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Regulatory Mechanism of Spindle Movements during Oocyte Meiotic Division

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ABSTRACT : Female germ cell meiotic divisions are typically asymmetric, giving rise to two daughter cells with different sizes. Spindle movements including spindle migration from the oocyte center to the cortex and spindle rotation from parallel to perpendicular (typically in the mouse) at the cortex are crucial for these asymmetric divisions and therefore are crucial for gamete production. Different regulatory mechanisms for spindle movements have been determined in different species and a wide variety of different molecular components and processes that are involved in spindle movements have also been identified in different species. Here, we review the current state of knowledge as well as our understanding of mechanisms for spindle movements in different systems with focus on three main aspects: microtubules (MT), microfilaments (MF) and molecules associated with cytoskeletal organization as well as molecules that are not directly related to the cytoskeleton. How they might interact or function independently during female meiotic divisions in different species is discussed in detail. (**Key Words :** Spindle Movement, Meiotic Division, Cytoskeleton, Oocyte)

INTRODUCTION

During female germ cell meiosis, asymmetric cell divisions take place to ensure that most of the maternal stores are retained within the oocyte, resulting in the formation of daughter cells with different sizes: the large oocyte and the small polar bodies. This asymmetry is essential to preserve the maternal resources for subsequent early development. Extensive studies of meiotic spindle motility in mouse oocytes have revealed a detailed series of movements during meiotic asymmetric divisions: during first meiotic division, the MI spindle forms initially at the center of the oocyte and migrates toward the periphery; the first polar body (PB1) is extruded after microtubule-cortex attachment (Maro et al., 1984; Longo and Chen, 1985; Maro et al., 1986; Verlhac et al., 2000; Maro and Verlhac, 2002; Wang et al., 2008). As the metaphase II-arrested oocyte resumes meiosis after fertilization or parthenogenetic activation, the spindle rotates from a parallel to a perpendicular orientation relative to the plasma membrane, and the PB2 is extruded (Gulyas, 1976; Maro et al., 1984; Verlhac et al., 1994; Liu et al., 2000; Maro and Verlhac, 2002; Ibanez et al., 2003; Zhu et al., 2003). The meiotic spindle in *Caenorhabditis elegans* undergoes similar spindle movements with different oocyte maturation processes, suggesting a conserved spindle motility mechanism during female meiotic division (Yang et al., 2003; 2005).

Spindle movements have also been found in many other systems. Peripheral spindle migration has been shown in meiotic divisions of rat (Ai et al., 2008a) and pig oocytes (Sun et al., 2001). Besides, oocyte spindles undergo rotation to the perpendicular orientation from a starting position parallel to the cortex in *Xenopus* meiosis I and II (Gard, 1992; Gard et al., 1995), *Drosophila* meiosis I (Endow and Komma, 1997), and hamster meiosis II (Gulyas, 1976).

These meiotic division processes involve extensive rearrangement of microtubules and microfilaments (actin filaments). The organization of the cytoskeleton - microtubules and microfilaments in particular- is well known to be involved in the regulation of several dynamic events that occur to ensure successful meiotic divisions and accurate union of the parental genomes (Sun et al., 2001).

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Based on the mechanisms of asymmetric division in mitotic cells (Kaltschmidt et al., 2000; Gonczy, 2002), a growing number of studies in meiosis have revealed female meiosis-specific mechanisms regulating either astral or anastral meiotic spindle movement during asymmetric division: aside from the cytoskeleton itself, molecules associated with cytoskeletal organization as well as molecules that have no direct relationships with the cytoskeleton are involved in these processes. A brief overview will be presented here to demonstrate the diverse mechanisms that regulate spindle movements during meiotic maturation in different systems. We have organized the review into three broad topics relevant to MT, MF and molecules that are not directly involved in cytoskeletal organization, followed by a discussion on some potential candidate molecules.

