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Massive cytoplasmic transport and microtubule organization in fertilized chordate eggs

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ABSTRACT

Eggs have developed their own strategies for early development. Amphibian, teleost fish, and ascidian eggs show cortical rotation and an accompanying structure, a cortical parallel microtubule (MT) array, during the one-cell embryonic stage. Cortical rotation is thought to relocate maternal deposits to a certain compartment of the egg and to polarize the embryo. The common features and differences among chordate eggs as well as localized maternal proteins and mRNAs that are related to the organization of MT structures are described in this review. Furthermore, recent studies report progress in elucidating the molecular nature and functions of the noncentrosomal MT organizing center (ncMTOC). The parallel array of MT bundles is presumably organized by ncMTOCs; therefore, the mechanism of ncMTOC control is likely inevitable for these species. Thus, the molecules related to the ncMTOC provide clues for understanding the mechanisms of early developmental systems, which ultimately determine the embryonic axis.

1. Introduction

Time-lapse video of normal embryonic development reveals dramatic deformation of the egg just after fertilization, involving contraction, compression, jostling, and rotation. These movements and changes within the cytoplasm of the egg have also been noted by histological observations. Certain cellular components such as mRNAs, proteins, protein complexes, vesicles, and other organelles are transported to and localized in a specific region of the egg. Given that these movements constitute the first symmetry-breaking event, they are likely to play a pivotal role in embryonic axis determination.

Different mechanisms are known to be involved in these massive transports and cytoplasmic movements observed during embryonic development. The mechanisms include cytoplasmic flow, cytoplasmic streaming, cytoplasmic segregation, cortical contraction, and cortical rotation, depending on the experimental systems under investigation (e.g., Gerhart et al., 1989; Shimizu, 1999; Fernández et al., 1998). Among these varied movements, both actin and tubulin cytoskeletal

filaments and their motor proteins are used to generate their motive force. For example, cytoplasmic flow in *C. elegans*, mouse embryos, and ascidian oocytes is actomyosin-dependent (Singh and Pohl, 2014; Prodon et al., 2008; Tokuhisa et al., 2017; Ajduk et al., 2017), whereas that in *Drosophila* oocytes is microtubule (MT)-dependent (Glotzer et al., 1997; Serbus et al., 2005; Ganguly et al., 2012). Cortical rotations in *Xenopus* and zebrafish eggs and the second phase of ascidian cytoplasmic and cortical reorganization are also MT-dependent (Elinson and Rowning, 1988; Abraham et al., 1995; Sawada and Shatten, 1988). All three of these movements have been well studied and are reported to be important for the determination of dorsoventral or anteroposterior axes (Gerhart et al., 1989; Tran et al., 2012; Sardet et al., 1989). Recently, parallel cortical MT arrays called CAMPs (cortical arrays of MTs in posterior-vegetal region) were found during observations of ascidian movement that are suggested to involve a mechanism similar to that of *Xenopus* and zebrafish cortical rotations (Ishii et al., 2017). In order to better understand the conserved mechanism for establishing egg polarity, this review focuses on

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cortical rotation and its related cytoskeletal structures, cortical arrays of MTs.

Various MT structures have recently been described in the field of cell biology and subsequently subdivided into two groups: 1) the centrosomal MT (cMT), which has a centriole, is nucleated by the centrosomal microtubule-organizing center (cMTOC), and usually forms a radially elongated structure; and 2) the noncentrosomal MT (ncMT), which has no centriole, is elongated from the noncentrosomal microtubule-organizing center (ncMTOC), and forms a wide variety of shapes. Most of animal cells have a centriole and their mitotic apparatus is centrosomal. To the contrary, eggs are thought not to contain a centriole because most of the female meiotic apparatus has a barrel shape (Karsenti et al., 1984). In fertilized eggs, there is only one sperm centriole, which is used in later development (Stewart-Savage and Grey, 1982). In this sense, all of the MT structures present during the one-cell embryonic stage are ncMTs, except for the sperm aster. In order to determine how the wide variety of MT structures, including the cortical parallel array, can be formed and regulated in the egg, an understanding of the molecular nature of the ncMTOC is necessary.

