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REVIEW

Roles of actin binding proteins in mammalian oocyte maturation and beyond

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ABSTRACT

Actin nucleation factors, which promote the formation of new actin filaments, have emerged in the last decade as key regulatory factors controlling asymmetric division in mammalian oocytes. Actin nucleators such as formin-2, spire, and the ARP2/3 complex have been found to be important regulators of actin remodeling during oocyte maturation. Another class of actin-binding proteins including cofilin, tropomyosin, myosin motors, capping proteins, tropomodulin, and Ezrin-Radixin-Moesin proteins are thought to control actin cytoskeleton dynamics at various steps of oocyte maturation. In addition, actin dynamics controlling asymmetric-symmetric transitions after fertilization is a new area of investigation. Taken together, defining the mechanisms by which actin-binding proteins regulate actin cytoskeletons is crucial for understanding the basic biology of mammalian gamete formation and pre-implantation development.

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Introduction

The most distinct difference between meiotic cell division in mammalian oocytes and somatic cell division in early embryogenesis is the asymmetric nature of cell division in meiosis.[1] Because the cell division plane is determined by the position of the midbody in the spindle,[2] meiotic spindle migration near the cortex is a crucial step for this asymmetric cell division process in mammalian gametes.[3,4]

Dynamic changes in actin filaments during mammalian oocyte maturation and the importance of actin filaments in asymmetric division in oocytes have been studied for over 30 y.[5-9] One of the most dramatic changes in the actin cytoskeleton during mammalian oocyte maturation is the formation of the cortical actin cap near the migrating spindle.[5] In addition to actin cap formation, cytoplasmic actin density[10,11] and the thickness of cortical actin[12,13] increases during oocyte maturation (Fig. 1). Although the actin cytoskeleton is the main driving force for asymmetric division in mammalian oocytes, including murine[7] and porcine[14,15] oocytes, the exact mechanism through which actin cytoskeleton remodeling contributes to asymmetric division in oocytes has not emerged until recently. The key molecules mediating actin filament remodeling are actin-binding proteins (ABPs),[16] of which more than 100 exist in mammals, that can be sorted into several classes (Table 1). One of most extensively characterized families of ABPs, particularly regarding its role in oocyte maturation, is the actin nucleator.[17] The generation of new actin filaments is a crucial regulatory step in actin filament remodeling.[18] To overcome the thermodynamic barrier for monomeric actin to polymerize as filament actin, actin nucleation seed, which usually consists of 3 actin monomers, must be stabilized to accelerate actin filament formation (Fig. 2A).[19] The ARP2/3 complex, a 7-subunit protein complex responsible for generating branched actin filaments from pre-existing filaments,[20,21] is the most extensively studied actin nucleator and is implicated in oocyte maturation [22,23] and early embryogenesis.[23-25] Formin family proteins are also involved in various aspects of actin filament remodeling.[26] Among them, formin-2 (encoded by *Fmn2* in mouse) is thought to be involved in oocyte maturation.[27]

In addition to actin nucleators, several other classes of ABPs exist, including monomeric actin (also called G-actin) binding proteins such as depolymerization/severing proteins,[28] filament capping proteins,[29,30] filament-binding/crosslinker protein,[31] and myosins, a family of actin-based motor proteins.[32] Considering that other cellular processes, including cell migration and cytokinesis, depend on classes of ABPs other than actin nucleators, ABPs may play crucial roles in actin cytoskeleton remodeling during oocyte maturation and early embryogenesis. However, the roles of these classes of ABPs in oocyte maturation have not been as well studied as those of actin nucleators.

Several previous reviews present general overviews of the roles of actin remodeling during oocyte maturation and asymmetric division.[4,33-35] In this review, we mainly focus on the roles of ABPs in terms of their effect on actin dynamics during oocyte maturation. We also describe the roles of ABPs in oocyte maturation and embryogenesis in relation to their previously studied biochemical and cellular roles in other systems. In particular, we discuss ABPs that have not been extensively studied in oocyte maturation and suggest their potential roles in oocyte maturation and early embryogenesis.

Actin nucleator and nucleation-promoting factors

Formin-2 and other formin family proteins

In mammals, there are 15 formin proteins containing formin-homology domain 1 (FH1) and 2 (FH2)[26]; these domains are responsible for actin nucleation and elongation activity of the

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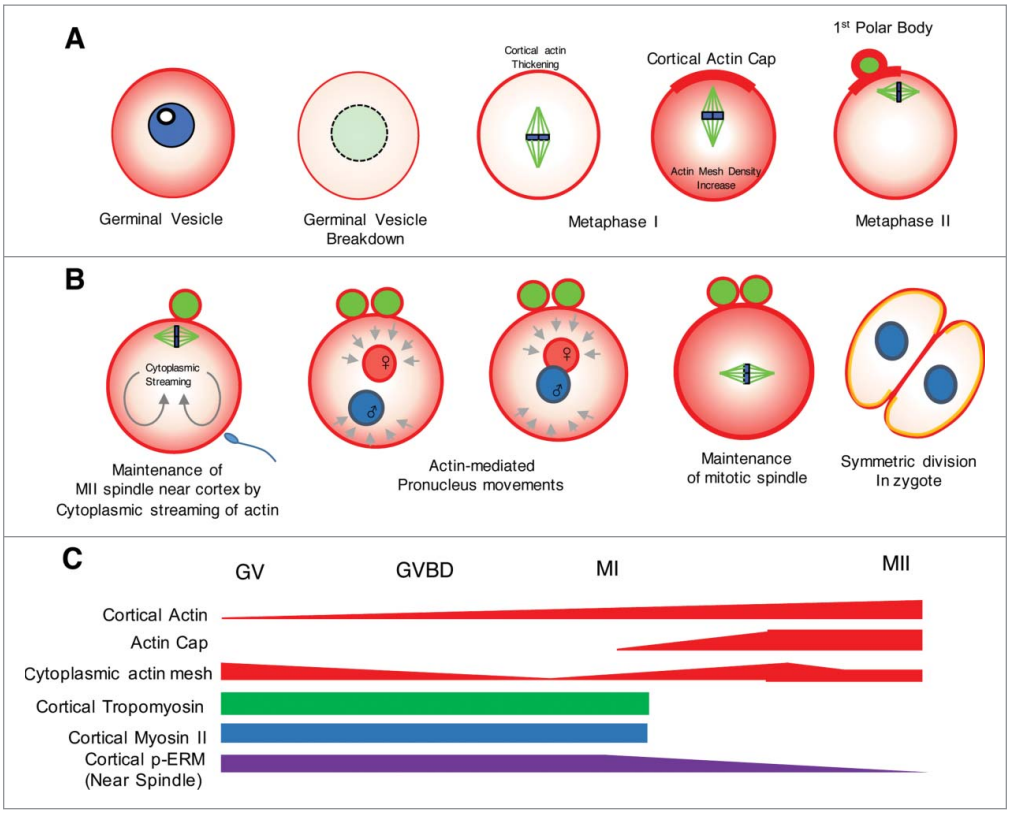

