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Phospho-Signaling at Oocyte Maturation and Fertilization: Set Up for Embryogenesis and Beyond Part II. Kinase Regulators and Substrates

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1. Introduction

This chapter is the sequel to the chapter entitled "Phospho-signaling at Oocyte Maturation and Fertilization: Set Up for Embryogenesis and Beyond Part I. Protein Kinases" by Mahbub Hasan et al.

2. Kinase regulators and substrates in oocyte maturation, fertilization and activation of development

2.1 Actin

Filamentous actin or **F-actin** is a major component of stress fibers and involved in cellular architecture. Its dynamic rearrangement supports not only cellular morphology but also intracellular signal transduction that regulate cell-cell or cell-extracellular matrix interactions, cell motility, and proliferation. Several lines of evidence demonstrate that, in several organisms, oocyte cortical cytoskeleton involving F-actin network undergoes a dynamic rearrangement during meiosis/oocyte maturation and that this is often involving phosphorylation of actin and/or actin-interacting proteins (e.g. ADF/coffilin, see below) catalyzed by PKC (in Tubifex, *Xenopus*) (Capco et al. 1992; Shimizu 1997). In *Drosophila*, PKC phosphorylation of a tumor suppressor protein-homolog named Lgl (lethal (2) giant larvae) is responsible for actin-dependent oocyte polarity formation (Tian and Deng 2008). In mammalian oocytes (rat), F-actin has been implicated in tyrosine kinase-dependent

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rearrangement of cortical structures (Meng et al. 2006). In unfertilized rat eggs, F-action is in association with PKC and RACKS and thought to suppress the cortical granule to exocytose, and after fertilization, PKC-dependent phosphorylation releases the actin suppression and cortical granule exocytosis occurs (Eliyahu et al. 2005).

2.2 ADF/coffilin

Actin-depolymerizing factor (**ADF**)/**coffilin** are an evolutionarily conserved F-actin-binding protein, whose function is essential for cortical actin cytoskeleton. It is well known that the actin-binding ability of ADF/coffilin can be regulated by its phosphorylation and dephosphorylation (Bamburg et al. 1999). This type of regulation of ADF/coffilin has been reported in maturing oocytes of starfish, where active transport of MPF from nucleus to cytoplasm is required for oocyte maturation (Santella et al. 2003), and dividing embryos of *Xenopus*, where cytokinesis involves the function of ADF/coffilin (Abe et al. 1996; Chiu et al. 2010; Tanaka et al. 2005). In the former case, MPF has been identified as a kinase for ADF/coffilin. In the latter case, protein phosphatase Slingshot is involved in Rho-dependent inactivation of ADF/coffilin, thereby promotes the rearrangement of actin cytoskeleton essential for cytokinesis.

2.3 ASIP/PAR-3

ASIP/PAR-3 (atypical PKC isotype-specific interacting protein/partitioning defective 3) is a PDZ-domain-containing adaptor protein that has been initially identified as a downstream element of PAR-6 in early embryos of the nematode *C. elegans* (Watts et al. 1996). Further studies have demonstrate the importance of PAR3 as an atypical PKC (aPKC)-interacting protein functioning in establishing asymmetric cell division and polarized cell structures in *C. elegans* and *Drosophila* embryos, and mammalian epithelial cells (Joberty et al. 2000). In *Xenopus* immature oocytes, ASIP/PAR-3 is shown to localize to animal hemisphere in association with aPKC, and upon hormone-induced oocyte maturation, aPKC undergoes kinase activity-dependent re-localization. These results suggest a potential role of ASIP/PAR-3 as a regulator and/or substrate of aPKC (Nakaya et al. 2000). Although phosphorylation of Ser-827 in ASIP/PAR-3 by aPKC has been shown in mammalian somatic cell systems (Hirose et al. 2002), its occurrence in oocyte/egg system is not yet demonstrated.

