

Molecular mechanisms of the initiation of oocyte maturation: general and species-specific aspects

Masakane Yamashita*, Koichi Mita, Noriyuki Yoshida and Tomoko Kondo

Division of Biological Sciences, Graduate School of Science,
Hokkaido University, Sapporo 060-0810, Japan.

* To whom correspondence should be addressed

Stimulated by maturation-inducing hormone secreted from follicle cells surrounding the oocytes, fully-grown oocytes mature and become fertilisable. During maturation, immature oocytes resume meiosis arrested at the first prophase and proceed to the first or second metaphase at which they are naturally inseminated. Paying special attention to general and species-specific aspects, we summarise the mechanisms regulating the initial phase of oocyte maturation, from the reception of hormonal signals on the oocyte surface to activation of the maturation-promoting factor in the cytoplasm, in amphibians, fishes, mammals and marine invertebrates.

INTRODUCTION TO OOCYTE MATURATION

The life of multicellular organisms begins at fertilisation, the union of germ cells (the egg and the spermatozoon). The production and maturation of germ cells and their fusion are indispensable for the maintenance of a species beyond the limited longevity of individuals. Oocytes are produced in ovaries by the entry of mitotically proliferating oogonia into meiosis. Oocytes stop their meiotic cell cycle at the first prophase, during which they grow by the accumulation of substances necessary for early embryonic development (vitellogenesis). In many species, fully-grown postvitellogenic oocytes arrested at the first meiotic prophase are immature, and they are unable to be fertilised until they mature. The oocytes that have been induced to mature resume meiosis from the first prophase and proceed to the first or second metaphase, at which time, in many invertebrates and vertebrates, they are inseminated (1). During the course of maturation, oocytes undergo drastic morphological changes associated with progression of the meiotic cell cycle, among which breakdown of the oocyte nuclear envelope (germinal vesicle breakdown, GVBD) occurring at the prophase/metaphase transition is frequently regarded as a hallmark of the progress of maturation, although it does not necessarily mean the completion of maturation (Figure 1).

Oocyte maturation is induced by sequential actions of three substances (2): gonadotropic hormone (GTH; or gonad-stimulating substance in starfish, GSS), maturation-inducing hormone (MIH; or maturation-inducing substance, MIS) and maturation-promoting factor (MPF) (Figure 2). Two species of GTH, a luteinizing hormone (LH) and a follicle-stimulating hormone (FSH), are secreted from the pituitary gland in vertebrates. Both LH and FSH consist of two glycoprotein subunits, α and β subunits; the former is also a component of the thyroid-stimulating hormone (TSH) and the latter characterises each hormone. FSH is responsible for oocyte growth, and LH triggers oocyte maturation by stimulating follicle cells surrounding the

oocytes to produce MIH. MIH in vertebrates is a steroid derivative and interacts with a membrane-bound receptor on the oocyte surface, and subsequent signal transduction from the surface to the cytoplasm is probably intermediated by GTP-binding proteins (G-proteins). The MIH signal finally results in the formation and activation of MPF. In contrast to GTH and MIH, the action of MPF on promoting oocyte maturation is ubiquitous, displaying no species-specificity. In addition to its function as the final inducer for meiosis reinitiation from the first prophase, MPF also acts as the dominant initiator of the mitotic M-phase in all eukaryotes (3). MPF is a complex of Cdc2 (a catalytic subunit) and cyclin B (a regulatory subunit), and its activity is controlled by inhibitory phosphorylation of Cdc2 on threonine 14/tyrosine 15 (T14/Y15) by Wee1 and Myt1 and activating phosphorylation on threonine 161 (T161) by cyclin-dependent kinase activating kinase (CAK) after a complex formation of Cdc2 and cyclin B (4, 5).

Since the discovery, 10 years ago, that MPF consists of Cdc2 and cyclin B, a big bang has occurred in the field of cell cycle research, resulting in significant progress toward elucidation of the regulatory mechanisms of the cell cycle and oocyte maturation at the molecular level. Since MPF is a common regulator for both meiosis and mitosis, we usually deduce the mechanisms of mitosis from the data obtained from oocyte maturation that includes meiosis, and *vice versa*. Actually, it is often assumed that oocyte maturation reflects the G2/M transition in mitosis. Based on classical morphological categorisation, however, fully grown oocytes are arrested at the prophase of the first meiotic M-phase. This implies that they have already passed through the G2-phase and have entered the M-phase, although the boundary between the two phases is unclear. They proceed to the first or the second meiotic metaphase after hormonal stimulation (Figure 1). Therefore, it might be conceivable that oocyte maturation is not comparable to the G2/M transition but to a transition within the M-phase.

