Chapter 2
Polarity and Asymmetry During Mouse Oogenesis and Oocyte Maturation

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Abstract Cell polarity and asymmetry play a fundamental role in embryo development. The unequal segregation of determinants, cues, and activities is the major event in the differentiation of cell fate and function in all multicellular organisms. In oocytes, polarity and asymmetry in the distribution of different molecules are prerequisites for the progression and proper outcome of embryonic development. The mouse oocyte, like the oocytes of other mammals, seems to apply a less stringent strategy of polarization than other vertebrates. The mouse embryo undergoes a regulative type of development, which permits the full rectification of development even if the embryo loses up to half of its cells or its size is experimentally doubled during the early stages of embryogenesis. Such pliability is strongly related to the proper oocyte polarization before fertilization. Thus, the molecular mechanisms leading to the development and maintenance of oocyte polarity must be included in any fundamental understanding of the principles of embryo development. In this chapter, we provide an overview of current knowledge regarding the development and maintenance of polarity and asymmetry in the distribution of organelles and molecules in the mouse oocyte. Curiously, the

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mouse oocyte becomes polarized at least twice during ontogenesis; the question of how this phenomenon is achieved and what role it might play is addressed in this chapter.

2.1 Two Keywords: Polarity and Asymmetry

Throughout the last century, extensive studies performed on the formation, structure, and physiology of animal oocytes and eggs indicated that the majority of invertebrate and vertebrate (including mammalian) oocytes and eggs are asymmetrical and/or polar (Albertini and Barrett 2004; Brunet and Verlhac 2011; De Smedt et al. 2000; Kloc et al. 2004a, b, 2008). Surprisingly, for many decades, the issues of mouse oocyte asymmetry and polarity and their effects on future embryo development have been, and still are, vigorously debated (Hiiragi et al. 2006; Zernicka-Goetz and Huang 2010; Johnson 2009; Kloc et al. 2008; VerMilyea et al. 2011). In dealing with this subject, it is important to recognize the fundamental conceptual difference between asymmetry and polarity, with the first being an asymmetrical distribution of organelles, molecules, or functions within individual cells of the same type, and the second being a situation in which the asymmetrically distributed entities have an invariable, noninterchangeable, and irreplaceable position in all cells of the same type. Additional confusion arises from the fact that asymmetry/polarity can be either permanent or temporary, i.e., limited to a specific stage/time frame of oocyte development (Brunet and Verlhac 2011; Kloc et al. 2008). Thus, only comprehensive studies of all stages of oogenesis or oocyte maturation, and not arbitrarily selected stages, can validate generalized conclusions. Because the natural or experimental disruption of the existing asymmetry/polarity of the oocyte can lead to disastrous developmental consequences in the resulting embryo (Anifandis et al. 2010; Eichenlaub-Ritter et al. 2011; Evans et al. 2000), knowledge of the asymmetry/polarity of the mature mammalian oocyte is of the utmost importance in this era of the ever-expanding usage of experimental manipulations and in vitro fertilization (Anifandis et al. 2010; Edwards 2000, 2001; Edwards and Ludwig 2003; Eichenlaub-Ritter et al. 2011).

2.2 The Balbiani Body, Mitochondria, and Centrioles

Over a century ago, a peculiar structure, subsequently called the Balbiani body (Bb) after its discoverer, was described in the oocytes of spiders and myriapods (reviewed in Kloc et al. 2004a, b). Since then, the term Balbiani body (also called a mitochondrial cloud) has been ubiquitously used to describe a variety of spherical structures with distinct morphologies and ultrastructures and probably unrelated functions, which are asymmetrically located within the oocyte cytoplasm in the majority of animals. These structures are not surrounded by a membrane and

usually consist of an aggregate of mitochondria (often interspersed with the electron-dense nuage), ER cisternae, and Golgi complexes (Kloc et al. 2004a, b). The function(s) of Bb in animal oocytes, with the exception of the oocytes of the frog *Xenopus laevis*, is completely elusive. In *Xenopus*, the Balbiani body (mitochondrial cloud) is a vehicle for the delivery of various developmentally relevant localized RNAs, proteins, germ cell determinants (nuage and germinal granules), and maternal mitochondria to the vegetal pole of the oocyte, and it is a prerequisite for the normal development of the germ cell line (Kloc et al. 1996, 1998, 2001; Kloc and Etkin 1995, 1998). Detailed studies of Bb formation during consecutive stages of oogenesis showed that *Xenopus* female germ cells are not only asymmetrical but also polar—in all oogonia (cystocytes), the Bb, from the time of its conception, is located at the vicinity of the centriole and the cytoplasmic bridges connecting the cystocytes, and in all oocytes, the Bb is located at the vegetal pole (Kloc et al. 2004a, b).