Figure 1. Dynamic changes in actin and actin-binding proteins during mammalian oocyte maturation. (A) During oocyte maturation, 3 types of actin reorganization processes occur. The first process is a change in cytoplasmic actin density. During the germinal vesicle (GV) stage, cytoplasmic actin mesh is formed at a higher density than germinal vesicle breakdown (GVBD) or that during the early MI stage,[11] and is increased during spindle migration and the anaphase-telophase transition.[10] The second process is the formation of the cortical actin cap,[5] which appears at the vicinity of the approaching spindle. Formation of the cortical actin cap is mediated by the RAN^{GTP} signal associated with chromatin.[76] Thickening of the cortex during the MI stage[12] also occurs. Actin is indicated in red, microtubules in green, and chromatin in blue. (B) Stages of symmetric division in the mouse zygote and involvement of F-actin dynamics. In MII-stage oocytes, the spindle position is maintained near the cortex by cytoplasmic actin streaming generated by ARP2/3-mediated actin polymerization.[23] The direction of actin-mediated cytoplasmic streaming is shown as an arrow. After fertilization, the second polar body is extruded after meiosis II. Pronuclei originating from male and female gametes (marked as blue and red, respectively) migrate to the center of zygotes, and their movement is dependent on actin dynamics and myosin Vb.[143] The fine control of pronucleus centering involves high cortical tension mediated by myosin II recruitment.[143] Maintenance of the mitotic spindle in the center of zygotes may depend on increased cytoplasm viscosity, which could be linked to an increased concentration of actin mesh.[143] ARP2/3 (shown as yellow) is maintained in cell cortex regions but absent from the cleavage furrow. This polarization of ARP2/3 is maintained until the morula embryonic stage[24] and thus results in apical polarization. Note that the SCMC,[23,146] a protein complex essential for pre-implantation development and symmetric cell division, shows a similar localization during embryogenesis.[142,146,147] The timing of each developmental stage of symmetric cell division is shown as the hour after fertilization. The directions of spindle or pronucleus movement mediated by actin polymerization are shown as arrows. (C) Temporal changes in actin and ABP levels during oocyte maturation. Temporal changes in actin or ABPs during each oocyte maturation stage are indicated by the height of the bars. Cortical actin thickness is increased after the MI stage[12] and is associated with the exclusion of non-muscle myosin II from the cortex.[12] ARP2/3-mediated actin polymerization is directly involved in this process.[13] TPM3.1 is localized in the cortex during oocyte maturation but disappears in MII-stage oocytes.[84] p-ERM is localized near the cortex but is excluded from the region near the spindle.[77,123] The RAN^{GTP} signal is associated with exclusion of p-ERM near the spindle.[77]

protein (Fig. 2B). Formin-2 (*Fmn2*) was the first actin nucleator shown to be associated with oocyte maturation.[27] Knockout of mouse *Fmn2* causes failure of spindle migration and fertilization and results in polyploidy due to arrest in metaphase I (MI) stage.[27,36] During oocyte maturation, formin-2 is localized in the cortex[10] and intracellular vesicles.[37,38] *Fmn2* is responsible for the generation of cytoplasmic actin mesh, which dynamically changes during oocyte maturation and is essential for spindle migration.[10,38,39]

Other formin proteins, including mouse homologs of *Drosophila* diaphanous (mDia) family formins, are regulated by autoinhibitory mechanisms and activated by the Rho-family GTPase RHOA,[26] but the specific mechanisms regulating formin-2 are unclear. Biochemical and genetic studies using the *Drosophila* formin-2 homolog *Cappuccino* demonstrate the presence of an autoregulatory mechanism through an interaction between N-terminal and C-terminal FH2 domains,[40,41] suggesting that formin-2 is regulated by similar autoregulatory mechanisms. However, the mechanisms through which upstream signaling molecules activate formin-2, particularly during oocyte maturation or embryogenesis, are unclear.

In addition to formin-2, at least 14 other formin family proteins have been identified in the mammalian genome, some of which may be involved in oocyte maturation. The biochemical properties of mDia family formins, including mDia1, mDia2, and mDia3, have been extensively studied,[26,42,43] and mDia1 and mDia2 have been shown to be expressed in mouse oocytes.[44,45] Knockdown of mDia1 or mDia2 decreases polar body extrusion and causes abnormal spindle morphology,[45,46] indicating that mDia family formins are involved in proper meiotic spindle formation, in concord with previous studies showing that mDia formins are involved in maintaining the stability of microtubules in somatic cells.[43,47] In addition to formin-2 and mDia family formins, mouse formin-like 1 (*Fmnl1*) was recently implicated in oocyte maturation.[48] However, it is unclear how many formin family proteins are involved in

Table 1. Actin-binding proteins involved in oocyte maturation. Known biochemical functions, roles in oocyte maturation and embryogenesis are listed.

Classes	Proteins	Known biochemical roles	Physiological roles in oocyte maturation
Actin nucleators and NPFs	ARP2/3 complex	Nucleate new actin filaments by branching from existing filaments	Cortical actin cap formation[22]; Subcortical actin thickening[12,13]; Generation of cytoplasmic flow to maintain position of spindle in MII oocytes[23]; Fast-phase migration of spindle[65]
	Formins	Nucleate actin filaments and facilitate filament elongation	Spindle migration[27,36]; Cytokinesis[36]; Cytoplasmic actin mesh formation (formin-2)[10,11]; Meiotic spindle formation (mDia family)[45]
	Spire	Cooperate with formin-2 and form straight actin filaments	Cytoplasmic actin mesh formation in collaboration with formin-2[39]
	N-WASP	Activate the ARP2/3 complex via cdc42	Cortical actin cap formation
	WAVE2	Activate the ARP2/3 complex via Rac	Spindle formation and migration[66]; Subcortical actin formation[12]
	JMY	Activate the ARP2/3 complex	Spindle formation and migration[68]
	WHAMM	Activate the ARP2/3 complex	Spindle formation and migraton[69]
Filament severing	ADF/cofilin	Sever existing actin filaments and promote recycling of filaments	Recycling of cortical and cytoplasmic actin
Filament binding and protection	Tropomyosin(TPM3.1)	Bind actin filaments and protect from depolymerization/modulation of actin-myosin interactions	Maintenance of cortical actin integrity[84]
Filament capping	Heterodimeric actin-capping protein (CP)	Bind to fast-growing ends of actin filaments and block elongation	Control of cytoplasmic actin mesh in competition with formin-2[99]
	Tropomodulin(TMOD3)	Bind slow-growing ends of actin filaments and protect from depolymerization	Maintenance of cytoplasmic actin mesh level

oocyte maturation. The novel small molecule inhibitor SMIFH2,[49] which binds to and inhibits the actin nucleation activity of the FH2 domain, inhibits several formin proteins in cells and has been used to treat immature oocytes, blocking various stages of oocyte maturation and resulting in phenotypes distinct from those of *Fmn2*(−/−) knockout oocytes.[45] These results indicate that other formin proteins besides FMN2 are involved in oocyte maturation; however, their precise roles in oocyte maturation and early embryogenesis remain to be investigated.