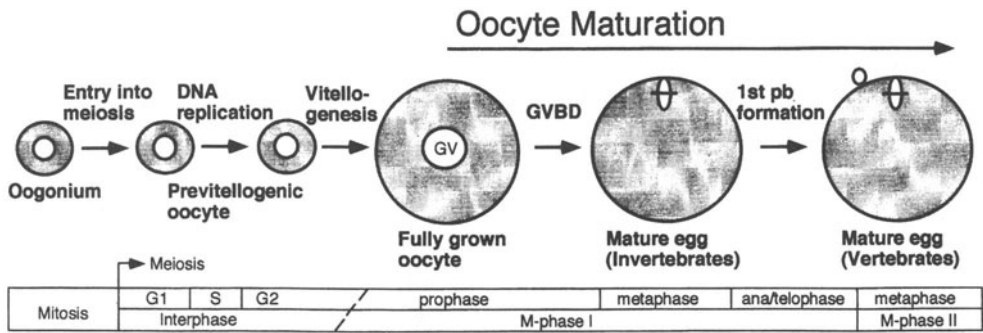


Figure 1. Oogenesis, oocyte maturation and meiotic cell cycle. Oocytes arrested at the first meiotic prophase grow by the accumulation of yolk (vitellogenesis) and become fully-grown but are still immature. Upon hormonal stimulation, the immature oocytes resume meiosis and proceed to the metaphase of the first meiosis (many invertebrates) or the second meiosis (many vertebrates), where they are naturally inseminated

It is well known that oogenesis of interspecific hybrids is arrested before vitellogenesis, probably because of the failure in pairing homologous chromosomes. This means that only those oocytes that have passed certain checkpoints before entering the first meiotic prophase can enter vitellogenesis and become fully grown. The fully grown oocytes are thus expected to have already passed the DNA replication checkpoint at the G2-phase, indicating that there is no need for their meiotic cycle to be arrested by Y15 phosphorylation of Cdc2, a main tool for arresting the mitotic cycle of cells having unreplicated DNA. Therefore, there seems little reason to insist that the Y15 dephosphorylation responsible for the G2/M transition in mitosis must also operate at the initiation of oocyte maturation in meiosis. In addition to the difference between meiosis and mitosis, consideration should be given to species-specificity in the mechanisms. The best example for this is the extent to which the inhibitory this Y15 phosphorylation of Cdc2 is involved in the DNA replication checkpoint (see Ref. 6 for review). The deduction of mechanisms of oocyte maturation from those of mitosis in somatic cells is too easy, although it is highly possible that some mechanisms are shared between them. Apart from mitotic cell cycle control (the G2/M transition), there must be some mechanisms of oocyte maturation that are specific to one species as well as mechanisms that are to all species. In events that lead to the activation of review, we first summarise the mechanisms of the initiation of oocyte maturation in amphibians, fishes, mammals and marine invertebrates (mainly starfish), with special reference to the early events that take place within the MIH-treated oocytes, from MIH signal reception on the oocyte surface to MPF activation in the oocyte cytoplasm. We then discuss the general and species-specific aspects of oocyte maturation.

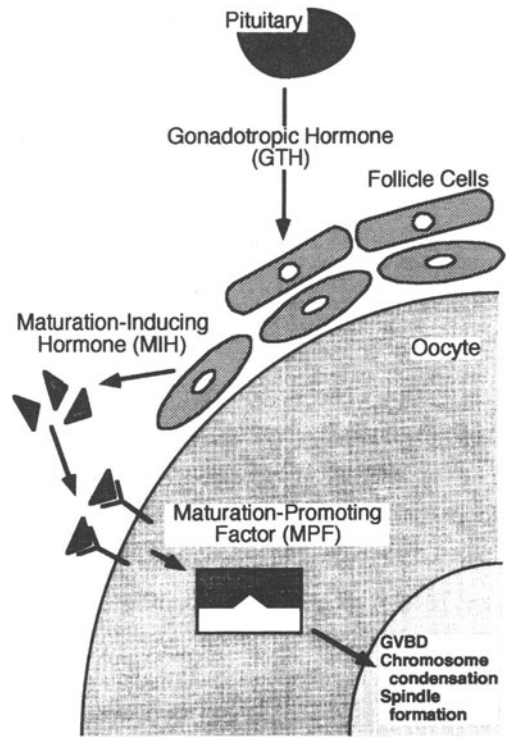


Figure 2. Three major mediators for inducing oocyte maturation. Under the influence of GTH secreted from the pituitary gland, follicle cells surrounding the oocytes produce and secrete MIH, which is received by the receptor on the oocyte surface. The MIH signal stimulates the oocyte to form and activate MPF, which finally triggers all of the changes accompanying oocyte maturation, such as germinal vesicle breakdown (GVBD), chromosome condensation and spindle formation.