Although the presence of the Bb in the oocytes of many mammals, including humans, has been well documented, until last decade it was believed that mouse oocytes are an exception among other mammalian species and that they do not contain the Bb (De Smedt et al. 2000; Kloc et al. 2004a, b). In 2007, Pepling and colleagues were first to describe the presence of the Bb in neonatal mouse oogonia and in the oocytes of primordial follicles (Pepling et al. 2007). This study also indicated that mouse oogonia and early oocytes are asymmetrical (the Bb was always located at one side of the nucleus) and that the Bb is a transient structure that disperses during late oogenesis. Subsequent three-dimensional reconstruction studies performed by Kloc et al. (2008) showed that mouse neonatal oocytes are not only asymmetrical but also polar and that the aspects of polarity in mouse oocytes are highly reminiscent of those in *Xenopus* early oocytes, i.e., in both species the Bb forms around the centriole in the vicinity of the cytoplasmic bridges connecting the oogonia (Fig. 2.1; Kloc et al. 2004a, b, 2008). In spite of this similarity, the structure of the mouse oocyte Bb differs from that of *Xenopus*. Whereas in *Xenopus*, the bulk of the Bb is composed of hundreds of thousands of mitochondria interspersed with some Golgi and ER cisternae, the mouse Bb contains an elaborate aggregate of Golgi cisternae surrounded at its periphery by mitochondria (Figs. 2.1 and 2.2; Kloc et al. 2008; Pepling et al. 2007). Although we do not know whether, in the mouse, the Bb Golgi apparatus delivers any molecules or organelles to the oocyte surface in a polarized manner, it is possible that the Golgi vesicles secrete certain components of the extracellular matrix in this way, such as the *zona pellucida* (ZP), which is involved in fertilization and early development (El-Mestrah et al. 2002; Hoodbhoy et al. 2006). If this supposition were true, then the transient polarity of the mouse oocyte leading to polar secretions from the Bb Golgi would translate into the polarity of the *zona pellucida*, which would have possible developmental consequences (Kloc et al. 2008). Another possibility is that the polar distribution of the Golgi in the mouse oocyte is related to the polar/asymmetric division during oocyte maturation. The most recent study by Zhang and collaborators (2011) showed that GM130, a Golgi resident protein, associates with the meiotic spindle and plays a key role (possibly via its cooperation with the MAPK pathway) in the

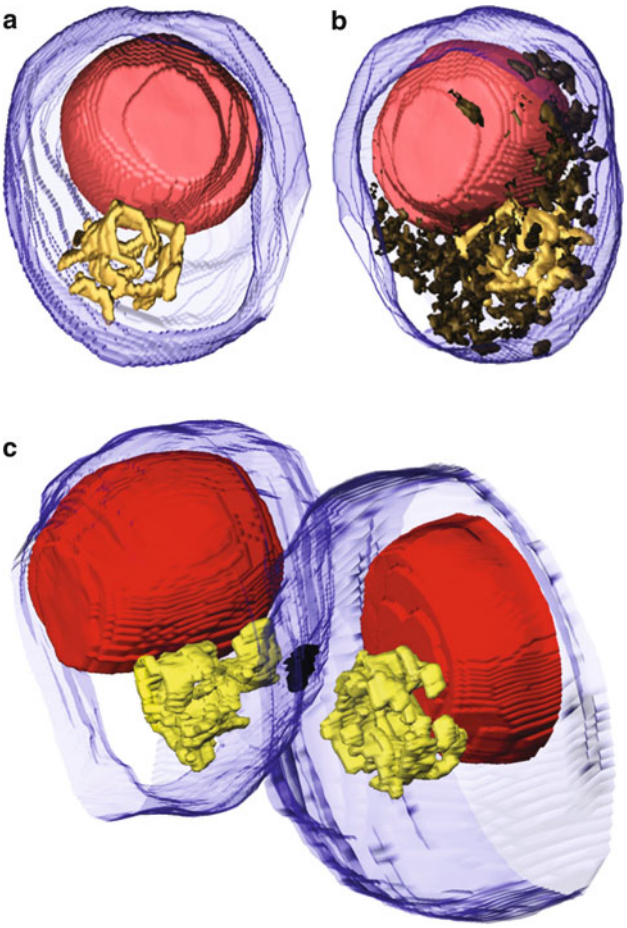

Fig. 2.1 Asymmetry and polarity of the mouse early oocyte. The three-dimensional reconstruction of mouse P0 oocytes from 16 semithin sections. (**a**, **b**) An image of a single P0 oocyte showing the asymmetrical distribution of the Balbiani body's Golgi complex (*yellow*) and mitochondria (*black*) at one side of the nucleus (*red*). **(c)** An image of two P0 oocytes connected by a cytoplasmic bridge (*black*), showing the polarity of the oocytes: in both oocytes, the Balbiani body faces the cytoplasmic bridge. For clarity, images (**a**) and (**c**) show only the nucleus and the Golgi complex. For further details and methods used for 3D reconstruction, see Kloc et al. (2008)

organization and polar migration of the spindle during the extrusion of the polar body in the maturing mouse oocyte.