We will review both historical and recent data about cortical rotations and endeavor to connect them to the recent findings about the formation and regulation of ncMTOCs in animal cells. We hope to reveal that the mechanism controlling ncMTOCs can direct morphogenesis in animal development by organizing a parallel MT array, thereby determining the embryo axis. In other words, a complete understanding of the cytoskeletal mechanisms of the one-cell stage embryo is imperative for understanding the animal morphogenesis. Furthermore, eggs are highly specialized cells with considerable volumes into which substantial maternal investment is deposited. Massive transport mechanisms, including cortical rotation, seem to be beneficial for large cells such as eggs to relocate adequate amounts of maternal information. In addition, eggs possess vast biological diversity, with each animal species bearing their own unique eggs. While we assume that cortical rotations are conserved within the three chordate species, *Xenopus laevis*, *Danio rerio*, and *Ciona intestinalis*, the known mechanisms controlling various ncMTOCs are diverse. We will therefore discuss the current state of our knowledge regarding developmental mechanisms within the egg.

2. Cortical rotation in the amphibian egg

Cortical rotation was clearly described by Vincent et al. (1986) using Nile blue and fluorescent lectin as markers of a subcortical region and the cell surface, respectively. It involved an approximately 30-degree rotation of the thin cortex (2–5 μm thick) relative to a deeper yolk-filled core cytoplasm occurring between 0.45 and 0.9 NT (normalized time of the 1st cell cycle), giving rise to a grey crescent on the future dorsal side. Although the cortical rotation of the *Xenopus* egg has been well studied (Gerhart et al., 1989), similar cortical movements have also been described in *Rana pipiens* and axolotl eggs (Manes and Elinson, 1980), suggesting that cortical rotation is a common event in amphibian eggs. This cortical rotation is a critical event for dorsoventral axis determination because it translocates the dorsalizing complex, including maternal *Wnt11* mRNA, maternal Dishevelled (Dsh) proteins, and GSK3-binding protein (GBP), to the dorsal side and activates the Wnt/β-catenin dorsalizing pathway on the dorsal side (Weaver and Kimelman, 2004).

The assembly of a parallel array of subcortical MTs is necessary for cortical rotation (Elinson and Rowning, 1988). This subcortical MT assembly is highly polarized, accompanying cortical rotation with plus ends pointing toward the dorsal equatorial region (Houliston and Elinson, 1991b). The region where this array is assembled is called the "shear zone," located 4–8 μm deep between the cortex and inner cytoplasm of the egg (Chang et al., 1996). The sperm aster is situated in the inner cytoplasm and its MTs are connected to the parallel MTs in the shear zone (Houliston and Elinson, 1991a). The cortex region

consists of a plasma membrane, actin cytoskeletal filaments, and the endoplasmic reticulum (ER) (Houliston and Elinson, 1991a). In addition to the MTs, the shear zone contains the ER, cytokeratin filaments (Klymkowsky et al., 1987), and kinesin (Houliston and Elinson, 1991b). Cortical rotation occurs between the shear zone and the cortex.

Recently, the molecular mechanisms of the formation of a cortical parallel MT array have been elucidated. Cortical MTs can be assembled in both an artificially activated egg and in an enucleated and activated egg, suggesting that this assembly is sperm- and centrosome- independent (Houliston and Elinson, 1991a). Although cortical parallel MTs represent a continuous structure from the sperm astral MTs, this finding clearly indicates the existence of the ncMTOC in the egg cortex. In order to explore the function of the maternal dorsalizing complex, loss-of-function experiments of certain factors resulted in defects in cortical MT array formation, the failure of cortical rotation, and ventralization of the embryo. Among them, the knockdown of tripartite-motif–containing 36 (*trim36*; Cuykendall and Houston, 2009) and dead end homolog 1 (*dnd1*; Mei et al., 2013) mRNAs induces the loss of a cortical MT array and cortical rotation. These data are conceivable because Trim36 is a ubiquitin ligase that can interact with MTs (Short and Cox, 2006). Dnd1 is an RNA-binding protein that can bind to *trim36* mRNA and anchor it to the vegetal cortex (Mei et al., 2013). Moreover, depletion of maternally localized *perilipin 2* (*plin2/fatvg*) mRNA, which encodes a protein localized to vesicles located at the vegetal cortex, gives rise to a similar effect (Chan et al., 2007). Given that the Dsh protein also localized to a vesicle-like organelle (Miller et al., 1999), and similar vesicles are transported along the MT array towards the dorsal side during cortical rotation (Rowning et al., 1997), such vesicles are thought to be involved in the translocation of the dorsalizing complex and formation of a parallel array of MTs.