ROLES OF MICROTUBULES IN SPINDLE MOVEMENT

Role of microtubules in spindle movement in mitotic cells

Microtubules, hollow, cylindrical polymers of α- and β-tubulin heterodimers (Desai and Mitchison, 1997), are ubiquitous cytoskeletal fibers essential for many important biological processes, such as mitosis, cell motility, intracellular transport, and cell polarity. To perform the variety of cellular functions, microtubules are organized into a wide range of higher order assemblies. At the same time, they are highly dynamic and undergo drastic changes in their subcellular distribution.

By now, a role for microtubules in spindle movements has been found in many systems. The most likely mechanistic basis for both rotation and spindle displacement is the interaction of astral microtubules with pulling forces generated at the cortex, acting through microtubule-based motors (Hyman and Karsenti, 1996; Pearson and Bloom, 2004).

Mitotic spindle positioning is known to depend on microtubule-cortical interactions in several animal systems (Lutz et al., 1988; Hyman, 1989; Goldstein, 1995; Reinsch and Gonczy, 1998; Yamashita et al., 2003). It has been reported that movement and orientation of mitotic spindles in animals and fungi occur through astral microtubules that emanate from centriole-containing centrosomes or spindle pole bodies (Gonczy, 2002; Sheeman et al., 2003).

In addition, experiments on asymmetric division of one-cell stage *C. elegans* embryos have demonstrated that microtubule pulling forces cause the spindle to shift from the center of the embryo towards the posterior (Labbe et al., 2004), this result, together with the recent report in *C. elegans* that certain dominant mutations of tubulin isoforms affect spindle positioning events (Ellis et al., 2004; Phillips et al., 2004; Lu and Mains, 2005), allow the conclusion that in the asymmetric division of *C. elegans* embryos, microtubules are also involved in spindle migration.

Roles of MT in astral spindle movement during meiotic maturation

Consistent with the mechanisms involved in mitotic spindle translocation (Hyman, 1989; Grill et al., 2001; Gonczy, 2002), in oocytes with astral meiotic spindles, specific cortex domains can pull on astral microtubules of the meiotic spindle and thus allow spindle migration. Female meioses in some organisms such as *Chaetopterus variopedatus* (Lutz et al., 1988), *Spisula solidissima* (Palazzo et al., 1992) and starfish (Hamaguchi, 2001; Zhang et al., 2004) have robust astral microtubule arrays nucleated by centriole-containing centrosomes. In these species, the spindle is translocated by the pulling forces on astral microtubules generated by the cortex, which is similar to that proposed for mitotic spindles (Gonczy, 2002; Sheeman et al., 2003). When the meiotic spindle is displaced from the cortex of *Chaetopterus* oocytes using a micro-needle followed by release, one of the spindle poles is rapidly pulled back towards the cortex, revealing that astral microtubules connect the moving spindle pole and the cortex in *Chaetopterus* oocytes and thus directly affect spindle migration (Lutz et al., 1988). Similar mechanisms also exist in fission yeast (Ding et al., 1998), in which the oscillatory nuclear movement is mediated by dynamic instability and selective stabilization of astral microtubules.

Roles of MT in spindle movement in anastral meiotic maturation

Female meiotic spindles of *Drosophila melanogaster* (Theurkauf and Hawley, 1992), *C. elegans* (Albertson and Thomson, 1993), mice (Gueth-Hallonet et al., 1993), cows (Navara et al., 1994), and humans (Sathananthan, 1997) do not contain centrioles in meiotic centrosomes and do not display astral microtubule arrays. In these anastral systems the roles of microtubules are different. It has been reported that spindle migration in mouse oocytes is microtubule-independent, which was based on the observation that the microtubule polymerization inhibitor nocodazole could destroy spindles completely but the condensed chromosomes could still migrate to the cortex (Longo and Chen, 1985; Verlhac et al., 2000). The same results were obtained in our previous study in pig oocytes (Sun et al., 2001), in which a microtubule-independent mechanism of spindle migration was suggested. However, in mouse oocytes, we found that nocodazole at lower dosage could impair spindle morphology partially with the spindle-chromosomes complex remaining near the center of the oocyte (Ai et al., 2008b), which indicates that dynamic