Another exciting possibility is that, in the mouse, the Bb Golgi apparatus plays a role in the transduction of stress/apoptotic signals to the Bb mitochondria. Recent studies on the role of the Golgi in neurodegenerative diseases indicate the existence of cross talk among the Golgi, the mitochondria, and the ER and suggest that the Golgi (via Golgi cisternal stacking protein Grasp65) plays a role of a common stress sensor, downstream effector, and transducer of cell death signals

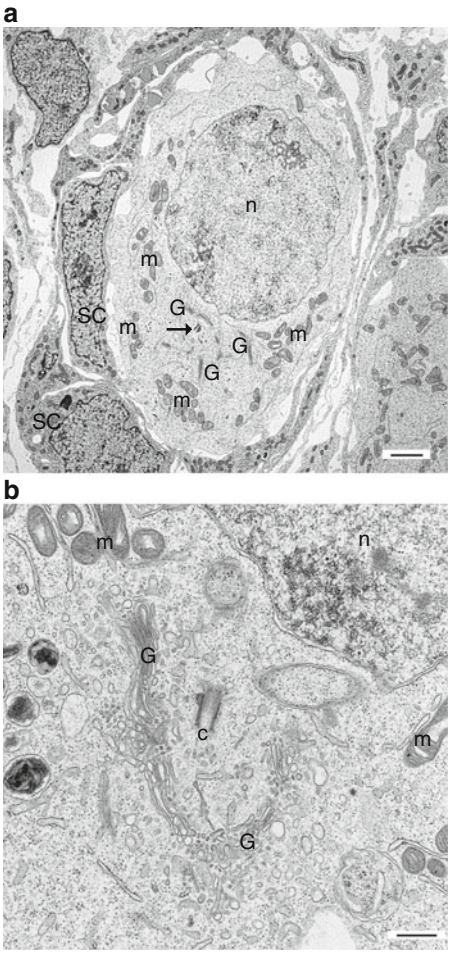

Fig. 2.2 Asymmetric distribution of the Balbiani body in the mouse early oocyte. (**a**) The electron microscopy image of a P0 oocyte surrounded by somatic cells (sc). The asymmetrically positioned Balbiani body composed of Golgi cisternae (G) and mitochondria (m) is organized around the centrally located centriole (*arrow*). (**b**) The electron microscopy image of the oocyte fragment showing structural details of the Balbiani body. The Golgi cisternae (G) and the mitochondria (m) are concentrically arranged around the centriole (C). Oocyte nucleus (n). The scale bar is equal to 2 μm in (**a**) and 500 nm in (**b**). For further details and methods, see Kloc et al. (2008)

(Nakagomi et al. 2008). Applying this scenario to the mouse oocyte, it is possible that the aggregation of mitochondria in the vicinity of the Bb Golgi facilitates perception of the stress signal by the mitochondria, eventually leading to the elimination of damaged or substandard mitochondria and preventing their inheritance by the offspring.

In the majority of animals, including the mouse, the mitochondria are one of the invariable components of the Bb (mitochondrial cloud). The importance of the health of maternally transmitted mitochondria for the quality of the future embryo and the role of mitochondrial DNA disorders related to aging and common diseases with maternal inheritance have been well documented in mammals, including humans (Bouchet et al. 2006; Dean et al. 2003; Eichenlaub-Ritter et al. 2011; Monnot et al. 2011). Studies in cattle and mice showed a dramatic shift in the variant/wild-type mtDNA ratio between the mother and offspring, indicating the

presence of a tight bottleneck that insures that new mutations are fixed rapidly or lost (Laipis et al. 1988; Bergstrom and Pritchard 1998; Roze et al. 2005; Jenuth et al. 1996; Cree et al. 2008; Cao et al. 2007, 2009; Wai et al. 2008). Recently, Zhang and colleagues (2008) showed that, in the zebrafish oocyte, the mitochondrial cloud attracts high-functional (i.e., high-inner membrane potential) mitochondria. These and other authors suggest that the mitochondrial cloud may function as a place for the selection of healthy mitochondria and the transmission of the fittest mitochondria to the offspring. Thus, by preventing deleterious mtDNA mutations from being passed to offspring, the mitochondrial cloud could play the role of a mitochondrial genetic bottleneck (Kloc et al. 2004a, b; Pepling and Spradling 1998; Cox and Spradling 2003, 2006; Zhou et al. 2010).

The polarity of mouse oogonia at the cytocyst stage may be related to the organization of the Balbiani body around the classical centriolar centrosome present at this stage (Fig. 2.2). Later in mouse oocyte development, the centrioles are lost. There is no information available describing at what stage this loss occurs. One may only speculate that the disappearance of the centrioles occurs during the long-lasting growth phase of the oocytes. If this supposition is true, then the transformation of centriolar into acentriolar centrosomes may have an important impact on the apparent loss of polarity of fully grown mouse oocytes.

2.3 Asymmetry of Maturation Division and Germinal Vesicle (GV) Positioning

The meiotic maturation of the oocyte is asymmetric and generates two unequal cells: the large mature germinal cell and the small polar body. The asymmetry of the meiotic division depends on the proper migration of the spindle containing the bivalents to the cortical region of the oocyte during the first meiotic M-phase. Because the starting point for spindle migration is the position of the GV (central or eccentric) within the oocyte, the proper positioning of the GV is paramount for the successful outcome of meiotic division, and the position of the GV has been used as a marker of oocyte quality (Gönczy 2002; Brunet and Maro 2007; Brunet and Verlhac 2011).