3. Cortical rotation in the teleost fish egg

Although the movement associated with cortical rotation in a fish egg is not as obvious when compared to that of a frog egg (Tran et al., 2012), a parallel MT array in the vegetal cortex was first described by Abraham et al. (1995). It exists in the vegetal cortex from 0.3 to 0.75 NT. Similar MT structures in the zebrafish egg are also reported at a depth of ~2 μm in depth of the vegetal cortex from 0.44 NT that disappear before the first cleavage (Jesuthasan and Strähle, 1996). Tran et al. (2012) clearly showed the cortical MT array with its plus end towards the dorsal side and ~20-degree relocation of vegetal cytoplasmic granules.

As in the frog egg, cortical rotation is a critical event for dorsoventral axis determination because it rotation translocates the dorsalizing complex. The maternal *wnt8a* and *grip2a* mRNAs and Syntabulin protein are localized to the vegetal cortex of the unfertilized egg and shift to the dorsal side during cortical rotation (Lu et al., 2011; Nojima et al., 2010; Ge et al., 2014). The *grip2a* gene encodes glutamate receptor–interacting protein 2a, which contains PDZ-domains, interacts with *Drosophila* Frizzled-2 receptor, localizes to trafficking vesicles in synapses, and is required for the transport related to Wnt signaling (Ataman et al., 2006). The *grip2a* (*hecate*)-mutant shows disrupted microtubule rearrangements at the vegetal pole (Ge et al., 2014). The *syntabulin* (*tokkaebi*)-mutant shows severely ventralized phenotypes (Nojima et al., 2010). Given that Syntabulin protein is a linker molecule that tethers cargo to the motor protein kinesin I in neuronal axons (Cai et al., 2007; Xiao et al., 2016), Syntabulin is thought to link the dorsal determinants (DDs) to Kif5B, the heavy chain of kinesin I, and to the transport and release of DDs at the dorsal side, and to activate zygotic gene expression for the dorsal organizer (Nojima et al., 2010). Moreover, CRISPR-Cas9 mediated zebrafish Kif5Ba mutants (Chang et al., 2013; Hruscha et al., 2013) show randomly oriented MT bundles or fragments at the vegetal cortex and fail to establish proper dorsoventral patterning (Campbell et al., 2015). These results strongly

indicate the importance of the cortical parallel MT array and suggest that the kinesin-dependent vesicular transport is the key event in the determination of the dorsoventral axis.

Cytoplasmic streaming was also described in the teleost egg as more obvious than cortical rotation (Kimmel et al., 1995 ; Fuentes and Fernandez, 2010). Cortical rotation is sometimes referred to as "short-range transport" and is followed by a general, animal-directed "long-range transport" involving a *grip2a*-independent pathway (Ge et al., 2014). To be precise, long-range transport consists of two different movements (Welch and Pelegri, 2014): one occurs in the outermost cortex, is MT-dependent, and transports DDs; the other occurs in deeper cytoplasm, is actin-dependent, and transports germ cell determinants.

