—Mini Review—

Upstream Factors Regulating Maturation/ M-phase Promoting Factor Activity during Oocyte Maturation

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Abstract: *Maturation/M-phase promoting factor (MPF) activity is regulated by the Cyclin B concentration and phosphorylation states of Cdc2 kinase. In the present review, we summarize the factors regulating the synthesis and degradation of Cyclin B and the phosphorylation and dephosphorylation of Cdc2. We focuse on Aurora A and cytoplasmic polyadenylation element binding protein (CPEB), which are involved in cytoplasmic polyadenylation, for Cyclin B synthesis; on anaphase-promoting complex (APC) activating factors, FZR1 and CDC20, for Cyclin B degradation; on Cdk7 and Wee1B for Cdc2 phosphorylation, and on Cdc25 for Cdc2 dephosphorylation. We describe our recent results concerning these factors in porcine oocytes, and discusse overall regulation of MPF activity during porcine oocyte maturation.*

Key words: *MPF, Cyclin B, Cdc2, Pig*

Introduction

Maturation/M-phase promoting factor (MPF) is a critical factor inducing mitosis and meiosis, including oocyte maturation, and is a heterodimer consisting of a catalytic subunit, Cdc2, and a regulatory subunit, Cyclin B. Cdc2 has three phosphorylation sites, threonine 14 (T14), tyrosine 15 (Y15) and threonine 161 (T161). Phosphorylation of T161 is essential for the Cdc2 activity [1–3], whereas phosphorylation of either T14 or Y15 inhibits the activity [3, 4]. The Cdc2/Cyclin B complexes inactivated by T14/Y15 phosphorylation are called pre-MPF. The three phosphorylation sites have been reported to be phosphorylated after Cdc2 binding with Cyclin B [2, 5]. Therefore, the Cyclin B level is of primary importance to the regulation of Cdc2 activity and the phosphorylation states of Cdc2 constitute a limiting factor on that activity in the presence of Cyclin B.

During oocyte maturation, MPF shows a bimodal fluctuation pattern which peaks at the first meiotic metaphase (MI) and the second meiotic metaphases (MII). The fluctuation patterns of the Cyclin B1 and Cyclin B2 levels and their localization in oocytes were previously reviewed [6]. In the present article, the upstream factors regulating MPF activity are reviewed. We summarize the factors regulating Cyclin B synthesis and degradation, and the factors regulating Cdc2 phosphorylation and dephosphorylation, including our recent results for porcine oocytes. The topic factors are shown in Fig. 1. We discusse the overall regulation of MPF activity during porcine oocyte maturation.

Regulation of Cyclin B Synthesis

Maternal *Cyclin B* mRNAs, which have short poly(A) tails and are translationally inactive, are stored in ovarian full-grown oocyte cytoplasm. The *Cylcin B* mRNAs contain an approximately 10-base uridine-rich sequence, called the cytoplasmic polyadenylation element (CPE), in their 3'-untranslated region (UTR), and their translation by a cytoplasmic polyadenylation mechanism has been reported in Xenopus oocytes [7]. In this mechanism, *Cyclin B* mRNAs are bound by CPE binding protein (CPEB) at the CPE sequence and are inhibited their translation. After CPEB phosphorylation by Aurora A kinase, a poly(A) polymerase is recruited at the short

Received: December 2, 2009
Accepted: January 18, 2010
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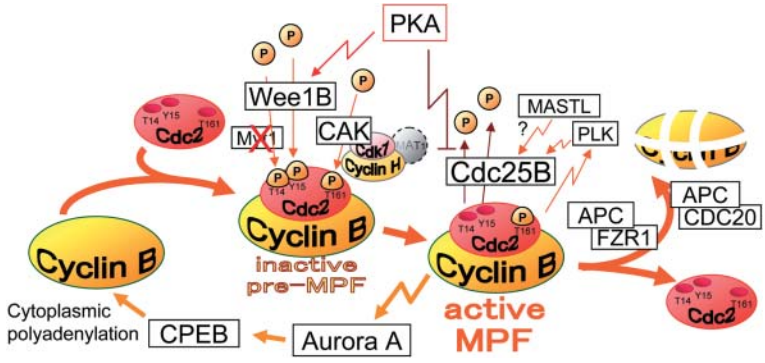

Fig. 1. Conceptual scheme for the factors described in the present review.

poly(A) tail by phosphorylated CPEB-mediation, which elongates the poly(A) tail, followed by the initiation of translation [8–10]. A constitutive active mutant of Aurora A can induce germinal vesicle breakdown (GVBD) in Xenopus oocytes without progesterone stimulation [11].