spindle polymerization is crucial for spindle migration in mouse oocytes. This contradicts the widely and traditionally held view of microtubule-independent mechanisms of meiotic spindle migration (Longo and Chen, 1985; Maro et al., 1986; Verlhac et al., 2000; Leader et al., 2002), suggesting that the roles of MT in anastral spindle movement in mouse oocytes may be more complex and need further clarification. In mouse oocytes, microtubules exist in two forms: either linked to DNA, or located in the cytoplasm (Maro et al., 1985). Contrary to the previous reports, newer investigations revealed that astral microtubules are indeed present in mouse oocytes (Moore and Zernicka-Goetz, 2005; Schuh and Ellenberg, 2007), and therefore it is possible that these astral microtubules are involved in asymmetric spindle positioning in mouse oocytes (Moore and Zernicka-Goetz, 2005). All current findings open up new avenues for future research to study the roles of MT in spindle movement in greater detail.

In *Drosophila* oocytes where the spindle is assembled adjacent to the cortex, the prophase-arrested nucleus (germinal vesicle) is positioned near the site of future spindle attachment at the cortex in a microtubule and Lis1/dynein-dependent manner (Swan et al., 1999; Lei and Warrior, 2000). Thus, some female meiosis-specific mechanisms might involve non-centrosomal microtubule arrays. Movement of *C. elegans* meiotic chromosomes to the oocyte cortex is dependent on microtubules (Yang et al., 2003); in tubulin (RNAi) worms, translocation of meiotic chromosomes to the cortex was blocked and bivalent chromosomes were stationary in the cytoplasm after ovulation.

Our recent research in rat oocytes showed that high dosage of nocodazole could depolymerize spindle microtubules completely and inhibit migration of the condensed chromosomes, while after low dosage of nocodazole treatment, a partially impaired spindle could still translocate to the cortex (Ai et al., 2008a). Further studies are needed to clarify the quite different involvement of microtubules in spindle migration between rat and mouse oocytes. Nocodazole was found to disrupt spindles and completely blocked the release from MII in mouse oocytes (Navarro et al., 2005). When low dosage of nocodazole was used during rat egg activation in our recent work, we obtained similar results to those in the mouse egg, i.e. low dosage of nocodazole which could only partially impair spindle morphology can inhibit MII release through inhibiting spindle rotation (Ai et al., 2008a; b), suggesting that microtubules are possibly required for spindle rotation.

MT-related molecules involved in meiotic spindle movement

Meiotic spindles of *C. elegans* oocytes lack centrioles and astral microtubules. During both meiosis I and II in wild-type *C. elegans* oocytes, the spindle is generally translocated to the cortex with its long axis parallel to the cortex, followed by spindle rotation and spindle shortening at the cortex (Yang et al., 2003). The microtubule-severing activity of MEI-I, which is the *C. elegans* ortholog of p60 katanin (Hartman et al., 1998), is required for meiotic spindle organization in *C. elegans* (Srayko et al., 2000). Yang reported that translocation of the MI spindle to the cortex requires microtubules and MEI-1/katanin (Yang et al., 2003) and these investigators also identified a complex which is composed of the kinesin-1 heavy chain orthologue, UNC-116, the kinesin light chain orthologues, KLC-1 and -2, and a novel cargo adaptor, KCA-1, suggesting that kinesin-I motor activity might directly translocate the spindle to the cortex. The results of these investigators also support a model in which kinesin-1 transports the spindle along cytoplasmic microtubules (Yang et al., 2005). The above findings strongly suggest that these molecules function in spindle translocation in *C. elegans* meiosis through regulating microtubule organization.

ROLES OF MF IN SPINDLE MOVEMENT

Functions of MF in spindle movement during meiotic maturation

Besides microtubules, microfilaments are other important cytoskeletal components that play important roles in many meiotic maturation systems (Sun and Schatten, 2006), primarily through cortically mediated events, including centrosome localization, spindle movement to the periphery, activation of constriction, and establishment of oocyte polarity (Calarco, 2005).