Spire

Spire was first identified as a maternal effect locus that mediates *Drosophila* embryogenesis.[50,51] Spire has 4 Wiskott-Aldrich syndrome homology 2 (WH2) domains,[52] monomeric actin-binding motifs which are necessary for its actin nucleation activity.[53] In addition to the WH2 domain, a kinase noncatalytic C-lobe domain (KIND), which interacts with the C-terminal of FMN2 or *cappuccino* (the *Drosophila* homolog of *Fmn2*), is located in the N-terminal region of spire,[54,55] whereas the putative zinc-finger domain and modified FYVE domains are located in the C-terminal region.[56]

Knockdown of 2 genes encoding spire in the mouse, *Spire1* and *Spire2*, impairs mouse oocyte maturation and ablation of actin mesh formation,[39] similar to the phenotype of *Fmn2* knockdown.[10,11,27,36] Based on the evolutionarily conserved protein-protein interaction between formin-2 (cappuccino in *Drosophila*) and spire, and their colocalization in Drosophila[55,57] and mouse oocytes,[39] formin-2 and spire appear to function as a single unit for actin nucleation in oogenesis in both *Drosophila* and mammals. *In vitro*, the spire protein has relatively weak actin nucleation activity; however, its activity is significantly increased by interaction with cappuccino.[55] Because formin family proteins exist as dimers, and artificial dimerization of the WH2 domain of spire significantly increases its *in vitro* actin nucleation activity[58] and the binding of spire inhibits nucleation activity of formin-2/cappucinno,[55,59] spire may function as an actin nucleator by associating with formin-2 only *in vivo*. Besides its interaction with formin-2, the regulatory mechanisms of spire are still elusive. Based on the presence of a putative rab-binding domain in spire and its colocalization with RAB11A and formin-2 at the vesicles and cortex in mouse oocytes,[37,38] spire may localize at vesicles via its interaction with RAB11A. As the expression of dominant-negative RAB11A impairs spindle migration and actin mesh formation in mouse oocytes,[38] localization of spire on vesicles could be a mechanism regulating spire activity and formation of cytoplasmic actin mesh. Mechanistic studies on the regulation of spire in concert with formin-2, particularly in terms of the signaling pathways involved in oocyte maturation such as the maturation promoting factor (MPF)[60] or mitogen-activated protein kinase (MAPK) signaling pathways,[61] would provide more detailed characterization of the roles of spire in oocyte maturation.

The ARP2/3 complex and nucleation-promoting factor

The ARP2/3 complex is a protein complex that initiates the formation of new actin branches on the side of pre-existing actin filaments (Fig. 2C).[20,21] This complex was the first known and is the most extensively characterized actin nucleator,[62] and its roles in various cellular processes, including cell migration, have been extensively studied.[63] During oocyte maturation, chemical inhibition or RNAi-mediated knockdown of ARP2/3 complex components causes failure of asymmetric division in murine[22,23] and porcine oocytes.[64] Recent studies provide a more detailed understanding of the role of ARP2/3 in oocyte maturation. Spindle migration includes 2 phases; the first slow phase mainly depends on the action of formin-2, whereas the second rapid migration phase involves ARP2/3-mediated actin polymerization.[65] In addition, ARP2/3-mediated actin polymerization generates cytoplasmic streaming inside oocyte cytoplasm and is the main driving force maintaining the localization of the meiotic spindle near the cortex