The positioning of the GV, and thus the route of mitotic spindle migration, varies between different animal species. In *Drosophila,* the eccentric migration of the GV in the vicinity of oocyte cortex employs microtubules, Lissencephaly1 (DLis1), Bicaudal (BicD), and dynein-dependent mechanisms (Lei and Warrior 2000; Swan et al. 1999). Similarly, in sea cucumber oocytes, the off-center positioning of the GV and the future spindle are both mediated by microtubule/centrosome-dependent mechanisms (Miyazaki et al. 2005). In some organisms, the eccentric migration of the GV is followed by the subsequent migration of the spindle to the oocyte cortex, and these two processes are mechanistically independent and mediated by different mechanisms and molecules. In *C. elegans,* the eccentric migration of the GV

depends on microtubules and zygote defective protein 9, whereas the migration of the spindle involves microtubules, microtubule-severing enzyme katanin, kinesin-1, and kinesin-cargo adaptor protein (Yang et al. 2003, 2005).

In mammalian oocytes, the GV is located in the oocyte center or slightly off-center, which is where the meiotic spindle forms before subsequently migrating towards the oocyte cortex. Studies on mice showed that the ability of the oocyte to complete maturation depends on the location of the GV within the oocyte and that the GV is positioned centrally in maturation-competent oocytes and at the periphery in maturation-incompetent oocytes (Brunet and Maro 2007). In addition, this study showed a positive correlation between mouse age, reduced ability to progress through meiosis, and decreased efficiency in GV centering. Although, at present, little is known about the molecular processes involved in the positioning of the GV in mammalian oocytes, recent studies on mice indicate that a complex meshwork of actin filaments physically connects the GV to the cortex and may lead to its centering by exerting counterpoising forces (Azoury et al. 2011). Interestingly, recent studies also show that the proper positioning of the GV, as well as the positioning and structure of the spindle, depends on the maintenance of the contact between the somatic (cumulus) cells and the oocyte (Barrett and Albertini 2010). It is known that in vitro culture reduces the integrity of the contact between the oocyte and its somatic cells, resulting in weakened developmental competence (Barrett and Albertini 2010; Sanfins et al. 2003, 2004). This observation underscores the importance of the somatic cell component and indicates that the bidirectional signaling between the oocyte and its somatic partners regulates intrinsic oocyte processes and has a lasting (and often undervalued) influence on oocyte developmental potential. The importance of the interaction between oocytes and somatic cells in the developing mouse ovary was recently underscored by the results of studies by Lechowska et al. (2011). These authors showed that, in the ovaries of Nobox-deficient mice, the somatic cells are unable to surround and separate individual primordial follicles, leading to the formation of syncytial follicles instead of primordial follicles. Because the NOBOX is a key regulator of oocyte-specific genes in mice and its expression is misregulated in women with premature ovarian failure (POF) syndrome, this study may shed light on the mechanism of POF in humans (Albertini 2011; Lechowska et al. 2011; Rajkovic et al. 2004).

The more or less central (with emphasis on "less") position of the GV in fully grown, prophase-arrested mouse oocytes may be the key factor determining the future direction of the spindle migration to the nearest subcortical region that therefore determines the axis of the future egg polarity. There is ample information on the molecular mechanisms responsible for the positioning and migration of the meiotic spindle from the center of the oocyte to its periphery. In mouse oocytes, the migration of the spindle from the slightly off-center position (where the GV was located) toward the nearest region of the cortex occurs along its long axis and involves actin filaments, actin nucleator factor formin-2 (Fmn2; Azoury et al. 2009, 2011; Dumont et al. 2007; Leader et al. 2002; Longo and Chen 1985; Verlhac et al. 2000; Terada et al. 2000), and possibly the function of Golgi resident protein GM130 (Zhang et al. 2011). It must be stressed in this discussion that the MI spindle

in mouse oocytes is acentriolar and that only the electron-dense pericentriolar material is found at the spindle poles (Szollosi et al. 1972). This description also applies to the MII spindle and, as mentioned earlier, the stage of oogenesis at which the centrioles disappear is unknown. In recent years, mounting evidence has pointed to the critical role of cytoplasmic sheets or lattices (CPLs) in the regulation of various stages of oocyte maturation, spindle movement, and emission of the polar body. The cytoplasmic lattices or sheets are functionally puzzling structures, unique to the oocytes and early embryos of all mammals studied so far, including mouse and humans. CPLs are composed of cylindrical bundles of keratin-containing intermediate filaments and undergo dramatic reorganizations at critical stages of oocyte maturation and early development (Capco et al. 1993; Esposito et al. 2007; Gallicano et al. 1994; Kan et al. 2011; Wright et al. 2003). One of the possible functions of CPLs is the regulation of microtubule dynamics through the storage of soluble tubulin (Kan et al. 2011). CPLs are enriched in peptidylarginine deiminase 6 (PADI6), which is necessary for their formation, and it seems that the PADI6/CPL superstructure plays a key role in regulating microtubule-mediated organelle positioning and movement (Esposito et al. 2007; Wright et al. 2003; Kan et al. 2011). Interestingly, the subcortical positioning of the acentriolar spindle and chromosomes results in subsequent local remodeling of the oocyte cortex.