The roles of the actin cytoskeleton have been widely studied in mouse oocytes. It is considered a necessary mediator for peripherial spindle movement since the metaphase I spindle remains centrally positioned after cytochalasin B (CB) treatment, shown in both live and fixed mouse oocytes (Kubiak et al., 1991; Verlhac et al., 2000; Dumont et al., 2007). Similarly, disrupting the actin cytoskeleton also affects metaphase II spindle rotation upon fertilization or parthenogenetic activation (Maro et al., 1984; Zhu et al., 2003; Navarro et al., 2005). In addition, jasplakinolide (JAS), which induces microfilament polymerization and stabilization and therefore acts as a microfilament inhibitor, prevents spindle migration to the oocyte cortex (Terada et al., 2000). Microfilament-mediated polarized movement of chromosomes has been reported in various other species, including *Xenopus laevis* (Ryabova and Betina, 1986), hamster (Terada et al., 1995), sheep (Le Guen and Crozet, 1989), cattle (Kim et al., 2000), pig (Sun et al., 2001) and human (Kim et al., 1998). Actin filaments are also required for meiotic spindle rotation in *Xenopus* and sheep oocytes. Bipolar spindles are observed in CB-

treated oocytes, however, rotation of the MI and MII spindles into an orientation orthogonal to the oocyte surface is inhibited by CB (Gard et al., 1995).

The process of *C. elegans* oocyte maturation is different from that of mammalian oocytes: in immature *C. elegans* oocytes arrested at prophase, sperm protein discharged from sperm before fertilization released oocyte meiosis inhibition (Miller et al., 2003), resulting in entry into M-phase and movement of the oocyte into the spermatheca and uterus sequentially (McCarter et al., 1999; Miller et al., 2001). By metaphase of meiosis I, the spindle was closely associated with the cell cortex (Albertson and Thomson, 1993), which occurred after assembly of a bipolar spindle, when most oocytes have exited the spermatheca (Yang et al., 2003). Studies in *C. elegans* oocytes indicate that translocation of the MI spindle to the cortex is F-actin-independent; similarly, meiotic spindle rotation is also F-actin-independent. These conclusions resulted from the observation that the actin-depolymerizing drug, latrunculin A, could not affect this process (Yang et al., 2003). The difference for MF-dependence of spindle movement between different species may be the result of different oocyte maturation processes.

Functions of MF-related molecules in spindle movement during meiotic maturation

By now, a growing number of cellular factors involved in spindle movement during female meiotic division has been studied. Polymerization of nonfilamentous (G-) actin into filamentous (F-) actin and actin patch formation requires numerous signaling molecules such as the ARP2/3 complex, Cdc42 and formins (Ma et al., 1998; Evangelista et al., 2002; Nishimura and Mabuchi, 2003; Gunst, 2004; Zigmond, 2004). Disrupting the function of actin, Rho, Rac, Cdc42, or myosin prevents polar body formation (Halet and Carroll, 2007; Ma et al., 2006; Na and Zernicka-Goetz, 2006; Sun and Schatten, 2006), but the roles of these molecules in the process appear to be different.

Rho family proteins

Rac, Rho and Cdc42 are the three best-characterized members of the Rho family (Etienne-Manneville and Hall, 2002), which can interact with and activate downstream effectors to control the assembly of actin filaments and their organization into complex structures (Bishop and Hall, 2000).

Rac, one of the Rho GTPases expressed in mouse oocytes (Natale and Watson, 2002; Kumakiri et al., 2003), controls spindle stability and anchoring to the cortex and thus the asymmetrical cell division; however, it is not involved in spindle migration during mouse oocyte maturation (Halet and Carroll, 2007). By contrast, another small GTPase, RhoA inhibitor caused abnormal organization of microfilaments, failure of spindle rotation and PB2 extrusion, suggesting its role in regulating spindle rotation through regulating microfilament organization (Zhong et al., 2005).

CDC42 is also a small GTPase that belongs to the Rho family which has multiple functions in regulating both the microtubule and actin cytoskeleton (Etienne-Manneville and Hall, 2003). CDC42 is involved in spindle migration in mouse oocytes (Na and Zernicka-Goetz, 2006). In CDC42 mutant mouse oocytes, spindles were centrally located and cortical actin was uniform, while in the control group, spindles had migrated to the cortex and induced a patch of cortical actin above them; mutant forms of CDC42 also abolished the MT-independent movement of chromatin to the cortex and formation of the patch of cortical actin in the presence of nocodazole (Na and Zernicka-Goetz, 2006). These results indicate that CDC42 may exert its function on spindle migration by regulating the cortical actin patch formation.