2.4 Astrin

Astrin is a spindle-associated non-motor protein that regulates mitotic cell cycle progression. In the meiosis of mouse oocytes, where centrioles are missing but multiple microtubule-organizing centers (MTOCs) are present, proper lining and segregation of homologous chromosomes and sister chromatids require the precise regulation of MTOCs by centrosomal protein kinases such as Aurora kinase and PLK1. It has been shown that inhibition of Astrin function by RNAi-mediated knockdown or overexpression of a coiled-coil domain of Astrin results in a defect in spindle disorganization, chromosome misalignment and meiosis progression arrest (Yuan et al. 2009). As Astrin localizes to the spindle apparatus, it is suggested that Astrin is a substrate of Aurora/PLK1. In support with this idea, site-directed mutation of Thr-24, Ser-66 or Ser-447, potential PLK1 phosphorylation sites in Astrin, causes oocyte meiotic arrest at metaphase I with highly disordered spindles and disorganized chromosomes (Yuan et al. 2009).

2.5 Bad

Bad is a member of BH3 (Bcl-2 homology 3) family proteins, the other members of which include Bax, Bak, Bik, Bid and Hrk. While Bcl-2, a firstly identified BH3 and other BH domain (BH1 and BH2)-containing protein, and its relative proteins (e.g. Bcl-xL) act as anti-apoptosis components, Bad and other BH3-only proteins participate in pro-apoptotic cellular functions (e.g. activation of caspases) (Danial 2008; Lutz 2000). Most of these anti-apoptotic or pro-apoptotic proteins localize to mitochondrial outer membranes and function as a sensor of intracellular damage as well as a trigger of mitochondrial death/survival pathway. Several species ranging from nematode, *Drosophila* and sea invertebrates to vertebrates including mammals undergo germline or ovarian/postovulatory oocyte apoptosis in an age-dependent or -independent manner (Buszczak and Cooley 2000; Chiba 2004; Morita and Tilly 1999). In particular, Bad has recently been identified as a factor for phospho-dependent mechanism of egg apoptosis in *Xenopus* (Du Pasquier et al. 2011). Bad in ovarian oocytes at the first meiotic propahse is negatively regulated by inhibitory phosphorylation on Ser-112 and Ser-136 by unknown mechanism (maybe PKA phosphorylation). Upon oocyte maturation, Bad becomes further phosphorylated on Ser-128 in a CDK- and JNK-dependent manner. The Ser-128 phosphorylation, if it exceeds the extent of those of Ser-112/Ser-136 phosphorylations during a long period of oocyte maturation in the absence of fertilizing sperm, will allow Bad to trigger a mitochondrial apoptotic pathway involving cytochrome c release and caspase activation. Whether normal process of oocyte maturation and fertilization involves anti-apoptotic mechanism is not known.

2.6 Brain-derived neurotrophic factor (BDNF)

BDNF is a member of neurotropic family of growth factors that include nerve growth factor (NGF). Its cellular functions are exerted by cell surface receptors such as TrkB, a tyrosine kinase/receptor, and p75 low-affinity NGF receptor (Chao and Hempstead 1995). In mammals including human, ovarian BDNF has been implicated in oogenesis, oocyte maturation, and pre-implantation embryogenesis (Kawamura et al. 2005; Zhang et al. 2010). In vitro maturation of mouse oocytes in the presence of cumulus cells is accompanied by BDNF-dependent activation of Akt/PKB and MAPK and its maintenance has been demonstrated (Zhang et al. 2010). Pharmacological experiments suggest that the Akt/PKB activation involves TrkB function (TrkB-PI3K-PIP_3 pathway), while the MAPK does not.

