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Review

The regulation of maturation promoting factor during prophase I arrest and meiotic entry in mammalian oocytes

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ABSTRACT

Mammalian oocytes arrest at prophase of meiosis I at around birth and they remain arrested at this stage until puberty when the preovulatory surge of luteinizing hormone (LH) causes ovulation. Prophase I arrest in the immature oocyte results from the maintenance of low activity of maturation promoting factor (MPF), which consists of a catalytic subunit (CDK1) and regulatory subunit (cyclin B1). Phosphorylation-mediated inactivation of CDK1 and constant degradation of cyclin B1 keep MPF activity low during prophase I arrest. LH-mediated signaling manipulates a vast array of molecules to activate CDK1. Active CDK1 not only phosphorylates different meiotic phosphoproteins during the resumption of meiosis but also inhibits their rapid dephosphorylation by inhibiting the activities of CDK1 antagonizing protein phosphatases (PPs). In this way, CDK1 both phosphorylates its substrates and protects them from being dephosphorylated. Accumulating evidence suggests thatthe net MPF activity that drives the resumption of meiosis in oocytes depends on the activation status of CDK1 antagonizing PPs. This review aims to provide a summary of the current understanding of the signaling pathways involved in regulating MPF activity during prophase I arrest and reentry into meiosis of mammalian oocytes.

Contents

1. Introduction

Meiosis consists of two rounds of successive cell divisions after a single round of DNA replication that halves the chromosome compliment in male (sperm) or female (oocyte) gametes. In mice, oocytes begin to arrest at prophase of meiosis I (prophase I) at embryonic day 17.5 and most oocytes reach this stage by postnatal day 5 (Borum, 1961). The meiotic process that gives rise to a mature egg is lengthy, complex, and discontinuous. Oocytes arrested at prophase I contain a large nucleus covered by a nuclear envelope also known as the germinal vesicle (GV). Resumption of meiosis occurs in response to thesurge of luteinizing hormone (LH) or upon

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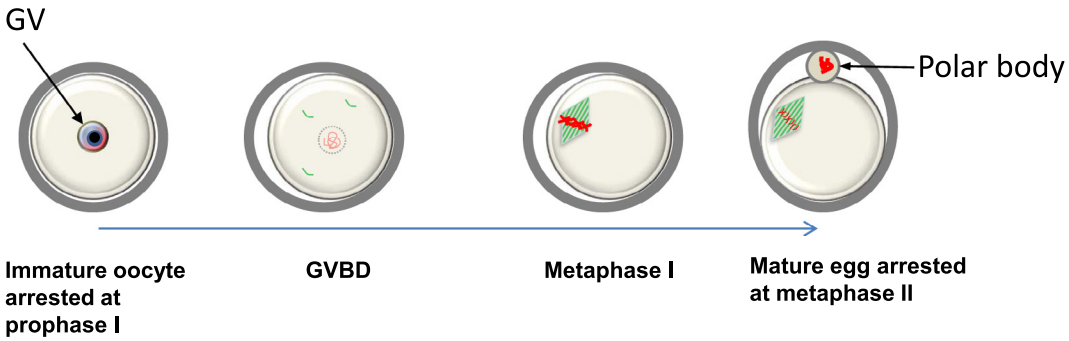

Fig. 1. Schematic representation of the mammalian oocyte meiotic maturation process. Within the follicle, oocytes remain arrested at prophase I and are characterized by a germinal vesicle (GV) in which the chromosomes (red) remain decondensed. Such a prophase I-arrested oocyte is known as a primary oocyte. A preovulatory LH surge under physiological conditions or mechanical release of the oocyte from follicle followed by *in vitro* culture causes GV breakdown (GVBD); chromosomes start to condense (red) and spindle fibres appear (green). Subsequently, chromosomes (red) condense and align at the metaphasic plate of the bipolar spindle (green) when the oocyte reaches metaphase I. Meiosis I is completed by extruding a polar body containing one set of chromosomes. The second set of chromosomes is retained in the oocyte, which is now referred to as a secondary oocyte (or an egg). The mature egg remains arrested at metaphase II until fertilization.

the mechanical release of the oocyte from the mature follicle and subsequent *in vitro* culture in a suitable medium. GV breakdown (GVBD) is the first morphological sign of reentry into meiosis. Following GVBD, meiosis I spindles are formed and bivalent chromosomes align along their chiasmata. Chiasmata are resolved once all bivalent chromosomes come under tension leading to anaphase I (Kudo et al., 2006). Meiosis I is completed by extruding a polar body containing one set of chromosomes. The other set of chromosomes is retained in the oocyte, and the oocytes subsequently enter into the second round of meiosis but arrest at metaphase of meiosis II until fertilization (Fig. 1).