4. Ascidian cortical and cytoplasmic reorganization

In 1905, Conklin described distinct cytoplasmic domains, including myoplasm, in a fertilized egg (Conklin, 1905). These cytoplasmic domains emerge during the 1st cell cycle via the cytoplasmic transloca-tion movement called "cytoplasmic and cortical reorganization" (pre-viously called ooplasmic segregation) and result in polarization of eggs establishing a dorsoventral axis (Sardet et al., 1989; Roegiers et al., 1999; Ishii et al., 2014). The myoplasm is a mitochondria-rich cytoskeletal domain composed of an intermediate-filament lattice and plasma membrane lamina (Jeffery and Meier, 1983; Jeffery and Swalla, 1990; Jeffery, 1995); it is retrospectively recognized during oogenesis in the entire subcortical region except for the animal pole, where the female meiotic spindle is situated (Swalla et al., 1991; Sardet et al., 1992; Prodon et al., 2005, 2006). This polarization during oogenesis is achieved by the cytoplasmic flow, which moves the female metaphase I–arrested meiotic apparatus to the animal pole and determines the animal-vegetal axis (Prodon et al., 2006; Tokuhisa et al., 2017). The cortical region corresponds to the myoplasm and consists of rough endoplasmic reticulum and maternal mRNAs (i.e., Type I *postplasmic/ PEM* RNAs; Yoshida et al., 1996; Sasakura et al., 2000; Yamada, 2006; Makabe and Nishida, 2012); it is called the cER-mRNA domain (Sardet et al., 1992; Speksnijder et al., 1993; Prodon et al., 2007, 2008, 2009).

Immediately after fertilization, intracellular Ca^{2+} concentration rises and triggers contraction of the cortical actin network toward the vegetal pole (Speksnijder et al., 1990; Roegiers et al., 1995; Sensui and Morisawa, 1996). This actin-driven cortical contraction causes trans-location of the myoplasm, cER-mRNA domain, and fertilize d sperm toward the vegetal pole. This movement is called the 1st phase of reorganization (Sawada and Schatten, 1989; Paix et al., 2009). After the completion of meiosis at ~30 min postfertilization, the sperm aster moves toward the future posterior pole along the posterior-vegetal cortex, then moves toward the center of the egg. Accompanied by this sperm aster movement, the myoplasm and cER-mRNA domain re-arrange and form a typical crescent domain at the posterior side, thereby establishing the anteroposterior axis (Sardet et al., 2003). This movement is called the 2nd phase of reorganization (Sawada and Schatten, 1988). Although some maternal proteins are known to be localized to the myoplasm, e.g., Ci-Pem-1 (Shirae-Kurabayashi et al., 2011), myoplasmin-C1 (Nishikata et al., 1987), microtubule-related protein 1 (MTR1: Nakamori et al., 1999), ATP synthase α-subunit (NN-18 antigen: Ishii et al., 2012; Chenevert et al., 2013), and *Ciona intestinalis* Y-box protein 1 (CiYB1: Tanaka et al., 2004), little is known about the importance of these factors.

Furthermore, as a result of the 2nd phase of reorganization, in addition to the localization of Type I *postplasmic/PEM* RNAs to the cortical region of myoplasm (Nishida, 2005; Kumano and Nishida, 2009), Type II *postplasmic/PEM* RNAs also localize to the posterior pole (Shirae-Kurabayashi et al., 2006). This localized cER-mRNA domain will form a centrosome-attracting body (CAB), which is thought to be a germ plasm at the posterior pole of an embryo at the early cleavage stage and directs the unequal cleavage for determining