2.4 Remodeling of the Oocyte Cortex During Maturation

It is well established that the oocyte cortex and its remodeling (reorganization and polarization) during maturation play pivotal roles in polar body emission and fertilization, as well as the subsequent proper spatiotemporal development of the embryo (Sardet et al. 2002; Kloc and Etkin 1995; Kloc et al. 1996, 1998). Although the usage of the term "cortex" varies between different authors, when defined in the broadest sense, the oocyte/egg cortex contains three major components: the plasma membrane, the submembrane cytoskeletal elements, which anchor different organelles (such as mitochondria and cortical granules) and molecules, and the extracellular matrix. After GVBD (GV breakdown) and the translocation of the spindle, the region of the cortex overlying the spindle becomes free of the cortical granules (CGs) and microvilli and forms an actin filament-enriched cap that is also enriched in the mammalian homologs of the evolutionarily conserved polarity proteins Par3 and Par6 (Vinot et al. 2004; Duncan et al. 2005) and Rac-GTP (Halet and Carroll 2007). In many animal species, the size and the position of this domain regulate the size of the polar body and mark the animal pole of the future embryo (Azory et al. 2008, 2009; Deng et al. 2003; Longo and Chen 1985; Van Blerkom and Bell 1986). The formation of a CG- and microvilli-free cortical domain requires the migration of the spindle (Longo and Chen 1985) but occurs also in the absence of intact microtubule components of the spindle, thus demonstrating that it is chromosome/chromatin dependent (Maro et al. 1986;

Deng et al. 2003, 2005). Other studies show that this remodeling of the cortex depends on the balanced spatial segregation of gamma-tubulin between the oocyte cortex and the meiotic acentriolar spindle (Barrett and Albertini 2007). Studies in mouse oocytes indicate that the formation of the actin cap and the cortical granule-free domain also depend on the Arp2/3 (actin-related protein 2/3) complex and its activator, the actin nucleation factor/p53-cofactor, JMY (Sun et al. 2011a, b; Zuchero et al. 2009). Thus, coordinated cytoskeleton rearrangements seem to be key phenomena leading to the development of oocyte polarity.

To achieve the highly asymmetric division required during the first meiosis of the mouse oocyte, two steps are necessary: (1) the meiotic spindle must be relocated from the position where it was formed to the oocyte cortex; and (2) the polar body must be extruded. Because it was shown that, in maturing mouse oocytes, the disassembly of microtubules does not affect the movement of the chromatin to the oocyte cortex (Longo and Chen 1985; Verlhac et al. 2000), but the destruction or stabilization of actin filaments does (Terada et al. 2000), the role of actin in this process was extensively studied. The nucleation of actin filaments requires the activity of several proteins: the Arp 2/3 complex (Mullins et al. 1998) and the members of two different protein families, Formin (Evangelista et al. 2003; Harris and Higgs 2004; Zigmond 2004) and Spire (Quinlan et al. 2005; Ducka et al. 2010). At the GV stage and during the early stages of maturation, the cortex of the mouse oocyte possesses numerous actin filaments that emanate from the plasma membrane, forming a uniform layer of filamentous actin (F-actin). The distribution of cortical actin changes during the progression of meiotic maturation, finally forming a thick cap over the spindle (Longo 1987). Except for this cortical actin, a network of cytoplasmic actin filaments surrounds the GV and the oocyte chromatin after GVBD. The relocation of the meiosis I spindle requires the interaction between the chromosomes, microtubules, and actin filaments. The studies on Fmn2 knockout mouse oocytes, in which the spindle does not relocate to the cortex because of the lack of cytoplasmic actin filaments nucleated by Formin2, have led to the creation of a mechanistic model of asymmetric spindle positioning (Dumont et al. 2007; Schuh and Ellenberg 2008). According to this model, Fmn2 nucleates the continuous remodeling of the actin network, which bridges the gap between the cortex and the spindle, which is located slightly off-center in the oocyte. The dynamic connection of F-actin to the spindle is mediated by myosin II, which accumulates at the poles (Simerly et al. 1998). The spindle poles pull on the actin network via activated myosin. The pulling force of the pole that was initially positioned closer to the cortex is stronger than the force of the opposite pole. This inequality generates a higher number of stable actin filaments and results in the relocation of the spindle toward the cortex (Schuh and Ellenberg 2008).

Formin2 is not the only actin nucleator involved in the generation of the cytoplasmic actin network and the regulation of spindle relocation in maturing mouse oocytes. Recently, it was demonstrated that two other proteins, members of the Spire family, are key regulators of this process and in first polar body extrusion (Pfender et al. 2011). In oocytes co-depleted of both proteins, not only the asymmetric spindle position but also the efficiency of the first polar body extrusion