2.7 Bub1/BubR1

Bub1 and **BubR1** (Mad3 in yeast, worms and plants) are multidomain-containing protein-serine/threonine kinases that have been characterized as components of the mitotic checkpoint of spindle assembly (Bolanos-Garcia and Blundell 2011). In mouse oocytes, BubR1 is shown to act as a spindle assembly checkpoint protein in the first meiotic arrest (Homer et al. 2009; Jones and Holt 2010; Schwab et al. 2001; Wei et al. 2010). In maturing *Xenopus* oocytes, Bub1 is activated by MAPK-dependent $p90^{Rsk}$ phosphorylation, and is suggested to be involved in spindle assembly checkpoint and, in collaboration with cdk2/cyclin E complex, cytostatic arrest of the meiosis II (Schwab et al. 2001; Tunquist et al. 2002). Precise mechanism of the cytostatic arrest, i.e. inhibition of anaphase-promoting complex, is not known, because a substrate of Bub1 has not yet been identified. In mammals, first meiotic anaphase also seems to be regulated by Bub1-dependent mechanism (McGuinness et al. 2009).

2.8 Calcineurin

Calcineurin is a protein serine/threonine-specific phosphatase that can be up-regulated by the binding of Ca^{2+}/calmodulin (Pallen and Wang 1985), another target of which is CaMKII. In *Xenopus* eggs and cell-free egg extracts, Ca^{2+}-dependent exit of meiosis II involves transient activation of calcineurin. When the activation of calcineurin is blocked, inactivation of MPF by means of cyclin degradation does not occur and sperm nuclei remains condensed. In addition, cortical contraction of the pigmented granules in the animal hemisphere is also blocked. On the other hand, if the activity of calcineurin is artificially kept up-regulated for a prolonged period, growth of sperm aster is inhibited and fusion of the female and male pronuclei is also inhibited. It has been shown that calcineurin dephosphorylates Cdc20, a key regulator of the anaphase-promoting factor that is a substrate of MAPK (Mochida and Hunt 2007; Nishiyama et al. 2007). These results highlight a requirement of calcineurin for Ca^{2+}-dependent inactivation of cytostatic factor and for the onset of the mitotic cell cycle in the early embryos.

2.9 Caspase 2

Caspase 2 is a member of caspase family, which regulates and/or triggers the apoptotic cell death in response to a wide variety of extracellular and intracellular signals. It has been shown that in caspase 2-deficient mice, excess number of ovarian oocytes is a major cause, suggesting that caspase 2 is involved in ovarian oocyte apoptosis. Oocytes deficient in caspase 2 expression also exhibit a marked resistance to cell death induced by chemicals (Bergeron et al. 1998; Morita and Tilly 1999). Further insight into the roles of caspase 2 in the control of oocyte survival has been demonstrated by the studies with use of cell-free extracts prepared form *Xenopus* eggs. In this system, glucose-6-phosphate has been identified as an important component to drive continual operation of the pentose phosphate pathway that prolongs cell survival. In addition, NADPH generation by this pathway is critical for promoting CaMKII-dependent inhibitory phosphorylation of caspase 2 (Nutt et al. 2005). As CaMKII is known as a crucial component that inactivates CSF activity in frog and mammals, it is intriguing whether the CaMKII-caspase 2 axis also functions at fertilization.

2.10 Cdc20/Fizzy

Cdc20 is an activator of anaphase-promoting complex (APC) that directs the onset and progression of the meiotic and mitotic cell cycle (Chung and Chen 2003; Rudner and Murray 2000; Shteinberg et al. 1999; Tang et al. 2004; Weinstein 1997). In *Drosophila*, Cdc20-related gene Fizzy serves a similar function (Dawson et al. 1993; Pesin and Orr-Weaver 2008). The activity of Cdc20 is negatively regulated by phosphorylation on its serine and threonine residues: in case of *Xenopus* Cdc20, Ser-50, Thr-64, Thr-68 and Thr-79. In *Xenopus* maturing oocytes, phosphorylation of Cdc20 is catalyzed by MAPK, a component of cytostatic factor, and/or Bub1/BubR1 kinases, key regulators of spindle checkpoint, and it is involved in the maintenance of cytostatic factor activity that involves the inactivation of APC. Analyses using cell-free extracts prepared from unfertilized *Xenopus* eggs demonstrate that the phosphorylated form of Cdc20 is a target of calcineurin, whose phosphatase activity is transiently activated in response to Ca^{2+} signals (Mochida and Hunt 2007).