the posterior pole (Hibino et al., 1998; Nishikata et al., 1999; Sardet et al., 2007; Costache et al., 2017). Moreover, MnK (MAPK-interacting kinase), S6K (S6 kinase), and 4EBP (eukaryotic translation initiation factor 4E–binding protein) are localized to the cER-mRNA domain and actually control the PEM1 protein translation (Paix et al., 2011). These are phospho-protein kinases and modulating factors for the translation initiation (Richter and Klann, 2009). Miyaoku et al. (2018) also revealed that the members of Type I *postplasmic/PEM* RNAs, Popk-1 (posterior protein kinase-1; serine/threonine kinase) and Zf-1 (zinc finger protein-1), control the protein level of PEM. In addition, CiYB1, which is localized to the myoplasm (Tanaka et al., 2004), is a well-known RNA-binding protein for translational suppression (Matsumoto et al., 2018) and has also been suggested to promote MT assembly (Chernov et al., 2008a, 2008b). As suggested in the *Xenopus* egg, localization of maternal mRNAs and their translation are important for controlling the formation of MT structures; therefore, a similar mechanism could also exist in the ascidian egg for determination of the embryonic axis. Moreover, interactions between MTs and the polysome, including ribosomal proteins, translation initiation factors, elongation factors, and RNA-binding proteins, have also been revealed and MTs themselves are an important scaffold for the translational control (Chierchia et al., 2015). Such translation-dependent MT-structure control and MT-dependent translational control have become a subject of considerable interest (Chudinova and Nadezhdina, 2018).

Previous studies using cytoskeletal inhibitors have clearly shown that posterior translocation of the cER-mRNA domain and myoplasm in the 2nd phase of reorganization depends on MTs (Chiba et al., 1999). Given that the sperm aster, until recently, was the only MT structure known in the 2nd phase of reorganization, it was believed to be responsible for the rearrangement movement. A cortical array of MTs in the posterior-vegetal region (CAMP) was newly described in the 2nd phase of reorganization (Ishii et al., 2017). CAMP is characterized by thick microtubule bundles aligned in parallel within the entire posterior-vegetal cortex and has a close relationship with the move-ment of the myoplasm. CAMP starts to form concomitantly with the start of the first mitotic cell cycle and is thus possibly under the control of cell cycle regulation. In fact, an inhibitor experiment showed that CDK activities direct CAMP formation (Goto et al., 2018). These characteristics of CAMP resemble both amphibian and teleost fish cortical parallel MT arrays, suggesting that this 2nd reorganization is the cortical rotation in the ascidian egg and that massive transport with a parallel MT array might be conserved at least in chordate eggs.

5. Formation of noncentrosomal MT structures

MTs form specific and dynamic structures for exerting a specific function on each cell. Distinct subcellular sites, called MTOCs (micro-tubule-organizing centers), are necessary for organizing these struc-tures, and are important for the organization of the entire structure by nucleating, stabilizing, and anchoring minus ends of MTs (Sanchez and Feldman, 2017). The most well-studied MTOC is the centrosomal MTOC (cMTOC), which contains a centriole and organizes a radially extended aster and mitotic apparatus in somatic cells. Recently, many types of noncentrosomal or acentrosomal MTOCs (ncMTOCs) have been described. For example, in epithelial cells, MTs are extended along the apico-basal axis, with ncMTOC at the apical side (Akhmanova and Hoogenraad, 2015). In neuronal cells, most axonal MTs are not anchored to the centrosome (Baas and Lin, 2011).

Recently, certain components of ncMTOCs were revealed (Silva and Cassimeris, 2014) as MT minus end proteins. γ-Tubulin is a component of MTOCs that forms a ring-shaped complex (γTuRC; γ-tubulin ring complex); it is indispensable for nucleating and organizing MTs in cMTOCs (Wiese and Zheng, 2006). γ-Tubulin is also reported as a component in certain ncMTOCs (Wang et al., 2015), while in some other ncMTOCs, γ-tubulin could not be detected as a component (Nashchekin et al., 2016). Ninein is a coiled-coil protein found in