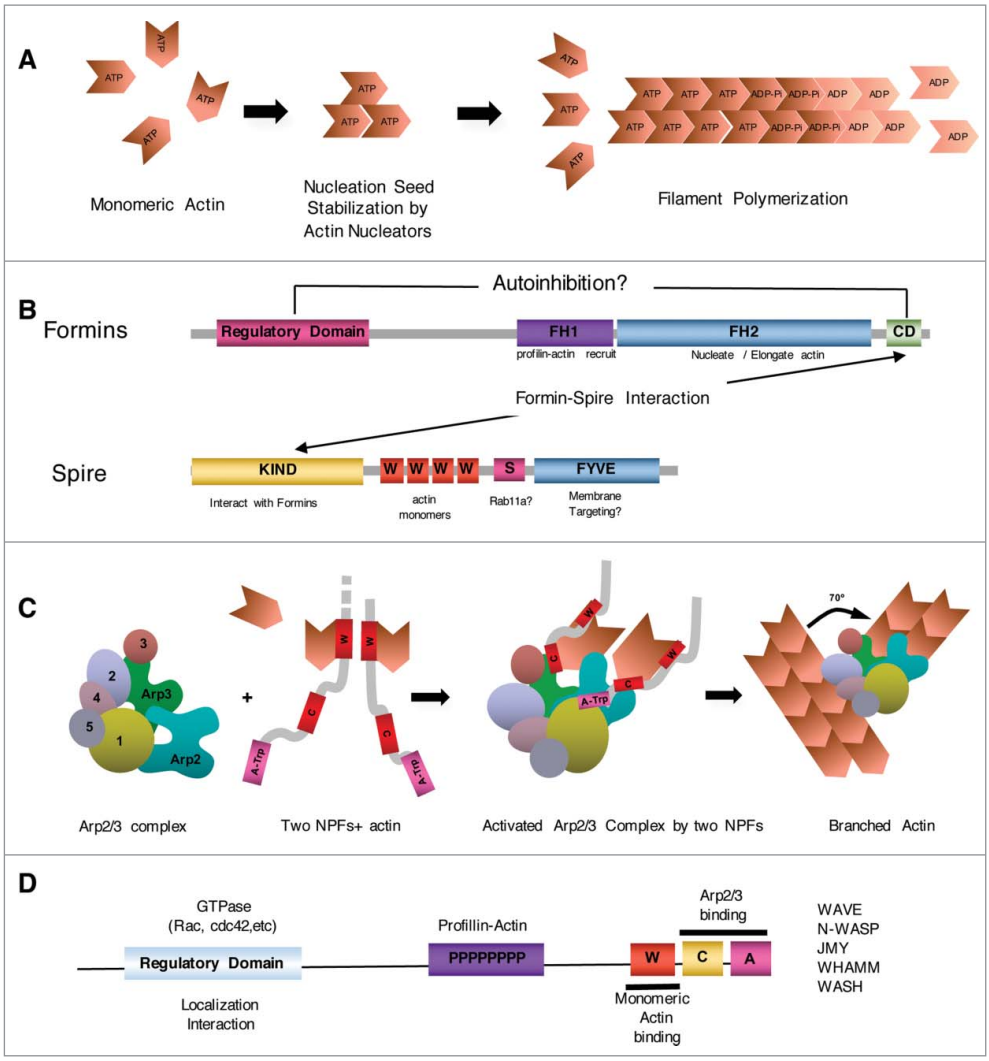

Figure 2. Actin nucleators and actin filament nucleation. (A) Actin polymerization is a kinetically unfavorable process and is accelerated by actin nucleators, which are families of proteins that stabilize unstable actin filament nucleation seeds. Whereas ATP-bound actin is mainly incorporated into fast-growing (also called barbed) ends of filaments, nucleotide hydrolysis occurs in the filaments, and ADP-bound actin is depolymerized at the slow-growing (also called pointed) ends of filaments. (B) Formin proteins and spire are important actin nucleators for the generation of actin filaments in oocytes. The domain architecture of canonical formin proteins (left). The proline-rich FH1 domain recruits profilin-actin complexes and directs them to the FH2 domain, which is responsible for the actin nucleation/elongation activity of the protein. Formins are usually regulated by an interaction between the C-terminal domain (CD) and the N-terminal regulatory domain. CD is essential for FMN2 catalytic activity and interaction with spire.[154] The domain architecture of spire (right). Four tandem WH2 domains (marked as W) are responsible for binding with monomeric actin. Spire interacts with formin proteins via the N-terminal KIND.[54] The putative Rab-binding domain[56] (Spire-box, marked as S) and a modified FYVE domain,[155] which usually target the protein to the membrane, are located in the CD. In mammalian oocytes, FMN2 interacts and cooperates with spire1/2[39] and is responsible for outer cortical actin and cytoplasmic actin mesh.[12] (C) The ARP2/3 complex is a 7-protein complex responsible for the generation of branched actin.[63] This complex contains 2 actin-related proteins (ARP2 and ARP3). Two NPFs recruit monomeric actin and bind to the ARP2/3 complex, activating ARP proteins.[156,157] (D) Domain organization of typical NPFs. Regulatory domains can bind various GTPases, including Rac1 in the case of WAVEs[158,159] and cdc42 in the case of n-WASP.[160] Regulatory regions can also be involved in the localization of NPFs and actin polymerization, such as in the case of WHAMM[161] or WASH.[162] All known NPFs contain C-terminal 'W-C-A' motifs consisting of WH2 (marked as W), cofilin homology (C), and acidic (A) domains. The WH2 motif is responsible for monomeric actin recruitment, whereas 'C-A' motifs are required for ARP2/3 binding. Illustrations were adapted from Dominguez and Namgoong[163] and modified to accommodate more recent findings.

in mature oocytes.[23] Moreover, the ARP2/3 complex is responsible for the formation of a thicker cortex region called the 'subcortex'; the formation of the subcortex by ARP2/3 may be a factor mediating the exclusion of non-muscle myosin II and can cause changes in cortex softening during oocyte maturation.[12,13]

Nucleation-promoting factor (NPF) family proteins are necessary for the activation of the ARP2/3 complex, and several NPFs, including Wiskott-Aldrich syndrome protein family member 2 (WAVE2),[66] neuronal Wiskott-Aldrich syndrome protein (N-WASP),[67] junction-mediated regulatory protein (JMY),[68] WASP homolog associated with actin, membranes, and microtubules (WHAMM),[69] and WAS protein family homolog 1 (WASH),[70] are implicated in oocyte maturation(Fig. 2D). Because activation of NPF is a pivotal regulatory step for ARP2/3-mediated actin polymerization, the upstream signal regulating NPF plays a crucial role in oocyte maturation. In the case of WAVE2, the small GTPase RAC1 activates WAVE2-mediated actin polymerization,[71] and the expression of a dominant-negative mutant of RAC1 impairs actin cap formation during oocyte maturation,[72] indicating that Rac1 is a pivotal signaling molecule upstream of ARP2/3-mediated actin polymerization during oocyte maturation. In addition, CDC42, which activates N-WASP, is involved in oocyte maturation and the protrusion of the polar body and formation of the actin cap.[67,73] Compared with WAVE2 or N-WASP, regulatory mechanisms of

other NPFs, including WHAMM, WASH, and JMY, are still elusive. Besides RAC1 or CDC42, the small GTPase RAN, which is localized as a gradient toward chromatin,[74,75] is involved in ARP2/3-mediated actin polymerization, especially cortical cap formation.[76] The RAN^{GTP} gradient is also involved in the polarization of the inactive Ezrin-Radixin-Moesin (ERM) protein in oocytes.[77] However, the signaling pathway connecting RAN with ARP2/3-mediated actin polymerization is poorly understood. In addition to the small GTPase pathway, the actin polymerization pathway may be connected with well-known signaling pathways governing the cell cycle, including the MPF or Mos-MAP kinase pathways, and elucidation of these mechanisms could be critical for increasing our understanding of the regulation of ARP2/3-mediated actin polymerization based on cell cycle progression. Recent studies[12,13] show that WAVE2 is phosphorylated by the extracellular signal-regulated kinase (ERK) pathway and activates ARP2/3-dependent actin polymerization as oocyte maturation progresses in mice, demonstrating the presence of crosstalk between the 2 signaling pathways. It is also possible that other NPFs and ABPs are regulated by MPF or MAPK pathways during oocyte maturation; however, the details of these mechanisms have not yet been elucidated.

Actin filament protection and depolymerization

Actin depolymerization factor/cofilin

Actin filaments initiated by actin nucleators must be depolymerized to recycle actin monomers. Therefore, active depolymerization or severing of existing actin filaments are crucial for dynamic actin filament reorganization.[78] The main workhorse for actin depolymerization is the actin depolymerization factor/cofilin (ADF/cofilin) family of proteins.[79] In mammals, there are 3 isoforms of cofilin (cofilin-1, cofilin-2, and destrin). Cofilins bind to actin filaments and monomers with a greater binding affinity for ADP-containing actin than for ATP-actin; therefore, cofilin binds to relatively old regions of the actin filament and severs them into shorter fragments(Fig. 3A).[79] Negative regulation of cofilin is achieved by phosphorylation of the serine (Ser3) residue at the N-terminal end of cofilin (Fig. 3B).[80,81] Phosphorylation by LIM kinase decreases the F-actin-binding affinity of cofilin.[76] Additionally, LIM kinase activity is activated by Rho-associated kinase (ROCK) (Fig. 3B).[82] Inhibition of ROCK by chemical inhibitors or siRNA decreases the phosphorylation of cofilin in oocytes, thereby increasing the activated portion of cofilin and impairing mouse oocyte maturation,[83] indicating that the maintenance of proper levels of activated cofilin is important for oocyte maturation control. Inhibition of ROCK or expression of the dominant-active form of cofilin decreases cortical actin levels and impairs oocyte maturation,[83,84] indicating that levels of activated cofilin should be regulated properly during oocyte maturation. Phosphorylated cofilin can be reactivated by slingshot phosphatases[85] through dephosphorylation of phospho-Ser^3 in cofilin, and functional studies in *Xenopus* oocytes show the importance of slingshot phosphatases in meiotic spindle assembly.[86] However, the involvement of slingshot phosphatases in mammalian oocyte maturation has not yet been investigated.