In mammals, the presence of the CPE sequence in 3'-UTR of *Cyclin B1* mRNA and the requirement of this sequence for the elongation of the poly(A) tail have been reported in mice [12, 13]. Mouse CPEB, which binds with this sequence, has also been identified [12]. The presence of Aurora A (IAK1/Eg2) in mouse oocytes [14, 15] and the phosphorylation of mouse CPEB by maturing mouse oocyte extract [14] suggest that the cytoplasmic polyadenylation mechanism reported in Xenopus oocytes also functions in mouse oocytes. Recently, we have cloned porcine Aurora A and CPEB from porcine oocytes, and showed in porcine immature oocytes that the expression of active porcine Aurora A or porcine CPEB increased the Cyclin B level and accelerated the meiotic resumption, whereas the inhibition of Aurora A expression or expression of unphosphorylatable mutant CPEB decreased Cyclin B accumulation and prevented GVBD [16, 17]. These results strongly suggest that Cyclin B synthesis is also regulated by an Aurora A-controlled and CPEB-mediated cytoplasmic polyadenylation mechanism in mammalian oocytes. Aurora A has been reported to be phosphorylated and activated by Cdc2 on meiotic resumption in Xenopus oocytes [18, 19], suggesting that the activation of Aurora A in this period is regulated by MPF activity.

The presence of two *Cyclin B1* mRNAs, which have different 3'-UTR length, has recently been reported in porcine oocytes [20]. We have also identified the same two porcine *Cyclin B1 mRNAs*, long-form and short-form, and analyzed the 3'-UTR sequences. The expression period has been shown to be regulated by the positional relationship between polyadenylation signals and CPE sequences [21]. We found three polyadenylation signals and five CPE sequences in the 3'-UTR of long-form *Cyclin B1* mRNA, and two polyadenylation signals and two CPE sequences in that of the short-form [Yamamuro, unpublished data]. Their positional relationship indicates that the long-form and short-form mRNAs are an early-type and a late-type, respectively, and we postulated that they are expressed at the first meiosis and the second meiosis, respectively. Our preliminary experiments support this expectation [Yamamuro, unpublished data].

Regulation of Cyclin B Degradation

Cyclin B is degraded by 26S proteasome after ubiquitination by anaphase-promoting complex (APC) [22]. The activation of APC is performed by binding with either CDC20 (Slp1/p55CDC/Fizzy) or FZR1 (Ste9/CDH1/Fizzy-related), both of which are known to be APC activators. In mitosis, CDC20 accumulates during the S- and G2-phases but does not activate APC until the M-phase, because the phosphorylation of APC subunits by the MPF is required for the binding of CDC20 to APC [23]. On the other hand, FZR1 is phosphorylated and inhibited by MPF during most of the M-phase, and activated after dephosphorylation at the end of the M-phase [24]. Thus, CDC20 works to activate APC mainly during the M-phase and FZR1 takes over from the end of the M-phase to the start of the G1-phase [25].

The requirement of APC activity for the transition from the meiotic metaphase to the anaphase has been reported in many species including yeast and nematodes [26, 27]. In mammalian oocytes, APC-CDC20 has been reported to be required for the meiotic metaphase/anaphase transition in mice and pigs [28,

Table 1. Key to abbreviations

Abbreviation	Full name	Function
APC	anaphase-promoting complex	A ubiquitin ligase, which ligates polyubiquitin chain to substrate proteins for their proteolysis
CAK	Cdk (cyclin dependent kinase) activation kinase	Phosphorylation of stimulatory sites in Cdc2 (T161)
CDC20	cell division cycle 20	An APC activating factor
Cdc25	cell division cycle 25	Dephosphorylation of inhibitory sites in Cdc2 (T14 and Y15)
CPE	cytoplasmic polyadenylation element	3'-UTR uridine-rich element, which regulates polyadenylation of mRNA
CPEB	CPE binding protein	A protein, which binds CPE and regulates mRNA polyadenylation
FZR1	fizzy-related 1 (CDH1)	An APC activating factor
MASTL	microtubule associated serine/threonine kinase-like	Inhibition of protein phosphatase type 2A
MAT1	menage à trois 1	An assembly factor of CAK
MPF	maturation/M-phase promoting factor	A principal factor for the regulation of M-phase
Myt1	membrane associated tyrosine/theronine 1	Phosphorylation of inhibitory sites in Cdc2 (T14 and Y15)
PKA	protein kinase A	Cyclic-AMP dependent protein kinase
Plk1	Polo like kinase 1	Phosphorylation and activation of Cdc25
Wee1B	(Gene name)	Phosphorylation of inhibitory site(s) in Cdc2 (T14? and Y15)