centrosomes and has a GTP-binding site, four leucine zipper domains, and an EF-hand-like domain (Bouckson-Castaing et al., 1996). Ninein is also found in ncMTOCs for capping and anchoring the MT minus end (Mogensen et al., 2000). Centrobin is a daughter centriole-specific protein that is required for centriole duplication and elongation (Zou et al., 2005). Its roles are differentially controlled by two different kinases: PLK1 enhances the MT stabilization during mitosis (Lee et al., 2010), and Nek2 (NIMA-related kinase 2) antagonizes it in interphase (Park and Rhee, 2013). Centrobin also forms cytoplasmic dots and controls ncMT formation (Shin et al., 2015). Moreover, three MT-minus-end-binding proteins, designated as CAMSAP1–3 (calmodulin-regulated spectrin-associated proteins 1–3), were found in mammals (Jiang et al., 2014). All CAMSAP proteins contain a CH (calponin homology) domain, three coiled-coil domains, and a CKK (CAMSAP1, KIAA1078, and KIAA1543 homology) domain, which is specific to CAMSAP members (Akhmanova and Hoogenraad, 2015). CAMSAP1 does not stabilize MT minus ends but binds at the very tip of minus ends for tip-tracking (Akhmanova and Steinmetz, 2008). The knock-down of CAMSAP1 in PC12 cells inhibits neurite outgrowth (King et al., 2014). CAMSAP2 localizes to the minus ends of ncMTs and regulates polymerization and stabilization of ncMTs and directional cell migration (Jiang et al., 2014; Sawada et al., 2006). CAMSAP3/Patronin/Nezha/Marshalin localizes to the apical side of epithelial cells, tethers ncMTs to the cortical actin network through MACF7 (microtubule-actin cross-linking factor 1), and plays a role in the maintenance of the apical-to-basal polarity of the cell (Noordstra et al., 2016; Toya et al., 2016). CAMSAP2 and −3 form a molecular complex with a microtubule-severing ATPase, katanin, control the length of CAMSAP-decorated microtubule stretches, and regulate the stability of the minus end (Jiang et al., 2018). Recently, the Golgi apparatus was recognized as a common location of interphase MT nucleation (Chabin-Brion et al., 2001; Efimov et al., 2007; Ori-McKenney et al., 2012; Oddoux et al., 2013). Such Golgi-derived MT arises from a distinct hotspot of Golgi, depending on the nucleation activity of γTuRC-mediated nucleation activator (γ-TuNA) (Sanders et al., 2017). In addition, microtubules can be nucleated from the lateral surface of preexisting MTs, thus forming branches (Petry et al., 2013). In such nucleation, augmin and γTuRC are necessary (Sanchez-Huertas and Luders, 2015).

We next focus on the nature of the MTOC. Approximately 20 years ago, free MTs, which appeared spontaneously in the cytoplasm or by breakage of long microtubules, were described in PtK$_1$ epithelial cells (Vorobjev et al., 1997). These were recognized as both plus and minus ends that were free from a centrosome (Bartolini and Gundersen, 2006). As mentioned above, even in the case of a single rod of an MT, its minus ends are stabilized or regulated by a CAMSAP-containing protein complex. Thus, these free MTs should have their own ncMTOC at their minus ends. Accordingly, all MT structures must have their own MTOCs at their minus ends. In terms of the component molecules involved, some proteins including γ-tubulin, ninein, and centrobin are commonly used in both cMTOC and ncMTOC, and CAMSAP1−3 are also sometimes in ncMTOCs depending on the cell type. This indicated that a large variety of MTOCs could be achieved by the combination of this repertoire of component proteins. Therefore, we would like to insist that all the protein complexes that have nucleating, stabilizing, and anchoring activities of MT minus ends can be called MTOCs. The largest complex is cMTOC, which contains a centriole and a large number of γTuRCs; the smallest one is the CAMSAP-containing complex, which can organize only a single MT. Three striking examples of diverse MT systems are shown as cartoons in Fig. 1: general mitosis (A), a nerve cell (B), and an epithelial cell (C). In addition to the radially extended MTs, which is nucleated by cMTOC, all other MT structures thought to be nucleated by their own ncMTOCs.

In parallel MT arrays in the egg, MTs should also have their own MTOCs. As mentioned earlier, unfertilized animal eggs have no centriole and the known parallel MT arrays in all eggs are sperm-independent structures. The MTOCs of these MTs should be ncMTOCs.

