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Review

Interactions between chromosomes, microfilaments and microtubules revealed by the study of small GTPases in a big cell, the vertebrate oocyte

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Abstract

Meiotic divisions during oogenesis in higher eukaryotes are extremely asymmetric giving rise to one gamete, the oocyte, and two polar bodies. In most species, this asymmetric partitioning relies on the eccentric positioning of meiotic spindles. Recent work performed in mouse and frog oocytes has suggested the involvement of small GTPases, such as Cdc42, Rac and Ran both in the control of spindle organization and positioning. The present review summarizes these findings that shed light on the molecular mechanisms by which small GTPases control asymmetric cell divisions in vertebrate oocytes.

Keywords: Meiosis; Small GTPases; Mouse; Oocyte

Spatial and temporal control of cell division ensures equal segregation of chromosomes between two daughter cells. Female meiotic divisions give rise to daughter cells of different sizes: a big oocyte and two tiny polar bodies. In vertebrate oocytes, asymmetric meiotic divisions require both the formation of a functional spindle, which positions at the cortex, as well as the restriction of the cleavage furrow at the plasma membrane overlying the chromosomes. Spatial and temporal coordination of these processes relies on signaling properties of meiotic chromosomes, which control proper microfilaments and microtubules organization.

With recent findings in mouse and *Xenopus* oocytes, we will review how small GTPases control essential aspects of meiotic divisions in vertebrate oocytes.

1. Morphological events of meiotic maturation

Oocytes of all species are arrested in prophase I of meiosis in the ovary. Meiotic maturation then ends the process of meiosis with the succession of two asymmetric divisions. Although they occur with different kinetics in mouse and *Xenopus*, the successive steps are very similar. Physiologically, a hormonal surge (luteinizing hormone in mouse and progesterone in *Xenopus*) releases oocytes from the prophase I arrest. However, meiosis resumption can also be triggered *in vitro* by using chemical treatments, which makes it possible to follow the various steps of maturation. It begins with nuclear envelope breakdown (NEBD), also called germinal vesicle breakdown (GVBD, Fig. 1). The first meiotic spindle emanates slowly from microtubule organizing centres (MTOCs) around the condensing chromosomes in the mouse or at the basal part of the nucleus in *Xenopus*. The migration of the spindle towards the egg cortex starts shortly after GVBD in *Xenopus* while it takes place only after a bipolar spindle has been assembled in the mouse (Verlhac et al., 2000). In mouse oocytes, the first meiotic spindle moves along its long axis with the pole closest to the cortex leading the way, via a microfilament-dependant process (Verlhac et al., 2000). As the chromosomes move to the close proximity of the cortex, they induce its differentiation, which results in a local accumulation of actin microfilaments and a lack of microvilli (Longo and Chen, 1985; Maro et al., 1986; Verlhac et al., 2000). This is supposed to restrict the progression of the cleavage furrow to the differentiated area overlying the chromosomes, both in meiosis I and II. By restricting the size of the polar bodies, oocytes retain most of the maternal stores for further development. After first polar body extrusion, oocytes enter the second M-phase

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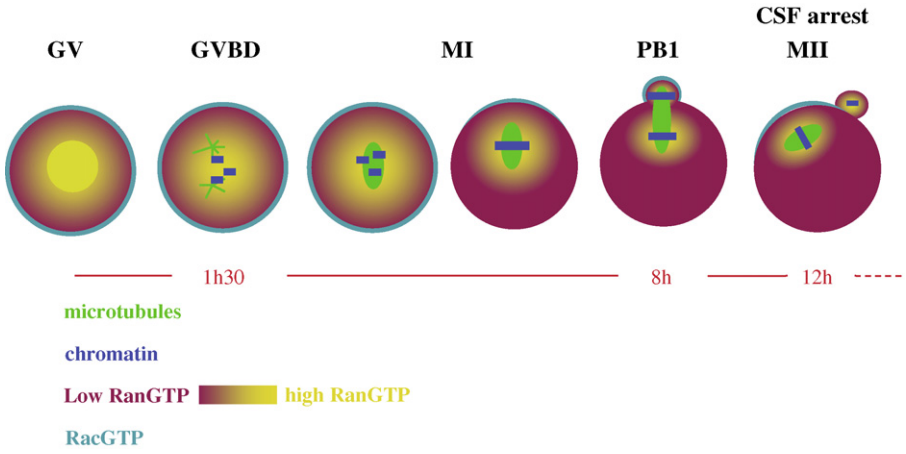

Fig. 1. Meiotic maturation in mouse oocytes showing the localization of active RacGTP and of the RanGTP gradient. GV: germinal vesicle; GVBD: germinal vesicle breakdown; MI: metaphase I; MII: metaphase II; PB1: first polar body; CSF: cytostatic factor arrest in MII.