2.11 Cdc25 phosphatase (Cdc25A/B/C)

Cdc25 is a protein-tyrosine phosphatase that has been originally identified and characterized as a yeast cell cycle regulator (Fleig and Gould 1991). A major target of this phosphatase is the Cdc2 protein-serine/threonine kinase, its cyclin-associated form of which functions as MPF. Before oocyte maturation in vertebrates, the activity of Cdc2 protein is down-regulated by the absence of cyclin and by phosphorylation by Myt1/Wee1 dual-specificity kinases on Thr-14 and Tyr-15 residues. During oocyte maturation, however, both accumulation of newly synthesized cyclin as well as removal of the phosphates from Cdc2 ensures the Cdc2 activation (Karaiskou et al. 1998; Kim et al. 1999b; Oh et al. 2010; Perdiguero and Nebreda 2004; Perdiguero et al. 2003; Pirino et al. 2009; Qian et al. 2001; Rime et al. 1994; Zhang et al. 2008; Zhao et al. 2008). There are several types of Cdc25: e.g. Cdc25A, Cdc25B, and Cdc25C. PKA phosphorylation and activation of Cdc25B has been reported in mammals (Pirino et al. 2009). In *Xenopus*, Cdc25C is up-regulated by Plx1-mediated phosphorylation on Ser-287 (Qian et al. 2001). Other reports have shown that Xp38γ/SAPK (Perdiguero et al. 2003) and Greatwall kinase (Zhao et al. 2008) can be responsible for the stimulatory phosphorylation of Cdc25C. Cdc25A has been implicated in embryonic cell cycle regulation (Kim et al. 1999b).

2.12 Cdh1/Cort/Fzy

Cdh1 is an activator of anaphase promoting complex/cyclosome (APC/C), an E3 ubiquitin ligase that regulates the onset of anaphase during meiotic and mitotic cell cycle (Visintin et al. 1997). Several cell cycle regulators are subjected to Cdh1- and proteasome-dependent degradation, by which APC/C-dependent cell cycle progression through anaphase is triggered. In *Xenopus* egg cell-free extracts, Cdh1-dependent degradation of Aurora A kinase plays an important role in mitotic exit (Littlepage and Ruderman 2002). The Aurora A-Cdh1 interaction requires the phosphorylation of Aurora A on Ser-53 residue, which is a substrate of M-phase-activated kinase(s). On the other hand, APC-independent cellular function involving Cdh1 has also been suggested in *Xenopus* oocyte maturation (Papin et al. 2004). In immature mouse oocytes, where the meiotic cell cycle is paused at the prophase I, Emi1-dependent mechanism of cdh1 inhibition (thereby inhibition of APC/C) functions for the MI arrest (Marangos et al. 2007). In *Drosophila* and *C. elegans*, Cdc20/Cdh1-related protein, Cort and Fzy, respectively, controls the meiotic cell cycle progression in a Cdh1-like manner (Kitagawa et al. 2002; Marangos et al. 2007; Swan and Schupbach 2007).

2.13 Cohesin/SCC1/Rec-8

Cohesin is a chromosome-binding protein that is involved in meiotic and mitotic assembly and segregation of sister chromatids (Heck 1997). In many vertebrate species, cell cycle progression through anaphase involves a proteolytic cleavage of cohesin, as catalyzed by separase and subsequent release of cohesin from the sister chromatids, so that the chromosomal segregation occurs. In *Xenopus*, however, proteolysis-independent release of cohesin from sister chromatids is working and it involves polo-like kinase phosphorylation of cohesin (Sumara et al. 2002). A similar phospho-dependent release of chromosome cohesion has been demonstrated in *C. elegans*, where the AIR-2 kinase (Aurora B kinase in this species) phosphorylation of the nematode cohesion Rec-8 (Rogers et al. 2002).