According to the efforts aimed at identifying the molecules that organize a parallel array in the amphibian egg, maternally localized *trim36*, *dnd1*, and *fatvg* mRNAs were revealed to perform some functions for organizing a parallel MT array; however, conserved ncMTOC components, such as γ-tubulin or CAMSAP, do not show up in cortical rotation. More extensive studies are required for revealing all the components of ncMTOCs in cortical rotation. Some conserved ncMTOC components could be involved in the formation of cortical MT arrays.

6. The enigmatic relation among a parallel MT array, ncMTOCs, and the heterogeneity of early developmental systems

As described above, parallel MT arrays in frog, fish, and ascidian eggs are very similar in appearance and behavior. They are nucleus- and centrosome-independent structures, thus thought to be organized by ncMTOCs and controlled by the similar cell cycle–regulatory mechanisms, that is, the egg activation pathway. In contrast, the localized maternal molecules, which affect the parallel MT array and embryonic axis formation are different. Even though the structures are similar, their details of controlling mechanisms might be different, suggesting the heterogeneity of early developmental mechanisms and the variety of the molecular complexes within ncMTOCs.

There have been intriguing reports about the MT-organizing mechanism in a *Xenopus* egg extract (Peset et al., 2005). In a depletion and reconstitution experiment, spindles and asters can be controlled as to their growing and shrinking in the egg extract. In the normal development of mouse oocytes and eggs, Schatten et al. (1985) described many cytoplasmic asters (CAs), which are radially extended MT structures, normally observed in mouse oocytes that gradually decreased with cleavage stage. The mitotic spindles at the early cleavage stage of the mouse embryo are barrel-shaped and gradually changed their shape to the bipolar-spindle. Moreover, centrosomal reduction, which is the loss of centrioles during mouse spermiogenesis, was reported; thus, a mouse sperm has no functional centrosome (Manandhar et al., 1998). All of these results suggest that no centrosome is available during the very early stages of normal mouse development, while a substantial number of ncMTOCs can compensate for centrosomes during this period. In the rabbit egg, although its sperm contains a centrosome, normal MT structures are also formed when a sperm head is microinjected after removal of the centrosome (Morita et al., 2005). This finding suggests that, even in the rabbit egg, ncMTOCs are present and can exert their MT-organizing activity when centrosomes are depleted. Furthermore, when the bovine and human eggs are parthenogenetically activated and treated with paclitaxel, a microtubule stabilizing reagent, many CAs can be induced (Morita et al., 2005; Terada et al., 2009). In our experiments with unfertilized eggs of an ascidian, *Ciona intestinalis*, many CAs could be induced via paclitaxel treatment (unpublished data). Combining these data altogether, even if the sperm centrosome is the major MTOC under normal development, chordate egg cytoplasm contains many effective ncMTOCs.

