formation. The assembly of branched F-action depends on the polarity complex Gα/PINS/MUD and the canonical SCAR/WAVE-ARP2/3 pathway. MYOSIN II is activated by RHO1 and is spatially restricted by PINS. (d) Asymmetric division of *Drosophila* sensory organ precursor (SOP). The division of SOP uses the spindle displacement mechanism (grey arrow) and the membrane expansion mechanism (black arrows). In the membrane expansion mechanism, branched F-actin is preferentially assembled at the posterior cortex at anaphase. This causes asymmetric membrane expansion and allows the generation of a 2-fold size difference in daughter cells. During cytokinesis, F-actin is depleted from the cortex and participates in contractile ring formation. The assembly of branched F-actin requires the polarity complexes LGL/PAR3/PAR6/aPKC and Gα/PINS/MUD, and the downstream WAVE-ARP2/3. MYOSIN II is involved in contractile ring formation. However, it does not show asymmetric cortical localization and cannot generate division asymmetry when artificially mislocalized.

Figure 3



Actin is involved in nuclear positioning and phragmoplast guidance in plant cells. (a) Asymmetric division of stomatal subsidiary mother cell (SMC) in the maize *Z. mays*. The division of SMC is preceded by the assembly of an actin patch and a local membrane expansion (black arrows) at the contact site between SMC and the guard mother cell (GMC) in preprophase/prophase. After actin patch initiation, the nucleus migrates toward it and an MT-based circular preprophase band (PPB) is formed in the cortex around the nucleus. Upon entry into metaphase, the PPB is disassembled, leaving various MT-associated proteins occupying the same region termed cortical division zone (CDZ). Nuclear positioning and PPB assembly are tightly coupled and can influence each other. Once the spindle is assembled, one of its poles is anchored to the actin patch. During late anaphase, the spindle shortens the distance between its poles and broadens in width, transforming into a phragmoplast. During cytokinesis, cell plate assembly is initiated in the center of the phragmoplast and the cell plate expands centrifugally along the leading edge of the expanding phragmoplast toward the CDZ, a mechanism known as phragmoplast guidance. The attachment and fusion of cell plate to the parental membrane above CDZ marks the end of cell division. (b) Actin-dependent pathways that regulate SMC polarization, nuclear migration, and phragmoplast guidance. BRK1 is the HSPC300 subunit of the WAVE complex, PAN1 and PAN2 are receptor-like kinases, and ROP is the plant homolog of the CDC42/RHO/RAC family. (c) Asymmetric division of protonemal subapical cell (SA) in the moss *P. patens*. During preprophase/prophase, the SA assembles an actin patch at the apical membrane and protrudes the membrane to form a bulge (black arrows). Concurrently, its nucleus migrates from the cell center into the bulge, followed by nuclear envelope breakdown and spindle assembly. Note that the moss protonemal cell does not assemble a PPB. However, a CDZ could be specified during preprophase as evidenced by MYOSIN VIII localization and persist from metaphase to cytokinesis. During anaphase and cytokinesis, the phragmoplast is assembled and functions to guide the cell plate expansion as it is during SMC development.

Figure 4



Simplified models for actin-dependent asymmetric division of animal and plant cells. The animal cell uses two actin-based models for ACD: actin-mediated asymmetric membrane expansion and MYOSIN−II−triggered membrane contraction (black arrows). In the first model, branched actin is polymerized preferentially at one side of the cortex and induces local membrane expansion. In the second model, non-muscle MYOSIN II accumulates at the opposite cortex and generates a contractile force that likely pushes the cytoplasm and membrane forward. The polar organization of actin and MYOSIN II occurs from metaphase to anaphase and is induced by polarity cues. These two mechanisms can operate separately or coordinatively in a cell. The plant cell employs a nuclear positioning mechanism and a phragmoplast guidance mechanism to achieve ACD. In prophase, the cell is polarized by polarity cues and establishes a polar array of F-actin that induces local membrane expansion (black arrows). Meanwhile, the nucleus is positioned eccentrically and a preprophase band (PPB) forms, which marks the future division site. During metaphase, the PPB is disassembled and the cortical division zone (CDZ) is established at a place where the PPB is located. In late anaphase, the spindle transforms into a phragmoplast. The phragmoplast expands centrifugally toward the CDZ and instructs the expansion of the cell plate. Although the PPB is not present in all types of plant cells, the phragmoplast guidance mechanism is highly conserved in plants and requires MYOSIN VIII and MYOSIN XI. Nuclear positioning may not be obvious in all asymmetrically dividing cells but is a prerequisite for the asymmetric division of cells that generates daughter cells with extreme size differences.

nuclear transport may be involved in plant ACD. Further studies are required to elucidate the mechanisms by which actin regulates nuclear migration and how actin regulators coordinate nuclear positioning with phragmoplast guidance [8]. Notably, actin also plays a critical role in nuclear migration across various animal cell types, where it has been implicated in controlling division asymmetry and cell fate determination [69]. Although the underlying mechanisms may differ, future comparative studies could help uncover a conserved molecular repertoire responsible for specifying nuclear position and division site.

Concluding remarks

Recent studies indicate a pivotal role of actin in ACD across kingdoms. Despite differences in the division process, some common features could be summarized (Fig. 4). First, actin-driven membrane remodeling is important for altering cell morphology and determining the division site in cells that generate significant size asymmetry. Second, specialized mechanisms are developed to further enhance division asymmetry. For example, in mammalian oocytes, the meiotic spindle is positioned to the cortex through actin-dependent cytoplasmic flow. In moss protonemal cells and maize SMCs, the nucleus undergoes conspicuous migration toward an actin-rich cortical region, enabling the specification of the spindle assembly site. This process may be functionally equivalent to the spindle displacement mechanism in animal cells. Collectively, actin appears to be widely involved in ACD and functions to regulate polar membrane remodeling and intracellular organization. The detailed mechanism may vary depending on the cellular context. However, a connection between polarity signals, regulators of F-actin assembly and organization, and actin-dependent motors is likely common. Furthermore, crosstalk between the actin cytoskeleton and MTs has been revealed and may represent another general feature in division apparatus positioning and asymmetry establishment [2,70]. Future studies of key elements in various cell models and the use of advanced tools such as optogenetics [10], proximal labeling [71], and conditional gene knockout [12], would lead to valuable insights into our understanding of ACD.

Author contributions

Peishan Yi: Conceptualization; Writing – original draft & figure preparation. Guangshuo Ou: Writing – review

& editing. Wei Li: Conceptualization; Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ceb.2025.102491.

Data availability

No data was used for the research described in the article.

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** of outstanding interest

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