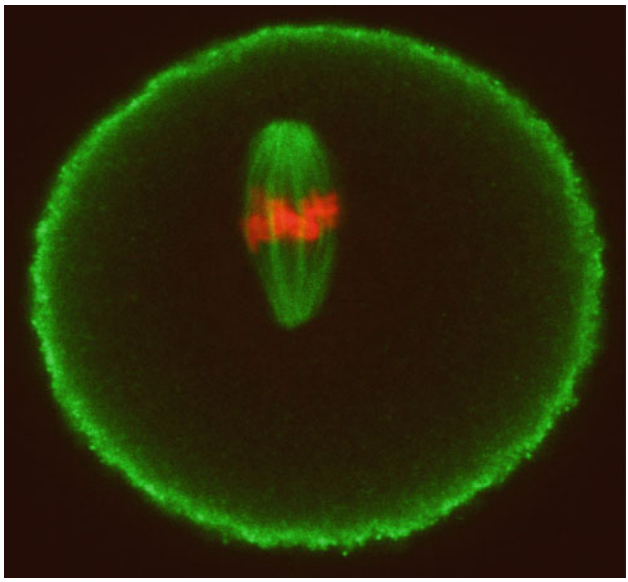

Fig. 2.3 Cdc42 localization in the MI mouse oocyte (Cdc42 *green*, DNA *red*)

becomes severely affected. In such oocytes, karyokinesis was completed, but cytokinesis failed because the cleavage furrow was not assembled. Groups of chromosomes separated in telophase I eventually fused together and formed one metaphase II spindle. Spire1 and Spire2 cooperate with themselves and associate with Formin2 in a functional unit to assemble the cytoplasmic actin network, which mediates the relocation of the meiotic spindle and is indispensable for the formation of the cleavage furrow during the first meiotic cytokinesis.

During cytokinesis, the separation of daughter cells occurs due to a properly functioning contractile ring, composed of actin and myosin (Guertin et al. 2002; Glotzer 2005). In mitotic cells, the formation of the contractile ring is regulated by proteins belonging to the Rho family of small guanosine triphosphatases (Rho GTPase) and Formins. The Cdc42 (cell division cycle 42) protein is, besides Rac1 and RhoA, one of the best-characterized members of the Rho GTPases (Kozma et al. 1995; Nobes and Hall 1995; Etienne-Manneville and Hall 2002). Cdc42 is involved in establishing the polarity of many cells, controlling the spindle positioning, the actin cytoskeleton, and the asymmetric distribution of determinants (Cau and Hall 2005). Its role in the polarization and asymmetrical cell division in vertebrate oocytes was demonstrated for *Xenopus laevis* (Ma et al. 2006) and mouse (Na and Zernicka-Goetz 2006; Cui et al. 2007). In MI and MII mouse oocytes, Cdc42 is localized on the microtubules of the spindle (Fig. 2.3), and it moves to the mid-body region at telophase of the first and second meiosis (Bielak-Zmijewska et al. 2008). Disruption of Cdc42 function causes the formation of abnormally elongated spindles, which fail to migrate to the oocyte cortex. Cdc42 disruption results in a reduction in the number of oocytes that are able to finish the first meiotic

division and extrude the first polar body (Na and Zernicka-Goetz 2006; Cui et al. 2007). Cdc42 is not the only Rho GTPase involved in the regulation of the meiotic spindle formation and its relocation. The effects of the inhibition of Rac1 in maturing mouse oocytes mimic the effects of Cdc42 inactivation. Additionally, in MII oocytes, the Rac1 protein is involved in the anchoring of the spindle in the cortical region (Halet and Carroll 2007). RhoA is engaged in the organization of actin filaments and, like Cdc42, accumulates in the region of the mid-body during telophase I and II (Zhong et al. 2005).

All of these data indicate that Rho GTPases and actin nucleators regulate the movement of the meiotic spindle to the oocyte cortex and the asymmetric cytokinesis of the first and second meiosis. In polarized mitotic cells, the regulation of asymmetric division requires coordination of the activity of Rho GTPases and their effector proteins, including IQGAP1 (IQ-domain GTPase-activating protein 1). This conserved protein is engaged in the organization of microtubules and microfilaments. Through its binding to selected partners, such as E-cadherin, beta-catenin (Fukata et al. 1999; Kuroda et al. 1998; Shannon and Li 1999), or F-actin (Bashour et al. 1997; Fukata et al. 1997), IQGAP1 participates in several signaling pathways. IQGAP1 interacts with Rho GTPases and is involved in the polarization of mitotic cells (Noritake et al. 2005; Yasuda et al. 2006). It binds Cdc42 and Rac1 in their active, GTP-bound forms (Kuroda et al. 1998), but it does not bind RhoA. In the GV of intact mouse oocytes, IQGAP1 is present in the cytoplasm and forms a continuous layer in the cortex in a pattern that resembles the localization of Cdc42 (Bielak-Zmijewska et al. 2008). The initiation of maturation causes a dramatic reorganization of IQGAP1, including the loss of its co-localization with its partner protein, Cdc42. IQGAP1 loses its cortical localization and remains dispersed in the cytoplasm until telophase I and II, when it accumulates in the contractile ring, a pattern that suggests its involvement in cytokinesis. This function of IQGAP1 seems to depend on its direct relationship with the Rho GTPases. Inhibition of this interaction by toxin B, a glucosyltransferase that keeps the Rho GTPases in their inactive, GDP-bound forms, blocks the extrusion of the first polar bodies. In toxin B-treated oocytes, the formation of contractile rings is abolished (Bielak-Zmijewska et al. 2008). This change is accompanied by a massive depolymerization of cortical actin and rearrangement of IQGAP1 localization. These data suggest that, in mouse oocytes, IQGAP1 acts downstream of Cdc42 and that the activity of both proteins could be necessary for the proper arrangement of actin filaments in the contractile ring. Although it was postulated that Cdc42 regulates the relocation of the meiotic spindle in mouse oocytes (Na and Zernicka-Goetz 2006), it seems that the step of asymmetric division is achieved mainly due to the activity of actin nucleators and motor proteins (Schuh and Ellenberg 2008; Pfender et al. 2011). Rho GTPases and their regulators or effectors (such as IQGAP1) are involved in the process of polar body extrusion, arranging the assembly of the cleavage furrow and the contractile ring.