In *Xenopus*, X-PAK2/Cdc42 pathway analysis linked p34cdc2 activity to major cytoskeletal rearrangements, leading to spindle migration and anchorage to the animal pole cortex (Cau et al., 2000). However, a recent report showed that CDC42 activity is not required for spindle translocation. In the presence of a dominant-negative Cdc42T17N, *Xenopus* oocytes are able to form a bipolar metaphase I spindle, translocate and anchor the spindle to the animal pole cortex, and initiate anaphase. Inhibition of PB emission only resulted from a failure to properly form and direct the actomyosin-based contractile ring but not from failure of spindle migration (Ma et al., 2006).

Formins

Formins are large multi-domain proteins required for the assembly of straight actin filaments found in the cytokinetic contractile ring, yeast actin cables, adherens junctions between epithelial cells and filopodial protrusions (Chang et al., 1997; Feierbach and Chang, 2001; Evangelista et al., 2002; Pruyne et al., 2002; Sagot et al., 2002; Severson et al., 2002; Kovar et al., 2003; Kobielak et al., 2004; Pellegrin and Mellor, 2005; Schirenbeck et al., 2005); observations on both fixed and live fmn2$^{-/-}$ oocytes suggested that formin-2 is required for spindle migration in mouse oocytes (Leader et al., 2002; Dumont et al., 2007). The results also indicate that *Fmn2* is involved in the movement of metaphase chromosomes to the oocyte cortex when the spindle is destroyed (Leader et al., 2002). However, whether formins exert their role in spindle movement in mouse oocytes through regulating MF, as we proposed, and how it functions in other systems needs to be further determined.

Arp2/3 complex

Aside from formins, the Arp2/3 complex is another actin nucleator, which is a seven-subunit complex that includes two actin-related proteins 2 and 3 (Welch and Mullins, 2002). Actin polymerization can be initiated by *de novo* nucleation by this complex (Pollard et al., 2000). The complex is also able to organize filaments into branched networks (Mullins et al., 1997; Mullins et al., 1998; Machesky and Gould, 1999). Presumably, the Arp2/3 complex is involved in meiotic spindle movement through regulating patch microfilament formation.

Myosin

Myosins are best known as F-actin-based motors (Sokac and Bement, 2000). Studies employing microinjection of myosin IIA specific antibody revealed that myosin IIA is involved in spindle migration in mouse oocytes (Simerly et al., 1998). In addition, myosin II together with MYLK2 (myosin light chain kinase), which has the important function of regulating cytoplasmic myosin II (Bersnick, 1999; Kamm and Stull, 2001), were involved in spindle rotation in mouse oocytes (Matson et al., 2006).

MOLECULES INTEGRATING MT AND MF

All biological processes during oocyte maturation are regulated by a network of signaling pathways. MF and MT arrays cooperate functionally during a variety of cellular processes (Gavin, 1997) including orientation of the spindle (Gunderson and Bretscher, 2003) and spindle rotation in asymmetric mitotic division (Schaerer-Brodbeck and Riezman, 2000). Their interaction and cooperation are also widely studied in anchoring the spindle to the actin-rich cortex in meiotic division (Alexandre et al., 1989; Gard et al., 1995; Kim et al., 2000; Lessman, 1987; Sardet et al., 2002; Sun et al., 2001). In the following we will introduce some molecules that may act as linking proteins between MT and MF and are therefore involved in meiotic spindle movement.

Formins

Formins are functional in spindle movement as microfilaments nucleators; they are able to localize to MTs *in vivo* (Ishizaki et al., 2001; Palazzo et al., 2001) and bind to MTs *in vitro* (Palazzo et al., 2001). This finding invites the speculation that aside from regulating MF polymerization, formins may also mediate interactions between MT and MF and thus are required for spindle movement.