Further questions remain to be answered. Why is the sperm centrosome dispensable only in mouse development? Inversely, why are ncMTOCs in the egg cytoplasm used only in mouse development? How can the fertilized sperm suppress the organizing activities of a maternal ncMTOC? All of these questions are related to either the coordination or the battle between the sperm and egg during animal development. The mechanisms underlying the control of the egg ncMTOC have a profound implication for understanding the heterogeneity of early developmental systems. Three different examples of MT structures, which are suggested to be directed by ncMTOC, in eggs are shown in Fig. 1: mouse normal development (D), *Xenopus* parallel MT array (E), and ascidian CAMP (F). These observations and experiments indicate that, in eggs, various kinds of molecules control
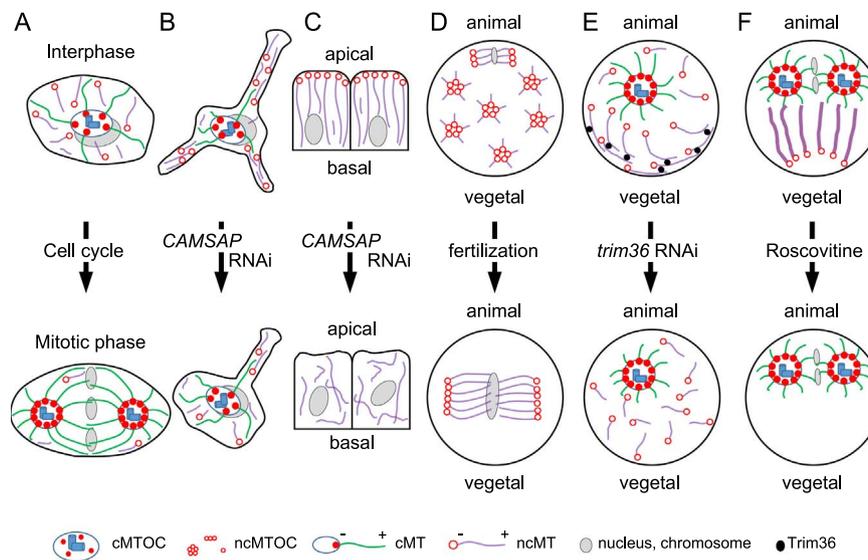
Fig. 1. Various noncentrosomal microtubule (MT) structures and their behaviors in various experimental systems. A) In cultured human cells, ncMTOCs are pooled in the cytoplasm during interphase. In metaphase, cMTOCs mature and form a mitotic apparatus (Wiese and Zheng, 2006; Akhmanova and Hoogenraad, 2015). B) In nerve cells, a thick bundle of MTs is formed in each axon and dendrite. These long bundles consist of many short ncMTs. When CAMSAP is knocked down, numbers of ncMTs decreased and axons and dendrites shrunk (Baas and Lin, 2011; Yau et al., 2014; Chuang et al., 2014; Lindström and Alvarado-Kristensson, 2018). C) In epithelial cells, CAMSAP proteins are localized in the apical cortex and orient the apical-to-basal polarity of MT arrays as ncMTOCs. When CAMSAP is knocked down, the MT array became disordered (Tanaka et al., 2012; Noordstra et al., 2016; Toya et al., 2016). D) In normal mouse development, many cytoplasmic asters (CAs) are formed in the oocyte. After fertilization, no sperm centrosome participates in early development, while CAs are accumulated and form a barrel-shape mitotic apparatus. A section of mid-plane, animal pole toward upside (Schatten et al., 1986). E) In a *Xenopus* fertilized egg, during cortical rotation, a prominent parallel array of MTs is formed in the vegetal half cortex. This parallel array is also organized by ncMTOCs and co-localized with maternally-inherited localized factors. When one of these factors, *trim36* mRNA, was depleted with siRNA, the parallel MT array was disappeared. Section of mid-plane, anterior side toward left (Cuykendall and Houston, 2009). F) In *Ciona* fertilized egg, CAMP (cortical array of MTs in posterior-vegetal region), which is thought to be organized by ncMTOCs, is transiently formed. When eggs were treated with roscovitine, a CDK inhibitor, CAMP was completely removed but the cMTOC-organized sperm asters were not affected. A posterior view of a transparent 3D model. The animal pole toward the upside (Goto et al., 2018). In this review, even the minus end of MTs, which was stabilized by the CAMSAP-containing protein complex, is also mentioned as an ncMTOC. Note that the open red circles represent heterogeneous ncMTOCs (e.g. Silva and Cassimeris, 2014).

various MT structures, and this control of MT structures is inevitable for early development.

7. Conclusion

Intracellular cytoplasmic movement in one-cell stage embryo is one of the most important developmental systems for transporting maternal information, polarizing the egg, and establishing a body axis. Among these massive transport, cortical rotation is directed by a parallel MT array and is conserved in several chordate eggs. In these eggs, the parallel MT array is thought to be organized by the cytoplasmic ncMTOCs and to be controlled by the egg activation pathway. In each egg, unique localized maternal proteins and mRNAs are reported to affect the MT organization. Thus, the mechanism of each cortical rotation consists of both a conserved MT-organizing machinery and its own unique molecules. For this reason, each species has its own unique developmental system within the egg. Conserved mechanism of the regulation of MT structures with ncMTOCs might provide clues to understanding developmental systems at the very beginning of life.

Acknowledgements

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