At birth, a young girl has about 600,000–800,000 primordial follicles, eachcontaining a single oocyte arrested at prophase I. However, during the reproductive life of a woman, fewer than about 500 eggs will ovulate and undergo the process of meiotic maturation while the rest of the oocytes maintain their prophase I arrest throughout their lifespan (Adhikari and Liu, 2009; McGee and Hsueh, 2000; Gougeon, 1996). Errors in oocyte maturation can cause aneuploidy in the resulting eggs and embryos, and this is one of the leading causes of spontaneous abortions and developmental abnormalities in humans (Jones, 2008; Hassold and Hunt, 2001). A proper understanding of the mechanisms underlying oocyte maturation would also improve the quality of fertility treatments. In this review, we discuss the signaling mechanisms that govern the maintenance of prophase I arrest and the reentry into meiosis through the regulation of the activity of maturation promoting factor (MPF). For obvious reasons, studies involving human oocytes to understand the molecular mechanisms of oocyte maturation are very limited. Most of our current understandings on the signaling pathways that govern oocyte maturation have come from studies on oocytes using animal models.

2. Mechanism of oocyte meiosis arrest at prophase I

Mammalian oocytes within fully-grown antral follicles remain arrested at prophase I and, unless otherwise mentioned, the mechanisms of oocyte maturation described in this review refer to oocytes already within the antral follicles. Such oocytes do not resume meiosis until there is a preovulatory surge of LH, which indicates that LH mediates the resumption of oocyte meiosis. However, it was noticed early on that fully-grown oocytes also resumed meiosis spontaneously and without the requirement for anyhormonal stimulation when freed from the follicle and cultured *in vitro* (Pincus and Enzmann, 1935). This observation led to the hypothesis that the somatic cells of the follicle function to prevent the resumption of meiosis in the oocyte and that the LH surge removes this inhibitory factor rather than providing any positive stimulus for the resumption of meiosis (Channing and Tsafriri, 1977).

3. Regulation of MPF activity for prophase I arrest and reentry into meiosis

The prophase I arrest in the follicle-enclosed oocyte is the result of low MPF activity, and resumption of meiosis upon the arrival of hormonal signals is mediated by activation of MPF (Adhikari et al., 2012; Eppig et al., 2004; Jones, 2004). MPF is a complex of a catalytic $p34^{cdc2}$ kinase (cyclin dependent kinase 1 (CDK1) or Cdc2) subunit and its regulatory subunit cyclin B1 (Doree and Hunt, 2002). CDK1 plays an essential role in the resumption of meiosis in immature mouse oocytes and no other CDKs can compensate for the loss of CDK1 function (Adhikari et al., 2012). The release from prophase I arrest in immature oocytes is usually compared to the G2/M-phase transition in mitosis, and CDK1 plays an essential role in the G2/M-transition as well (Santamaria et al., 2007; Diril et al., 2012). Several signaling pathways interact to ensure the maintenance of low MPF activity in the prophase I-arrested oocyte and then to activate MPF when it is time to reenter meiosis.

3.1. Regulation of CDK1 by cAMP

The pioneering observations of Pincus and Enzmann (1935) that oocytes resume meiosis spontaneously upon release from the antral follicle suggested the inhibitory role of somatic cells on the re-initiation of oocyte meiosis. Although the preovulatory LH surge overcomes this inhibitory action, LH cannot have a direct effect on the oocyte because LH receptors are not expressed on the oocyte surface (McGee and Hsueh, 2000; van Tol et al., 1996; Peng et al., 1991). It was believed for many years that factors present in the follicular fluid were essential for maintaining the prophase I arrest in oocytes. Accumulating evidence suggests that a high level of cAMP (cyclic adenosine 3′,5′-monophosphate) in the oocyte is responsible for preventing CDK1 activation and for maintaining oocyte arrest at prophase I.

Cho et al. (1974) reported that the spontaneous meiotic maturation of mouse oocytes is prevented when they are cultured in the presence of the cAMP analog dibutyryl cAMP. Similarly, the cAMP phosphodiesterase (PDE) inhibitor isobutyl methyl xanthine (IBMX) reversibly inhibits spontaneous resumption of meiotic maturation *in vitro* in mammalian oocytes. PDE inhibitors maintain high levels of oocyte cAMP by preventing its degradation (Schultz et al., 1983). Accordingly, the oocytes from mutant mice lacking