Dynein and dynactin

Studies in budding yeast revealed that myosin and dynein are molecular motors that walk along microtubules or actin filaments and can contribute to spindle positioning directly by generating a pulling or pushing force (Huisman and Segal, 2005; Person and Bloom, 2004). Dynein is involved in spindle positioning by transporting cargo proteins (Carvalho et al., 2004), and the dynactin complex has emerged as the key agent to mediate actin/microtubule interactions at the cortex (Schaerer-Brodbeck and Riezman, 2000). The functions of the microtubule motor dynein and its dynactin regulator complex are required for spindle rotation during germline cell divisions and oocyte differentiation in *Drosophila* and in early cell divisions of *Caenorhabditis elegans* development (McGrail and Hays, 1997; Skop and White, 1998). These findings suggest that further research is needed to fully explore the involvement of these motor proteins in meiotic spindle movement.

INVOLVEMENT OF OTHER FACTORS IN MEIOTIC SPINDLE MOVEMENT

MOS/MEK/MAPK pathway

Verlhac et al found that in mouse oocytes, *mos*$^{-/-}$ oocytes extruded their first polar bodies without migration of the spindle (Verlhac et al., 2000); these investigators also established that the MOS-MAP kinase pathway controls spindle migration by regulating the activity of the actin microfilament network, perhaps through myosin IIA, suggesting a possible signaling pathway of myosin IIA and MOS in regulating MF and the MF-dependent spindle movement in mouse oocytes. In addition, our previous work has shown that MEK is important for maintaining normal meiotic spindle morphology and for targeting peripheral spindle positioning (Tong et al., 2003). Our recent results also suggest that MEK1/2 may play roles in microtubule organization, spindle pole tethering and asymmetric division during mouse oocyte maturation (Yu et al., 2007), thereby suggesting a role for the MOS/MEK/MAPK pathway in spindle movement in mouse oocytes.

PAR proteins

The localization of homologs of PAR6 and PAR3 to a cortical actin cap near the meiotic spindle and establishment of polarity has been reported for mouse oocytes (Vinot et al., 2004; Duncan et al., 2005), which may be also required for spindle migration. mPARD6a (mouse homolog of the PAR6 gene of *C. elegans*), a member of the PAR (PARtitioning Defective) family, is first localized on the spindle and then accumulates at the pole nearest to the cortex during spindle migration, while during migration of the chromosomes to the cortex in the absence of microtubules, it is relocalized to the chromosomes, facing the cortex (Vinot et al., 2004). The specific cortex-facing localizations of this protein to either