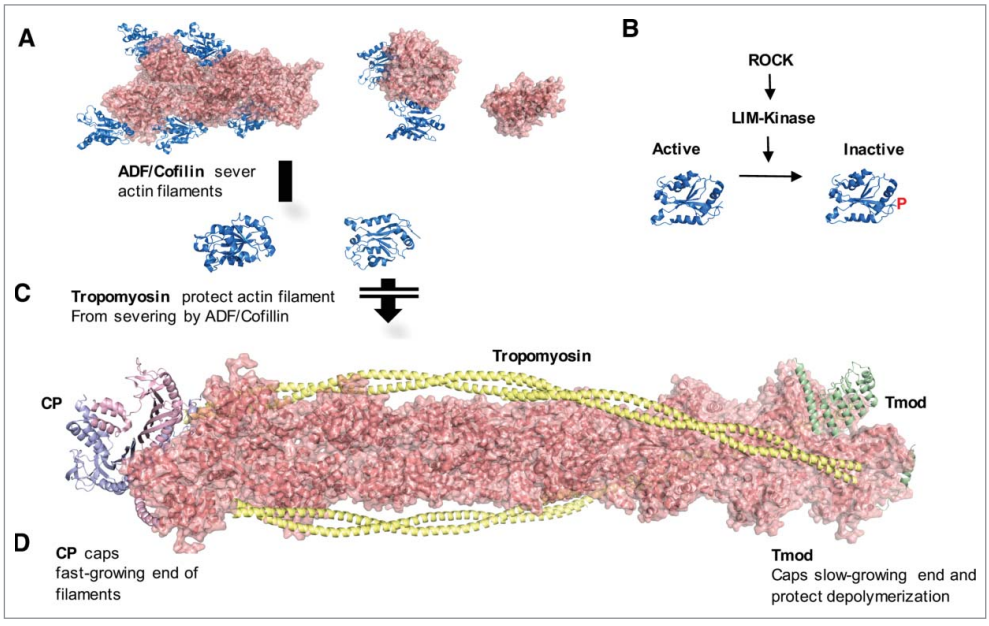

Figure 3. Roles of ABPs in the maintenance of actin filaments. (A) ADF/cofilin (shown as red) binds to and severs actin filaments, thereby promoting the depolymerization and recycling of actin filaments. The actin and cofilin binding model shown is based on the electron microscopy (EM) model of actin decorated by cofilin(PDB:3J0S).[164] (B) ADF/cofilin activity is regulated by phosphorylation at Ser3 in the N-terminal[80] and is mediated by the ROCK-LIM kinase signaling pathway.[82] C. Tropomyosins (shown as yellow) are proteins that bind to the sides of filaments and protect actin filaments from ADF/cofilin.[88,165] The actin-tropomyosin model shown is based on the EM-based actin-tropomyosin structure (PDB:3J8A).[166] In oocytes, knockdown of tropomyosin decreases cortical actin levels and impairs cortical integrity during cytokinesis.[84] (C) The 2 ends of actin filaments have different affinities for the addition of actin monomer.[167] The fast-growing ends of actin filaments are capped by heterodimeric CP (shown as light blue and blue), which blocks the additional polymerization of actin filaments,[168] whereas the slow-growing ends of actin filaments are protected from depolymerization by tropomodulin (shown as green), which also binds with tropomyosin.[169] Both CP and Tmod3 are essential for maintaining cytoplasmic actin mesh levels in growing oocytes.[99] Tmod3 and actin binding at the slow-growing end of actin filaments is shown based on the Tmod-actin complex structure (PDB:4PKI, 4PKH).[170] CP and actin binding on the fast-growing ends of filaments was modeled based on the EM reconstitution of actin with CP[171] and the structure of dynactin complex,[172] which contains CP, Actin-related protein 1 (ARP1), and β actin (PDB:5ADX).

Tropomyosin

Whereas ADF/cofilin can sever and promote depolymerization of existing actin filaments, tropomyosin, a long coiled-coil protein that binds to the sides of actin,[87] protects actin filaments from depolymerization.[88] In mouse oocytes, knockdown of the non-muscle isoform of tropomyosin (TPM3.1) decreases cortical actin levels and promotes formation of the membrane bleb structure, which is caused by the collapse of cortical actin during cytokinesis,[84] indicating that the maintenance of cortical integrity via the protection of actin filaments is crucial for proper asymmetric division. These phenotypes are similar to those induced by ROCK inhibition (i.e., increased amounts of active cofilin)[83] or overexpression of dominant-active cofilin.[84] Notably, decreasing cortical actin levels by the expression of dominant-active cofilin can be suppressed by co-expression of tropomyosin,[84] demonstrating that non-muscle tropomyosin can protect cortical actin from depolymerization, presumably by protecting actin filaments from cofilin.

Cortical tropomyosin is excluded as oocytes mature to the MII stage.[84] The moment of exclusion of tropomyosin from the cortex during oocyte maturation coincides with the exclusion of non-muscle myosin II,[12] which is directly related to cortex softening, a driving force for asymmetric spindle migration.[12,13,35,89] It is unclear whether exclusion of tropomyosin from the cortex is the consequence or cause of myosin II exclusion, and the relationship between these proteins needs to be clarified. However, based on the functional roles of tropomyosin in the regulation of myosin-actin interactions,[90-93] the exclusion of tropomyosin could directly facilitate the exclusion of myosin II.

Filament end capping proteins and actin mesh control

Actin filaments have 2 ends; one is the fast-growing end (also called the barbed end), and the other is the slow-growing end (also called the pointed end).[94] Because actin filaments can be depolymerized from both ends or can grow indefinitely, both ends should be capped by filament-binding proteins, called capping proteins(Fig. 3D).[95,96]

At the fast-growing barbed end of a filament, heterodimeric actin-capping protein (CP) binds and blocks further elongation.[96,97] CP is a core factor involved in ARP2/3-mediated actin polymerization.[98] When CP expression is reduced by RNAi or inhibited by overexpression of the CP antagonist CARMIL in mouse oocytes, asymmetric division of oocytes is compromised, and cytoplasmic actin mesh levels are significantly reduced.[99] How can CP affect cytoplasmic actin mesh that has been nucleated by formin-2/spire[10,39]? Recent biochemical studies show that CP and formins can simultaneously bind to the barbed ends and form a ternary complex called a 'decision-complex' involved in elongation or filament end blocking,[100,101] indicating that CPs regulate formin-mediated actin polymerization. Owing to the processivity of formin-mediated actin elongation *in vitro*,[42] the length of actin filaments generated by formin should reach more than tens of micrometers before detachment,[101] which is comparable to the diameter of mammalian oocytes. However, actin mesh lengths are much shorter than this,[10,37] suggesting the presence of a regulatory mechanism preventing formin-mediated elongation and the start of a new cycle of actin polymerization. CP in the cytoplasm of oocytes may regulate actin filament length by competition with FMN2; however, the detailed mechanisms involved in these processes are still elusive. Whereas CP binds to and blocks elongation at the barbed ends of filaments, tropomodulin is responsible for capping the slow-growing pointed ends of actin filaments and protects actin filament from depolymerization.[102,103] The physiological roles of tropomodulin have been investigated in various cells, including blood erythrocytes, skeletal muscle cells,[104] and lens cells,[105] and loss of tropomodulin impairs actin structure by promoting depolymerization from the pointed end. The ubiquitous isoform of tropomodulin, TMOD3, is expressed in mouse oocytes, and knockdown of tropomodulin causes a significant decrease in cytoplasmic actin mesh and impairs oocyte maturation (Jo et al., manuscript submitted).