29]. We have cloned CDC20 and FZR1 (CDH1) from porcine oocytes and inhibited their expression by the injection of their antisense RNAs during porcine oocyte maturation. We found that the inhibition of CDC20 increased Cyclin B accumulation and MPF activity in MI, resulting in MI arrest, whereas FZR1 inhibited oocytes matured normally [29]. Therefore, only CDC20 works for the Cyclin B degradation at the exit from MI, and FZR1 has no function at this time.

In contrast, the inhibition of FZR1 expression increased Cyclin B accumulation during the GV stage and accelerated MPF activation and GVBD in porcine oocytes, whereas the overexpression of FZR1 inhibited GVBD [29]. These results suggest that the APC-FZR1-mediated Cyclin B degradation retards meiotic resumption in porcine oocytes, and a similar effect of FZR1 has been reported in mouse oocytes [30, 31]. As APC-FZR1 also degrades CDC20 in immature oocytes [32], CDC20 is almost absent in immature oocytes [29, 33]. Therefore, only FZR1 has a retardation effect on meiotic resumption, and the overexpression of CDC20 in immature oocytes conversely accelerates GVBD by competitive inhibition of Cyclin B-degradation by APC-FZR1 [29].

In contrast with mammalian oocytes, it has been reported that APC activity in Xenopus oocytes is not always required for the exit from MI, although it is necessary for the exit from MII [34, 35]. Moreover, FZR1 accelerates GVBD in Xenopus oocytes [36]. Thus, special attention should be paid to the large differences between Xenopus and mammalian oocytes in APC requirement and FZR1 functions.

Regulation of T161 Phosphorylation in Cdc2

Identification of $p40^{MO15}$, a subunit of Cdk activation kinase (CAK) that phosphorylates T161 and activates Cdc2, was first reported in Xenopus oocytes [37, 38] and starfish oocytes [39] in 1993; human MO15 was cloned in the following year [40]. MO15 belongs to the cyclin dependent kinase (Cdk) family as Cdk7, and the partner subunit belonging to the cyclin family, Cyclin H, has been identified [41, 42]. Although a part of Cdk7/Cyclin H in Xenopus and starfish oocytes associated with MAT1 (an assembly factor) [43], it has been suggested that Cdk7/Cyclin H dimmer works as CAK, and Cdk7/Cyclin H/MAT1 trimmer works as a transcription factor, TFIIH, rather than CAK [44, 45]. In budding yeast, another monomeric CAK, Cak1 (Civ1), has been identified [46–48], and the presence of a similar factor has also been suggested in humans [49], although its *in vivo* function is unclear.

There are two phosphorylation sites, serine 170 and threonine 176, in Cdk7, and the phosphorylation of these sites increases the affinity for Cyclin H and CAK activity [50, 51]. As Cdk7 activity does not fluctuate during the cell cycle, it has long been believed that Cdk7 is phosphorylated and has sufficiently high activity throughout the cell cycle, and that MPF activity is not regulated by CAK [42, 52]. Recently, we have cloned Cdk7, Cyclin H and MAT1 from porcine oocytes, and found that the inhibition of Cdk7 expression caused the delay of GVBD and arrest at the prometaphase. Surprisingly, the overexpression of Cdk7 in immature porcine oocytes dramatically accelerated meiotic

resumption and the time course of maturation [Fujii, unpublished data]. This result indicates that the Cdk7 activity in porcine immature oocytes is low and insufficient for the full activation of MPF.