There are also recent studies indicating the paramount importance of strictly mechanical properties of the oocyte/egg, such as cortical tension and stiffness, on the subsequent molecular events that lead to the remodeling of the maturing oocyte.

Larson et al. (2010) showed that the meiotic maturation of the mouse oocyte is accompanied by a sixfold drop in tension. After fertilization, the tension increases by approximately 1.6-fold. In addition, they showed that there is a 2.5-fold mechanical tension differential between the actin- and myosin II-enriched microvilli-free cortical domain overlaying the spindle and the opposite microvillar cortex, which is enriched in radixin. Experimental perturbation of the expression of radixin, actin, and myosin II resulted in the reduction of tension during maturation and in spindle abnormalities (Larson et al. 2010).

In summary, all of these studies indicate that the extremely complex and multifaceted signaling between the multitude of mechanical, structural, and molecular components of the oocyte and the somatic cells leading to egg polarization still remains a worthwhile challenge.

2.5 Polarity of Cell Cycle Regulators

Besides the polarity of the cytoskeleton elements and the cortex, the more "fluid" elements are also clearly polarized in the mouse oocyte. The notion of the potential "fluidity" of certain enzymes may be controversial because they are potentially linked to the cytoskeletal elements. Some examples are the M-phase regulators (oocytes spend the vast majority of the time during meiotic maturation in M-phases), such as the CDK1 (Cyclin-Dependent Kinase 1) and MAP (Mitogen-Activated Protein) kinases from the ERK (Extracellular-Regulated Kinases) family (including ERK1, 2, 3, and 5), which are major serine/threonine kinases.

CDK1, also called MPF for M-phase Promoting Factor, is a major kinase active during M-phase that was first identified in amphibian oocytes (Masui and Markert 1971) and later in mouse oocytes (Balakier and Czolowska 1977). It is activated by binding to the regulatory subunit cyclin B (Labbé et al. 1988; Gautier et al. 1988, 1990), which is followed by a series of phosphorylation reactions at the activating sites as well as coordinated dephosphorylations at the inhibitory sites. CDK1/cyclin B is activated upon M-phase entry (during GVBD in oocytes) and inactivated at the end of each M-phase (upon anaphase I during oocyte maturation and anaphase II during fertilization). Inactivation of this kinase requires the separation of cyclin B from CDK1 and its proteolytic degradation by the proteasome (Glotzer et al. 1991; Ledan et al. 2001). Cyclin B separation from CDK1 and its further degradation is mediated by polyubiquitination via the ubiquitin ligase, APC/C (Anaphase Promotin Complex/Cyclosome) (Nishiyama et al. 2000; Chesnel et al. 2006). CDK1/cyclin B exhibits typical histone H1 kinase activity in oocytes of different species (e.g., sea urchin: Arion and Meijer 1989, starfish: Labbé et al. 1989, and mouse: Kubiak et al. 1991; Kubiak et al. 1992; Ciemerych et al. 1998; Kubiak 2012). In mouse MII-arrested oocytes, H1 kinase activity is clearly more concentrated within the spindle-containing oocyte half (Kubiak et al. 1994). Accordingly, the CDK1 and cyclin B proteins concentrate within the spindle in mouse oocytes (Mitra and Schultz 1996; Huo et al. 2005), as well as in somatic cells (Bailly et al. 1989; Pines and Hunter 1991;

Ookata et al. 1995). Thus, active CDK1/cyclin B concentration with the spindle is not a unique characteristic of oocytes. However, in contrast to somatic cells, which are small and have spindles positioned in the center, in large cells like oocytes, the high concentration of active CDK1 within the asymmetrically positioned meiotic spindle creates a highly polarized gradient of this kinase in the cytoplasm (Kubiak et al. 1994). Cyclin B undergoes turnover during MII, which requires the presence of the intact meiotic spindle (Kubiak et al. 1994). Interestingly, cyclin B is stable in MI oocytes (Winston 1997). It is therefore likely that the components of the molecular machinery involved in cyclin B degradation (e.g., the APC/C components and regulators) are also asymmetrically distributed, at least within MII oocytes. Indeed, ubiquitin concentrates around the meiotic spindle in mouse oocytes, especially during anaphase and telophase, when cyclin B is ubiquitinated and degraded (Huo et al. 2004). Additionally, a regulatory subunit of the proteasome, the high molecular weight protease complex that degrade cyclin B, was shown to concentrate within the spindle of the mouse oocyte (Tan et al. 2005). Altogether, the distribution of CDK1, its regulator cyclin B, and the inactivating molecular machinery is highly asymmetric and polarized within the mouse oocyte, with the meiotic spindle acting as a concentration and/or diffusion point. Recent study by the group of Rong Li has shown the presence of a cytoplasmic stream in MII-arrested oocytes, which is involved in localization of the second meiotic spindle to the restricted subcortical area (Yi et al. 2011). This indicates that the seemingly stagnant MII state is much more dynamic than previously thought. Not only the dynamic state of cyclin B regulating stable CDK1 activity (Kubiak et al., 1993), but also the physical movement of the cytoplasm fixing the meiotic spindle in a stable position argues for the dynamic equilibrium preserving the polarity of mouse MII oocyte.