Tropomodulins interact with tropomyosin and stabilize tropomyosin binding on actin filaments.[106,107] In mouse oocytes, overexpression of the N-terminal part of TMOD3, which has a tropomyosin binding region, produces dominant-negative effects similar to the phenotype caused by TMOD3 knockdown (Jo *et al.*, manuscript submitted). Simultaneous knockdown of TPM 3.1 and TMOD3 has an additive effect on decreasing cytoplasmic actin mesh levels, indicating that interaction and cooperation between TMOD3 and TPM 3.1 is essential for maintaining tropomyosin. Collectively, these results show that the capping of both ends of actin filaments by ABPs is essential for maintaining cytoplasmic actin mesh. However, it is not yet clear whether regulation of filament end-binding protein activities are responsible for the dynamic changes in cytoplasmic actin mesh levels during oocyte maturation. CPs are regulated by several factors, including phosphatidylinositol 4,5-bisphosphate[108] and various 'decapping' proteins such as CARMIL[109,110] and CD2AP.[111] In the case of TMOD3, protein phosphorylation by AKT2 is implicated in the regulation of Tmod3 in mouse fibroblasts.[112,113] Based on reports showing that chemical inhibition of AKT2 affects oocyte maturation,[114-116] TMOD3 could be regulated by phosphorylation through AKT during oocyte maturation. However, the potential regulation of TMOD3 by AKT or other signaling pathways needs to be investigated.

Myosin motors in oocyte maturation

Non-muscle myosins play roles in various cellular processes including cell adhesion, cell migration, and cell division.[117] In mouse oocytes, myosin IIA and IIB are expressed on the cortex in germinal vesicle (GV)-stage oocytes, whereas myosin IIA is only expressed on meiotic spindles in mature oocytes (Fig. 4A).[118] Anti-myosin II antibody injection[118] or chemical inhibition of myosin light chain kinase[119] effectively blocks spindle migration, supporting the essential role of non-muscle myosin II in oocyte maturation. Recently, myosin II exclusion from mature oocytes was shown to mediate cortex softening in MII-stage oocytes and to be essential for spindle migration during meiosis.[12,13] Interestingly, ARP2/3 complex-mediated actin polymerization in the cortex is implicated in myosin exclusion,[13] although the underlying mechanisms are still not clear. Biochemical studies show that tropomyosin has antagonistic effects on ARP2/3-mediated actin polymerization,[120] whereas ARP2/3 and cofilin, in turn, control the binding of tropomyosin