Regulation of T14/Y15 Dephosphorylation in Cdc2

Dephosphorylation of T14/Y15 in Cdc2 is catalyzed by Cdc25 phosphatase, and three isoforms, Cdc25 A, B and C, have been identified in humans [53, 54]. In somatic cells, Cdc25A initiates Cdk2 activation at the G1/S transition [55]. For the G2/M transition, Cdc25B initiates partial activation of Cdc2, then Cdc25C completes full activation of Cdc2 [56]. In contrast to somatic cells, only Cdc25B is functional for Cdc2 activation during oocyte maturation and Cdc25C has no function [57]. Cdc25C-deficient mice are fertile [58], whereas Cdc25B-deficient mice are sterile and their oocytes arrest at the GV stage [59]. The injection of CDC25C mRNA or antisense RNA into porcine immature oocytes had no effect on meiotic resumption of porcine oocytes [60]. Recently, it has been suggested that Cdc25A initiates meiotic resumption, MI spindle formation and the MI/MII transition in oocytes [61].

Intracellular localization of Cdc25 is largely involved in the functional activity of Cdc25. Cdc25B has a nuclear localization signal in its C-terminal amino acid 335–354, and its N-terminal amino acid 28–40 is necessary for the cytoplasmic localization [62–64]. During the GV stage, Cdc25 phosphorylation at serine 321 in mammals (serine 287 in Xenopus) by cAMP dependent protein kinase (PKA) induces it to bind to 14-3-3 protein and its localization in the cytoplasm, thereby maintaining G2 arrest [65, 66]. The inactivation of PKA on meiotic resumption leads to S321/S287 dephosphorylation and dissociation from 14-3-3, resulting in translocation into the nucleus and meiotic resumption [65, 66]. However, Cdc25 localization in the nucleus during the GV stage has been reported in bovine oocytes [67].

Cdc25B has a regulatory region in its N-terminal and a catalytic region in its C-terminal. The activation of Cdc25B is induced by hyperphosphorylation of the N-terminal [68], which is catalyzed by Polo-like kinase (Plx1 in Xenopus, PLK in human) [69–71]. Plx1 is activated not only by xPlkk1 [72] but also by MPF itself, resulting in the formation of a positive feedback loop for the MPF activation [69, 70]. In addition, ERK has also been reported to activate Cdc25C by phosphorylation at threonine 48, threonine 138 and serine 205 [73].

Recently, Greatwall (MASTL in mammals) has been reported to be a Cdc25 activating factor in Xenopus oocytes [74, 75]. The immunodepletion of Greatwall from a Xenopus oocyte extract resulted in the accumulation of inhibitory phosphorylation of Cdc2 which prevented the progression to the M-phase [74, 75]. Furthermore, it has been suggested that Greatwall inhibits protein phosphatase 2A activity and exerts an effect resembling okadaic acid [76, 77]. Recently, we partially cloned Geatwall from porcine and mouse oocytes and observed its involvement in GVBD in mouse oocytes [Suzuki *et al.*, unpublished data].

Regulation of T14/Y15 Phosphorylation in Cdc2

In mammalian somatic cells, it has been reported that Wee1 phosphorylated only Y15 [78, 79], and that phosphorylation of T14 is dependent on Myt1 [80, 81]. On the other hand, the presence of Wee1B instead of Wee1 has recently been shown in mouse oocytes, and the involvement of Wee1B for the maintenance of meiotic arrest has been suggested [82]. Although the presence of Wee1B has also been reported in humans, the testis is the major tissue showing high Wee1B expression and its effect on meiotic arrest has never been studied [83]. Recently, we have cloned porcine Wee1B, and found that the knockdown of pig Wee1B, by injection of antisense RNA, induced meiotic resumption in porcine oocytes, in which spontaneous GVBD was inhibited by 3mM cAMP [84]. This fact indicates the importance of Wee1B in the meiotic arrest of porcine oocytes. The overexpression of porcine Wee1B induced by the mRNA injection inhibited GVBD of porcine immature oocytes only under the presence of a low concentration of cAMP, suggesting that porcine Wee1B is activated by cAMP [84]. Mouse Wee1B has been reported to be activated by PKA-dependent phosphorylation at serine 15 (S15) [82], however S15 is replaced by asparagine in porcine Wee1B [84]. In order to find the PKA-dependent activation site of porcine Wee1B, we constructed mutant Wee1Bs, in which individual PKA-phosphorylable serines (S17, S77, S118, S133, and S149) were replaced by non-phosphorylable alanine, and examined their activation states after cAMP treatment. Our preliminary experiments indicate that serine 77 might be the activation site of porcine Wee1B [Shimaoka, unpublished data].