2.14 Crk adaptor protein (Crk/CRKL)

Crk is an SH2/SH3-containing adaptor protein that has been originally identified as an oncogene product (viral Crk or v-Crk) of avian sarcoma virus CT10 (Feller et al. 1994; Mayer et al. 1988; Mayer and Hanafusa 1990). Its SH2 domain-dependent phosphotyrosine-binding property and SH3 domain-dependent binding to proline-rich sequences in other molecules are required for malignant cell transformation. Three cellular homologues of v-Crk have been found in mammals: c-Crk I, c-Crk II, and c-Crk-like (CRKL). These cellular Crk family proteins have been identified as a major substrate of Bcr-Abl tyrosine kinase that causes chronic myeloid leukemia (CML) (Feller et al. 1998). Another aspect of Crk function has been demonstrated in the studies of *Xenopus* egg cell-free extract: apoptosis in aged egg extracts is shown to involve interaction between the SH2 domain of Crk and the tyrosine-phosphorylated form of Wee1 dual-specificity kinase (Evans et al. 1997; Smith et al. 2000). Further study has demonstrated that the SH3 domain of Crk is important for interacting with the nuclear export factor Crm1, an antagonistic factor for apoptosis in cell-free extract, and that mutually exclusive interaction between Crk and Crm1 or Wee1 in the nucleus regulates the onset of apoptosis.

2.15 Cyclin B

Cyclin is a family of CDK activator proteins, whose first example has been discovered in fertilized sea urchin eggs (Evans et al. 1983) and starfish maturing oocytes (Evans et al. 1983; Standart et al. 1987). Cyclin family consists of several proteins: cyclin A, B, D, E and others, and cyclin B are a component of MPF, another subunit of which is Cdc2/CDK1 serine/threonine-specific protein kinase (Hunt 1989; Maller 1990). In many species, hormone-induced MPF activity in maturing oocytes is generally dependent on *de novo* synthesis and accumulation of cyclin B (and subsequent phospho-dependent regulation of Cdc2/CDK1 by the actions of Wee1/Myt1 kinases and Cdc25 phosphatase is also important) (Gaffre et al. 2011). Fertilization triggers an ubiquitin/proteasome-dependent degradation of cyclin B that causes a rapid decrease of MPF activity (Edgecombe et al. 1991; Huo et al. 2004b; Lapasset et al. 2005; Lapasset et al. 2008; Meijer et al. 1989a; Meijer et al. 1991; Meijer et al. 1989b; Sakamoto et al. 1998). Other cyclins (e.g. cyclin A, D) serve a similar CDK-activating property, but have distinct physiological functions (e.g. G_1/S transition, spindle checkpoint) by interacting with a specific CDK member(s) (e.g. CDK2, CDK5).

2.16 *sn*-1,2-diacylglycerol (DG)

DG is one of two hydrolyzed products by phospholipase C of phosphatidylinositol 4,5-bisphosphate, another product of which is inositol 1,4,5-trisphosphate (IP_3). DG serve as a second messenger in a variety of extracellular signals such as hormones and neurotransmitters, and is well characterized as a direct activator for PKC, a family of serine/threonine kinase (Nishizuka 1984; Nishizuka 1986). DG also acts as a substrate of DG kinase that produces phosphatidic acid or PA, which has pleiotropic cellular functions. In *Xenopus* eggs, fertilization promotes a rapid increase in intracellular DG concentration, a large part of which seems to be due to phospholipase D (PLD)-mediated cleavage of phosphatidylcholine (PC) (but not PIP_2). In support of this, choline, another product of PC hydrolysis by PLD, is also accumulating in a similar time course of fertilization. Whether DG is involved in the activation of egg PKC remains to be clarified (Stith et al. 1997). Production of DG has also been examined in mouse eggs (Stith et al. 1997; Yu et al. 2008). In this species, sperm-derived PLCζ seems to be mainly responsible for DG production and subsequent PKC activation.