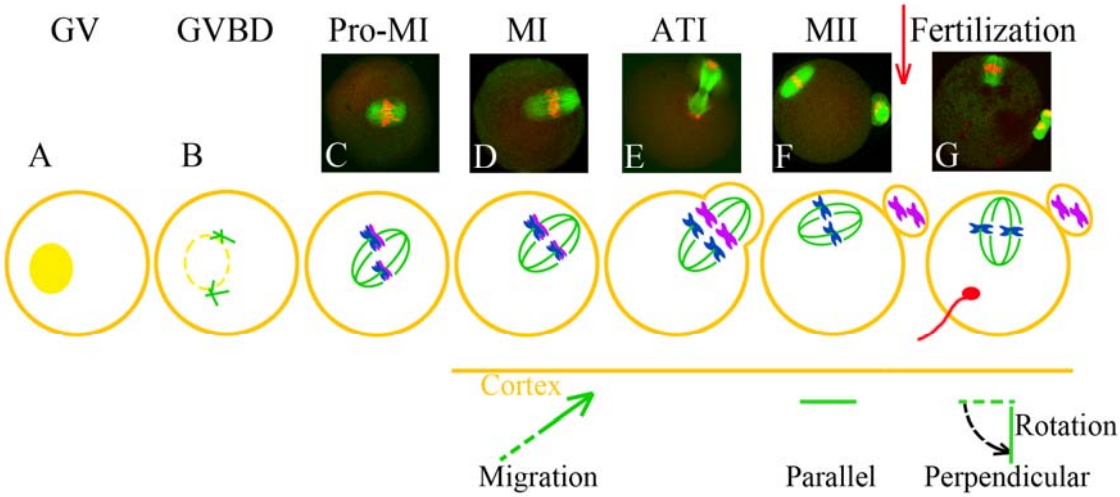

Figure 1. Spindle movement in mouse oocytes during meiotic maturation and fertilization. In GV and GVBD stages, no spindle exists within the oocyte. After GVBD stage, spindle assembly is initiated (A and B). During Pro-MI stage, a clear spindle can be observed in the center of the oocyte (C). Then the spindle migrates toward the periphery along the orientation of its long axis. By MI stage, the spindle has finished the migration (D). When oocytes progress to the ATI stage, homologous chromosomes are segregated by the pulling force of the spindle (E). After this time, half of the spindle is extruded into the polar body while the other half remains in the ooplasm, which reforms a new spindle in the oocyte with its long axis parallel to the cortex, waiting for fertilization (F). After fertilization, the spindle rotates from parallel to perpendicular to the cortex in a short period of time (G).

spindle or no-spindle chromosomes during their migration strongly suggests that mPARD6a is crucial for directing spindle movement.

BFA

Recently, it was shown that brefeldin A (BFA), a highly specific inhibitor of ARF-mediated, Golgi-based vesicle fusion (Donaldson et al., 1992), inhibited spindle migration in denuded oocytes. BFA also inhibited spindle rotation to assume a perpendicular position in metaphase II eggs activated with strontium. The investigators' results showed that BFA did not significantly distort the actin or microtubule cytoskeleton, suggesting a cytoskeleton-unrelated pathway involved in meiotic spindle movement of mouse oocytes.

Calcium pathway

A series of studies has determined the important roles of Ca^{2+} in several events during egg activation (Kline and Kline, 1992; Swann and Ozil, 1994; Schultz and Kopf, 1995; Ducibella et al., 2002); studies by others and ourselves further showed that Ca^{2} function is mediated by CaM and CaMKII during first meiotic maturation in mouse and pig oocytes (Su and Eppig, 2002; Fan et al., 2003). In our recent work, all three specific drugs that can block calcium/calmodulin/CAMKII activity, respectively, were able to inhibit spindle rotation. In addition, spindle morphologies after different drug-treatments are impaired to different extents (Ai et al., 2008b). We therefore implied calcium/calmodulin/CAMKII pathway in the regulation of spindle rotation during mouse egg activation, perhaps through regulating microtubule polymerization.

Mitochondria

Mitochondria, the most significant ATP-generating organelles in mammalian oocytes and embryos (Motta et al., 2000; Sathananthan and Trounson, 2000), provide high levels of ATP during oocyte maturation (Dumollard et al., 2004).

We found that oocytes failed to extrude the PB2 after specific inhibitor-FCCP treatment and displayed parallel spindles, suggesting that mitochondria and the energy they provided are crucial for spindle rotation in mouse oocytes (Ai et al., 2008b). It has been reported that mitochondria as well as ATP production also act as an important intracellular Ca^{2+} regulator in various cell types (Duchen, 2000; Dumollard et al., 2003; Rizzuto et al., 2000), including activated mouse oocytes (Dumollard et al., 2004); therefore, it is possible that the function of mitochondria in regulating spindle rotation may also be mediated by affecting calcium oscillations and thus the downstream pathways in mouse egg activation.

CONCLUSIONS

In humans, it is estimated that 20% of oocytes display chromosome abnormalities linked to segregation errors (Pellestor et al., 2005). Furthermore, the crucial, asymmetrical divisions of the oocyte are highly error prone in humans, resulting in frequent chromosomal aneuploidy

(Leader et al., 2002). Spindle movement is one of the most important processes responsible for the asymmetric division; thus, understanding the mechanism regulating spindle movement is crucial for resolving such reproductive problems. In this review, a collective of current findings as well as our understanding about regulatory mechanisms in meiotic spindle movement in different systems have been discussed. The roles of MT, MF, their regulatory proteins, molecules integrating MT and MF interactions, and cytoskeleton-unrelated factors in spindle peripheral movement and rotation during female meiotic maturation have been discussed in different species.

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