MAP kinases from the ERK family show a very similar asymmetry in their localization in the oocyte. ERK1 and 2, ERK3, and phosphorylated ERK5 MAP kinases are localized to the mouse oocyte spindle and form a gradient in the cytoplasm (ERK1/2: Verlhac et al. 1993; ERK3: Li et al. 2010; ERK5: Maciejewska et al. 2011). Additionally, MEK1, the ERK1/2 MAP kinase activating kinase, localizes to the spindle and especially to the pericentriolar material foci at the spindle poles (Yu et al. 2007). Most importantly, the phosphorylated, and thus active, form of MEK1 has a very similar localization within the specific region of the spindle. This observation suggests that the activation of ERK1 and 2 occurs in this specific region of the spindle and that it is followed by the distribution of the active MAP kinases throughout the whole spindle and in the ooplasm (Xiong et al. 2007). The fact that the ERK1/2 MAP kinase pathway (including the ERK 1/2 MAP kinase kinase kinase Mos) has an essential role in the meiotic maturation and spindle positioning in MI mouse oocytes, as well as in the sizing of the first polar body, indicates its functional relevance to oocyte polarity (Weber et al. 1991; Colledge et al. 1994; Verlhac et al. 1996; Araki et al. 1996). Thus, the polarized localizations of these MAP kinases and the components of their activation pathways seem to be essential for the asymmetric division of mouse oocytes. These major kinases are not the only spindle-associated kinases in mouse oocytes. Fyn kinase, a member of the Src family of tyrosine kinases, also has a similar distribution (see Levi et al. 2012 in this issue).

Protein kinase action is counterbalanced by specific phosphatases, which dephosphorylate their substrates and form the equilibrium between the turnover of phosphorylated and dephosphorylated substrates. The role of the phosphatases PP2A and PP1 in the regulation of the cell cycle was described in detail in both mouse oocytes (Rime and Ozon 1990; de Pennart et al. 1993; Schindler 2011) and rat oocytes (Zernicka-Goetz et al. 1997). So far, the localization pattern of these two essential cell cycle-regulating phosphatases in mouse oocytes remains unknown, but another cell cycle-regulating phosphatase, CDC14, has been found to be concentrated within the meiotic spindle (Schindler and Schultz 2009). This observation suggests that other phosphatases could also accumulate in the meiotic spindle, where they would counterbalance kinase-dependent phosphorylation. This arrangement, in turn, would imply the polarized distribution of a number of phosphorylated substrates. Such complex organization of various molecules in the oocyte cytoplasm would play a key role in the formation and temporal maintenance of oocyte polarity.

Other examples of the asymmetric distribution of proteins guided by the meiotic spindle are the mouse PAR polarity proteins, such as the PAR6-related proteins mPARD6a and mPARD6b (Vinot et al. 2004). During the first meiotic M-phase, the two proteins are located within the MI acentriolar spindle as it forms and migrates to the cortex. The similar amounts of mPARD6a and b found in each spindle half demonstrate an equal distribution of these proteins within the spindle. However, by the end of the first meiosis, mPARD6a concentrates at this spindle pole, which is closer to cortex, i.e., its localization within the single spindle becomes polarized. During the MII arrest of oocytes, mPARD6b becomes rapidly relocated to the neighboring cortex. Interestingly, when MTs are experimentally disassembled during MI, the MT-free bivalents still migrate towards the oocyte surface and mPARD6a accumulates preferentially on their side facing the cortex, suggesting that this protein may play an active role in migration (Vinot et al. 2004). This behavior of mPARD6a and b seems to be limited to the oocytes, as it was not observed in early embryos, where this protein is equally distributed in the mitotic spindles (Vinot et al. 2005). The asymmetric distribution of mPARD6a within the meiotic spindle and the delocalization of mPAR6b from the spindle to the MII oocyte cortex suggest that the meiotic spindle not only is the central structure involved in polarization of the oocyte but also becomes an active vector bringing the cortical proteins necessary for asymmetric division to the right place. It is absolutely unknown whether the evolution of mPARD6a and b proteins described earlier is causally related to the acentriolar character of the meiotic spindle.

2.6 Conclusions

Oocyte polarity is a prerequisite for the proper completion of embryogenesis. In mouse oocyte ontogenesis, polarity develops twice. The final polarity of the mature egg involves spindle migration and successful anchoring at the cortex.

Once harbored at the cortex, the acentriolar spindle induces modifications of the cell cortex and the cytoplasm, which maintain the polarity until fertilization and permit asymmetric division to occur properly. In addition, the meiotic spindle is a vector that brings the proteins necessary for unequal meiotic division (such as CDK1, ERK1/2, and mPARD6a and b) to the right place. The complete understanding of mouse oocyte polarity will enable us to understand many important aspects of mammalian (including human) embryo development and answer such fundamental questions as when and how the embryo axes and body plan become determined.

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