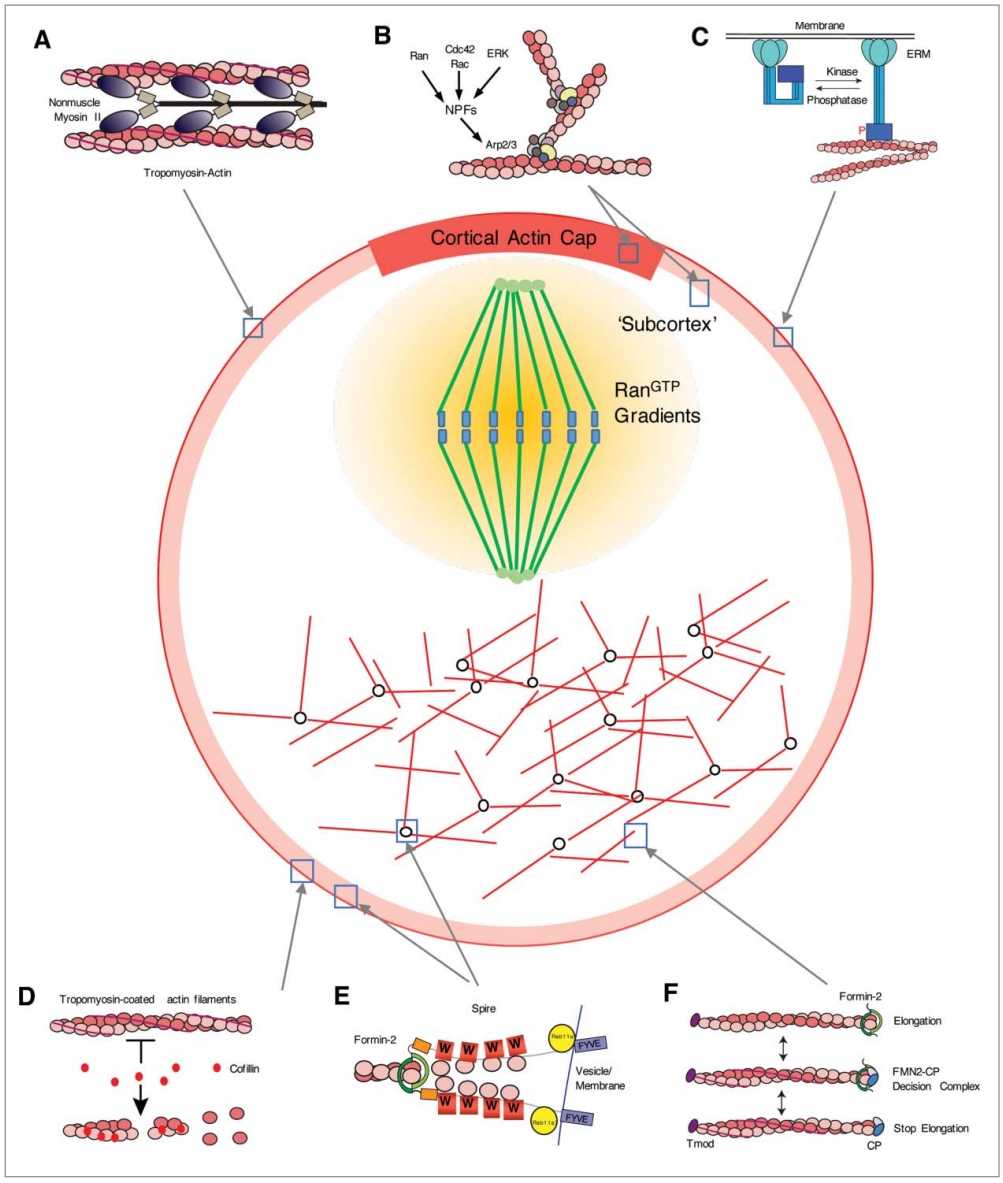

Figure 4. Various molecular events governed by ABPs in maturing oocytes. Localizations of ABPs in the oocyte are also indicated. Actin in oocytes were marked as red. (A) Actomyosin contraction between actin filaments and non-muscle myosin II is responsible for maintaining the cortical tension of the oocyte cortex.[12,13,123] During oocyte maturation, delocalization of myosin II decreases cortical tension and is crucial for spindle migration.[12] (B) ARP2/3-mediated actin polymerization is responsible for the formation of the cortical actin cap[67,73,76] and cortex thickening during oocyte maturation.[12,13] Small GTPases including RAC1,[72] CDC42,[67] and RAN[GTP/GDP][76] are implicated in the activation of NPFs, which in turn activate the ARP2/3 complex. The MOS-MAPK pathway[173] is also involved in triggering WAVE2-dependent ARP2/3-mediated actin polymerization.[12] (C) ERM proteins localize in the oocyte cortex, act as link between the plasma membrane and cortical actin, and are involved in maintaining cortical tension.[123] ERM protein is activated by phosphorylation on the C-terminal tail domain and deactivated by dephosphorylation.[122] A recent study suggests that p-ERM is excluded at the cortex near the approaching spindle, which is mediated by RAN-based signaling.[77] (D) In the oocyte cortex, Tpm3.1 is present with cortical actin and protects against depolymerization by cofilin.[84] Cofilin activity in oocytes is regulated by phosphorylation by ROCK-LIM kinase cascades.[83] (E) Formin-2 and spire are both responsible for the generation of cytoplasmic actin mesh or cortical actin[10,11,38,39] in mammalian oocytes. Biochemical results[55,59,154] suggest that both proteins synergistically promote actin nucleation. WH2 domain (marked as W) recruit monomeric actin. The presence of a potential Rab-binding domain and membrane-binding FYVE domain in the C-terminal part of spire[56] suggests the possibility that spire mediates the recruitment of formin-2 in vesicles and the membrane in cooperation with Rab11a.[38] (F) Formin-2 and heterodimeric CP compete against each other at the fast-growing filament end and regulate actin elogation[100,101] Because the length of actin filaments generated by formins is much longer than that of cytoplasmic actin mesh[10,37,101], some mechanism must regulate the elongation of actin filaments by formin-2. Impairment of CP in mouse oocytes decreases cytoplasmic actin density,[99] suggesting that CP regulates actin mesh.

to filamentous actin.[121] A recent report showed that tropomyosin is excluded during the MII stage of mouse oocytes,[84] suggesting that tropomyosin plays important regulatory roles in ARP2/3-mediated actin polymerization in the cortex and myosin exclusion in mature oocytes. However, the detailed roles of tropomyosin in ARP2/3-mediated actin polymerization and myosin recruitment/exclusion in the cortex need further investigation.

In addition to non-muscle myosin II, myosin Vb is also present in the cytoplasm in oocytes and plays roles in the movement of vesicles and the formation of cytoplasmic actin mesh.[37,38] In contrast to the long-range movement observed in most somatic cells, vesicles in oocytes move along microfilaments, and myosin Vb carries vesicles as cargo along actin filaments formed by the actin nucleators FMN2 and spire localized at the vesicular surface.[37,38] Expression of dominant-

negative mutant myosin Vb impairs spindle migration,[38] indicating the importance of myosin Vb in vesicle movement and actin mesh formation.

ERM family proteins and linking with the plasma membrane

ERM family proteins crosslink the plasma membrane and actin filaments, providing structural links to strengthen the cell cortex(Fig. 4C). These proteins also participate in cellular signaling cascades.[122] In oocytes, ERM proteins are localized in the cellular cortex, and the activation of ERM by phosphorylation is important for maintaining cortex integrity and cortical tension.[123] Interestingly, activated phospho-ERM (p-ERM) in the cortex is excluded when the meiotic spindle approaches the cortex,[77,123] and polarization of p-ERM is induced by the RAN^{GTP} signal,[77] which migrates along chromatin and is responsible for the formation of the cortical actin cap.[76] These findings suggest that inactivation of ERM in the cortex near the actin cap and cortical granule-free domain is involved in polar body extrusion by modulation of cortical tension.[123] How $RAN^{GTP/GDP}$ induces cortical polarization of p-ERM and the actin cap is still not clear, but the polarization of p-ERM has been shown to be independent of RAC or CDC42 signaling.[77]

Recently, kinetochore-localized protein phosphatase 1 (PP1)-SDS22 holoenzymes were shown to dephosphorylate p-ERM in the cell cortex and break cortical symmetry.[124] It is not clear whether PP1-SDS22 is responsible for p-ERM exclusion in the region of the cortical actin cap in oocytes, and further studies are needed to validate these results. However, because the PP1 targeting subunit SDS22 contains a predicted leucine-rich repeat domain, which is frequently found in many RAN-binding proteins including RANGAPs,[125] this finding suggests the possibility that the protein phosphatase activity of SDS22-PP1 is regulated by the RAN^{GTP} gradient.

Actin monomer-binding proteins: Potential roles in oocyte maturation?

Because the cellular concentration of total actin is more than 0.1 mM, and actin tends to polymerize under physiological salt concentrations *in vitro*,[126] most cellular actin should exist as filaments; however, approximately 40% of total actin in cells is present as monomers.[127] One explanation for this disparity is that most monomeric actin exists as a complex with ABPs, including profilin and thymosin β4.[128] Besides preventing spontaneous actin polymerization, profilin binds to actin monomers and facilitates rapid exchange of actin-bound ADP to ATP.[129] The *Drosophila* profilin mutant(*chickadee*) is implicated in oogenesis defects,[130] and ablation of profilin in bovine embryos impairs early embryonic development,[130] indicating the essential roles of profilin in mammalian embryogenesis.

Although profilin-bound actin is a better substrate for formin-mediated elongation, it is a poor substrate for ARP2/3-mediated actin nucleation.[131,132] Therefore, upregulation of the ratio of profilin-bound actin could promote actin polymerization by formin instead of ARP2/3. In budding yeast, the different actin structures generated by formin or the ARP2/3 complex can be regulated by manipulation of the fraction of profilin-bound actin in monomeric actin.[133]

Because ARP2/3- and formin-mediated actin polymerization processes are both important for oocyte maturation, profilin may play important roles in controlling the balance of the actin polymerization pathway between ARP2/3- and formin-mediated actin polymerization, thereby controlling oocyte maturation, as has been observed for *Drosophila* oogenesis.[130] However, the specific roles of profilin in mammalian oocyte maturation are still unclear.