2.17 Initiation factor 4E-binding protein (4E-BP)

4E-BP is a binding protein for eukaryotic initiation factor 4E (eIF4E), an mRNA cap-binding protein that facilitates the initiation of protein synthesis in association with eIF4F. The interaction between 4E-BP and eIF4E depends on the phosphorylation state of 4E-BP: hypo-phosphorylated form of 4E-BP has an ability to bind to and inhibit eIF4E, whereas the phosphorylated form of 4E-BP releases eIF4E so that eIF4E-eIF4F complex is formed and promotes active translation of mRNA (Lasko 2003). In sea urchin eggs, fertilization is accompanied by a rapid burst of protein synthesis. It has been shown that fertilization also promotes a rapid decrease in 4E-BP as well as an increase in phosphorylated form of 4E-BP (Cormier et al. 2001). Two-dimensional electrophoresis demonstrated that 4E-BP is phosphorylated on multiple sites after fertilization. In mitotic sea urchin embryos, further decrease in 4E-BP expression has been demonstrated and it is mediated by a rapamycin-sensitive mechanism of proteolysis of 4E-BP (Salaun et al. 2003), suggesting that mTOR (mammalian target of rapamycin)-like kinase is involved in the phosphorylation of 4E-BP. A rapamycin-sensitive mechanism of global protein synthesis involving 4E-BP regulation (but not translation of some proteins such as cyclin B and Mos, whose translational control involves the phosphorylation of CPEB phosphorylation) has also been demonstrated in maturing oocytes of starfish (Lapasset et al. 2008).

2.18 EGG-3/4/5

C. elegans **EGG-3** is a member of protein-tyrosine phosphatase-like (PTPL) family, whose mutant egg undergoes fertilization normally but has a defect in polarized dispersal of F-actin, formation of chitin eggshell, and production of polar bodies (Maruyama et al. 2007). Although enzymatic substrate for EGG-3 has not yet been demonstrated (PTPL proteins are supposed to be pseudo-phosphatase), its functional interaction with CHS-1, which is required for deposition of egg shell, plays a role for proper distribution of MBK-2 kinase that regulates degradation of maternal proteins and egg-to-embryo transition (Nishi and Lin 2005; Qu et al. 2006; Qu et al. 2007; Stitzel et al. 2007; Stitzel et al. 2006). Other members of PTPL family such as EGG-4 and EGG-5 have also been characterized as components of meiotic cell cycle progression and egg-to-embryo transition. These two EGG proteins have no phosphatase activity, however, interact with YTY motif of MBK-2 kinase, which is autophosphorylated in the active kinase, and inhibit the kinase activity (Cheng et al. 2009; Parry et al. 2009).

2.19 Emi1 and Emi2/xErp1

In vertebrate unfertilized eggs, cytostatic factor (CSF) is responsible for maintaining the meiotic cell cycle at MII (metaphase of second meiosis) (Masui 2000; Tunquist and Maller 2003). As a candidate of molecule involved in CSF activity, several kinase proteins have been suggested and evaluated (e.g. Mos, MAPK, Rsk). On the other hand, APC/C (anaphase promoting complex/cyclosome) has been identified an initiator of meiotic resumption (thus, as a disruptor of CSF-mediated arrest or a main target of CSF activity). **Emi1** has been identified first as a negative regulator of APC/C in *Xenopus* eggs and cell-free extracts (Reimann et al. 2001a; Reimann et al. 2001b; Reimann and Jackson 2002). Thereafter, an Emi1-related protein named **Emi2/xErp1** has been identified and characterized as an essential component of CSF inhibition of APC/C (Hansen et al. 2006; Liu and Maller 2005; Rauh et al. 2005; Tang et al. 2008; Tung et al. 2005; Wu et al. 2007a; Wu et al. 2007b). In the current scenario, CSF arrest by Emi2/xErp1 of APC/C involves recruitment of PP2A to the Rsk-phosphorylated Emi2/xErp1 (this phosphorylation has stabilizing effect on Emi2/xErp1) and its phosphatase action on other phosphates in Emi2/xErp1 catalyzed by Cdc2/cyclin B complex (this phosphorylation weakens Emi2/xErp1). After fertilization, CaMKII and Plx1 phosphorylation promotes ubiquitin-dependent proteolysis of Emi2/xErp1, thereby APC/C is released from the inhibitory interaction with Emi2/xErp1 (Wu and Kornbluth 2008).