In Xenopus, Myt1 works on meiotic arrest of ooytes by phosphorylating both T14 and Y15 [85], and meiotic resumption is induced by Mos- or Rsk-dependent Myt1 phosphorylation [86, 87]. As the presence of Myt1 in

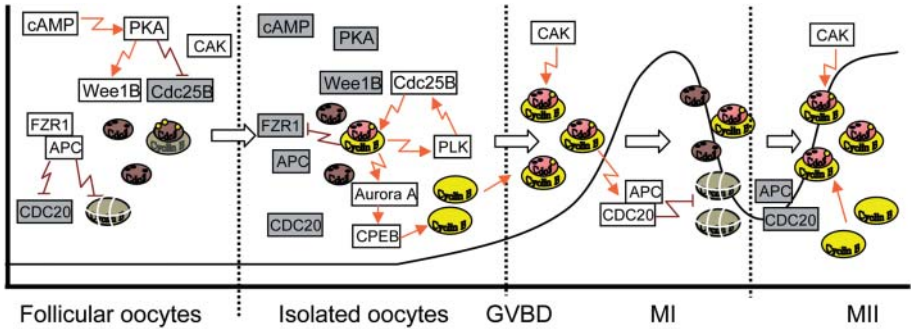

Fig. 2. Schematic diagram of the MPF regulation during porcine oocyte maturation.

addition to Wee1B has been demonstrated in mouse oocytes [82], we also cloned porcine Myt1 and examined its involvement in meiotic arrest by inhibiting its expression by the antisense RNA injection into spontaneous GVBD-inhibited porcine immature oocytes. Unlike Wee1B, Myt1 inhibition did not induce GVBD in porcine oocytes [84], indicating that Wee1B is the main factor involved in the meiotic arrest of mammalian immature oocytes, and Myt1 has no important function in this process. In addition, the inhibition of Cdc25 by vanadate completely prevented the Wee1B inhibition-induced GVBD in porcine oocytes [84]. Therefore, Cdc25 activation in addition to Wee1B inhibition is essential for the meiotic resumption of porcine oocytes.

Conclusion

We have reviewed the upstream factors regulating MPF activity in the present article. We propose a hypothesis for MPF regulation during meiotic maturation in porcine oocytes based on the findings reviewed above (Fig. 2). Within the porcine follicular oocytes, a high cAMP level activates Wee1B and inhibits Cdc25 by PKA-mediated phosphorylation of serine 77 and serine 321, respectively. Under these conditions, although a small amount of Cyclin B is present and binds with Cdc2 in porcine immature oocytes, MPF is inactivated by the phosphorylation of Cdc2 inhibitory sites (T14/Y15). During this period, Myt1 plays no important role in the meiotic arrest of oocytes. APC-FZR1 is active in the immature oocytes and the accumulation of Cyclin B and CDC20 originating from basal protein synthesis is inhibited. After stimulation by hormones or isolation from follicles, the decrease of the cAMP level in oocytes triggers Wee1B inactivation and Cdc25 activation, followed by the conversion of pre-MPF to active MPF by the dephosphorylation of Cdc2 inhibitory sites. The MPF activity during this period might be insufficient for the induction of GVBD because of the low Cyclin B concentration, but it is sufficient for the phosphorylation of Aurora A and the activation of Cyclin B synthesis by a cytoplasmic polyadenylation mechanism, resulting in the increase of Cdc2/Cyclin B complexes. At this point, Cdk7/Cyclin H works as CAK and activates MPF by the phosphorylation of T161 in Cdc2. The high MPF activity inactivates FZR1 by phosphorylation, and Cyclin B accumulation is further accelerated, further elevating MPF activity. These changes induce the meiotic resumption of porcine immature oocytes and their progression to MI. The inactivation of APC-FZR1 also induces CDC20 accumulation, and the high MPF activity phosphorylates CDC20 to form a complex with APC. The active APC-CDC20 degrades Cyclin B and inactivates MPF, and the oocytes progress from MI to the first meiotic anaphase. The decrease of MPF activity induces the attenuated APC-CDC20 activity followed by reaccumulation of Cyclin B1 from the short-form mRNA. Then, MPF is reactivated by CAK-mediated phosphorylation, resulting in the MII transition.

Research into the kinetics of cAMP concentration and PKA activity, the detailed Cdc2 activation by CAK, and the function of Greatwall (MASTL), which has recently received a lot of attention, in meiotic maturation, should provide interesting topics for furthering knowledge in this field.

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