In addition to profilin, thymosin-β4, another monomeric actin-binding protein, is involved in maintaining monomeric actin pools.[134] Apart from its role in monomeric actin sequestration, thymosin-β4 is involved in the regeneration and proliferation of cardiac cells[135,136]; therefore, thymosin-β4 may play a role in early embryogenesis (e.g., cell fate specification). However, its roles in oocyte maturation and embryogenesis have not yet been investigated. Collectively, actin-monomer—binding proteins, such as profilin and thymosin-β4, have the potential to function in oocyte maturation and embryogenesis, but further studies are needed to determine their specific roles in these processes.

Transition between asymmetric and symmetric division: Roles of F-actin

The most dramatic changes from meiotic cell division to the first mitotic division include the transition from asymmetric-to-symmetric cell division. Because the position of the midzone in the spindle determines the cleavage planes in cytokinesis,[2] spindle movement near the cortex during oocyte maturation is the main reason for asymmetric division in oocytes and is mainly driven by actin cytoskeleton remodeling. We then wonder how the first mitotic spindle maintains its position in the zygote and mediates symmetric division. Although most animal cells depend on astral microtubules for the positioning of the spindle at the center of the cell,[3] most mammalian zygotes lack astral microtubules[137]; therefore, the positioning of the spindle in zygotes may not rely on microtubule interactions.

As previously mentioned, both formin-2/spire- and ARP2/3-mediated actin polymerization processes are important for spindle migration in oocytes, and cytoplasmic streaming generated by ARP2/3-mediated actin filaments maintains the localization of meiotic spindles near cortex in MII oocytes. Studies have also examined changes that block the movement of the spindle in fertilized zygotes.

Early mitotic spindle formation until the 8-cell stage in oocytes is similar to the acentriolar microtubule-organizing center-mediated spindle formation that occurs during oocyte maturation[138]; therefore, transitions from asymmetric division in oocytes to symmetric division in zygotes may not be caused by different spindle assembly mechanisms. Moreover, because parthenogenetic activation of mammalian oocytes by chemical or electric stimulation results in symmetric division,[139,140] asymmetric-to-symmetric division in mammalian oocytes may not be affected by sperm-derived factors.

Several studies[141,142,143] show that the actin cytoskeleton is responsible for maintaining symmetric division in one-cell zygotes. For example, treatment with actin depolymerization

agents (e.g., latrunculin-A) in one-cell zygotes impairs symmetric division in the first cleavage of mouse zygotes.[141] A recent study shows that symmetric division in zygotes is achieved by modulation of F-actin dynamics in multiple steps.[143] First, male and female pronuclei centering is mediated by F-actin/Myosin-Vb actin mesh. Second, cortical tension, which is implicated in spindle movement during meiosis,[12] is responsible for the fine centering of the first mitotic spindle. Finally, maintenance of spindle position relies on a passive mechanism, presumably by increased cytoplasm viscosity, although the underlying mechanism is not clear. Previous work in oocytes[38] showed that an increase of cytoplasmic actin mesh by overexpression of formin-2/spire or dominant Rab11a impairs spindles, therefore changes in cytoplasmic actin density may be responsible for restricting spindle movement.

Additional studies show that the subcortical maternal complex (SCMC) contains 4 proteins (MATER, FILIA, FLOPED, and TLE6)[144-147] that are essential for maintaining early cell division in embryos and are involved in the control of F-actin dynamics, presumably by controlling ADF/cofilin.[142] The potential interactions of other ABPs with SCMC are not well understood. In mouse embryos, ARP2/3 is localized in the cortex of embryos and not in the cell-to-cell junction,[24] similar to the localization pattern of SCMC.[142] Inhibition of ARP2/3 by chemical inhibitors results in the failure of embryogenesis in the 2- or 4-cell stage,[142] similar to the phenotypes of Mater-, Filia-, or Floped-knockout embryos, suggesting that ARP2/3 interacts directly or indirectly with SCMC and that ARP2/3-mediated actin polymerization is involved in symmetric cell division in early embryos.

In addition to the ARP2/3 complex, FMN2/spire regulation after fertilization should be examined. Because knockout of FMN2 or RNAi-mediated downregulation of spire causes failure of spindle migration in oocytes,[27,39] the activity of FMN2 and/or spire could be regulated after fertilization. However, our lack of knowledge of the mechanisms regulating FMN2 and spire prevents our understanding of how these proteins are regulated after fertilization; therefore, elucidation of the mechanisms regulating FMN2 and/or spire is crucial.

Concluding remarks

During the last 10 years, our understanding of the mechanism of asymmetric division in mammalian oocytes has increased substantially, particularly regarding the roles of actin nucleators and their regulators in spindle migration and asymmetric division, as summarized in the Figure 4. However, studies of the roles of other ABPs and their regulatory mechanisms during oocyte maturation and early embryogenesis are still in their infancy. Several profound questions remain. 1) How are FMN2/spire regulated during oocyte maturation and early embryogenesis? Because dynamic changes in cytoplasmic actin mesh are crucial during oocyte maturation and spindle migration, the regulation of FMN2/spire may be a critical step in these processes. 2) How are asymmetric division and spindle migration transformed into symmetric division during first cleavage at the zygote stage? Although the functional roles of several actin nucleators, including ARP2/3, FMN2, and spire, are involved in asymmetric division, their roles in symmetric division during embryogenesis are unclear. 3) Several NPFs, including n-WASP, WAVE2, JMY, WASH, and WHAMM, are implicated in oocyte maturation, but the mechanistic roles of each NPF are poorly understood. Some actin nucleators, especially WASH, WHAMM, and JMY, have been characterized in terms of their ability to activate ARP2/3-mediated actin polymerization at distinct cellular locations, including golgi, endocytic structure, and membrane ruffles.[17] Further studies could clarify the exact functional roles of each NPF in terms of actin filament formation in different cellular contexts. 4) Are there other ABPs that have roles in oocyte maturation and embryogenesis, and if so, how is their activity regulated during these processes, particularly with regard to connections with signaling pathways governing the cell cycle? For example, filament crosslinker proteins like filamin,[148] actin polymerases like Ena/VASP proteins,[149] and filament-bundling proteins like α-actinin[150] or fascin[151] are actin binding-proteins studied extensively in other cellular process but not in oocyte maturation and early embryogenesis. In addition to cell division, recent studies suggest that controlling actin dynamics can also affect cell fate specification between trophoblasts and the inner cell mass during embryogenesis[152] via the Hippo signaling pathway.[153] The involvement of various ABPs in the regulation of the Hippo signaling pathway, and thus the control of cell fate specification during embryogenesis, should be elucidated in future studies.

Collectively, a mechanistic understanding of the functional roles of ABPs in biochemical or cellular studies in other model systems may provide insight into their roles in oocyte maturation and early embryogenesis. In turn, oocyte maturation and early embryogenesis could provide a simple and physiologically relevant model system for the functional study of ABPs.

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