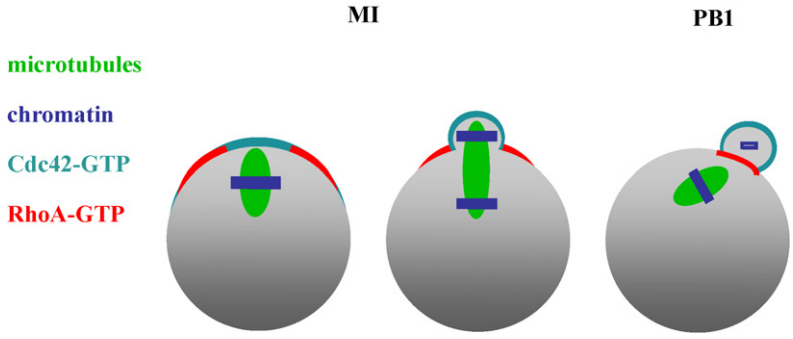

Fig. 2. First polar body extrusion in *Xenopus* oocytes showing the localizations of active Cdc42 and RhoA.

where a meiotic spindle forms rapidly at the periphery of the oocyte with its long axis parallel to the cortex (Figs. 1 and 2) . In most vertebrate species, the cell cycle arrests in metaphase II, with a stable spindle anchored to the cortex. After fertilization, a microfilament-dependant rotation of the spindle takes place allowing its perpendicular orientation relative to the cortex, and the second polar body is extruded.

Hence, both meiotic divisions require a cortical differentiation to restrict the progression of the cleavage furrow. In addition, the asymmetry of the first division is achieved by the migration of the spindle and its anchoring to the cortex while the second division requires the cortical anchoring of the spindle and its rotation.

2. Small GTPases

The superfamily of small GTPases can be divided into five major subfamilies: Ras (the founding member), Rab, Arf, Rho and Ran. This review will focus only on the last two. The Rho subfamily can be subdivided into three groups: Rho, Rac and Cdc42. Each small GTPase functions as a molecular switch cycling between an active GTP-bound and inactive GDP-bound forms (for review Van Aelst and DSouza-Schorey, 1997). There are two main classes of regulatory proteins that control this cycle: guanine-nucleotide exchange factors (GEFs) promote the GTP loading of small GTPases and GTPase activating proteins (GAPs) stimulate the low intrinsic GTPase activity and thus their inactivation (for reviews Jaffe and Hall, 2005; Moon and Zheng, 2003; Zheng, 2001). Hence local activation/inactivation of these small GTPases can be controlled by the subcellular localization of their regulatory proteins.

Although GTPases of the Rho subfamily are involved in various processes such as regulation of gene expression or enzymatic activities and control of microtubule dynamics, their best-characterized function is the control of the actin cytoskeleton. The activation of Rho, Rac, or Cdc42 leads to the assembly of contractile acto-myosin filaments, actin-rich lamellipodia, and actin-rich filopodia, respectively (Hall, 2005). Schematically, Cdc42 and Rac promote actin polymerization by activating Arp2/3, one of the major actin polymerization factors. Activation of Arp2/3 initiates a branched microfilament network. Proteins of the Rho subgroup interact with formins, another class of actin polymerization factors, leading to the assembly of straight microfilaments.

The small GTPase Ran is the only member of its family. Ran was first identified as a regulator of nucleo-cytoplasmic trafficking. Most of our understanding of the mode of action of the Ran GTPase comes from early studies on nuclear trafficking. Cargos, containing nuclear localization signal (NLS), are imported into the nucleus through binding to import receptors, such as Importins. Once inside the nucleus, RanGTP binds to Importins thereby promoting the release of the car-