2.20 FKHRL1/FOXO3a

FKHRL (forkhead in rhabdomyosarcoma) is a transcription factor, whose activation has been implicated in the onset of apoptosis and Akt phosphorylation (on Thr-24, Ser-256, and Ser-319) leads to suppression of its function (Brunet et al. 1999; Tang et al. 1999). Its genetic loss or ablation can be a trigger of carcinogenesis, thus FKHRL is a tumor suppressor (Gallego Melcon and Sanchez de Toledo Codina 2007). Akt-dependent phosphorylation of FKHRL1 has been demonstrated in follicular oocytes that receive stem cell factor (SCF) for mammalian oocyte development (Reddy et al. 2005). SCF is a ligand for c-Kit receptor/tyrosine kinase that, upon its ligand-induced activation, promotes sequential activation of PI3K, PDK, and Akt. Thus, follicular development of oocytes involves the suppression of pro-apoptotic signal transduction by FKHRL1. In support of this, FKHRL1 gene-deficient mice exhibited excessive activation from primordial to primary follicles as well as enlarged oocyte sizes (Reddy et al. 2005). A similar pathway involving FOXO3a, a rat homologue of FKHRL transcription factor, has been shown in rat oocytes (Liu et al. 2009).

2.21 XGef

XGef is a *Xenopus* homologue of mammalian guanine nucleotide exchanging factor, RhoGEF that activates Rho-family small GTP-binding protein such as Cdc42. XGef has been initially identified as a CPEB-binding protein and in fact, it has been shown that XGef is involved in polyadenylation and translation of Mos mRNA during oocyte maturation (Reverte et al. 2003). GEF activity of XGef is required for Mos synthesis. In addition, interaction between XGef is responsible for an increase in CPEB phosphorylation during oocyte maturation, which is important for CPEB activation (Martinez et al. 2005). Further studies have shown that MAPK interacts with XGef and acts as a kinase of CPEB on Thr-22, Thr-164, Ser-184, and Ser-248 (Keady et al. 2007). These phosphorylation sites seem to be required for another and most important phosphorylation event on CPEB: Ser-174 phosphorylation (maybe catalyzed by XRINGO/CDK1 kinase complex) (Kuo et al. 2011).

2.22 Grb2/7/10/14

Grb is a growth factor receptor-bound protein family that has one or more phosphotyrosine-binding and proline-rich interacting domains (i.e. SH2 and SH3 domains) and plays crucial roles in tyrosine kinase receptor-dependent signal transduction (Rozakis-Adcock et al. 1993). There are several Grb family members (e.g. Grb2), most well known of which is Grb2, whose *Drosophila* homologue is *drk* (Olivier et al. 1993). Grb2/*drk* directly interacts to receptor/tyrosine kinase with phosphotyrosine residue(s) (e.g. EGFR in mammals, *sevenless* in *Drosophila*). Because Grb2 interacts constitutively with Sos (*son of sevenless* in *Drosophila*), a guanine nucleotide-exchanging factor (GEF) for Ras, its recruitment to the plasma membranes leads to Ras activation and subsequent MAPK cascade propagation. In *Xenopus* oocytes expressing fibroblast growth factor receptor/kinase (FGFR), some Grb family members (Grb7, Grb10, and Grb14) have been implicated in tyrosine kinase-dependent signal transduction (Cailliau et al. 2003). Microinjection of Grb2 into immature *Xenopus* oocytes has been shown to cause oocyte maturation in a Ras-dependent manner (Browaeys-Poly et al. 2007; Cailliau et al. 2001). In this unusual, but interesting oocyte maturation system, SH2 domains and SH3 domain of Grb2 interact with tyrosine-phosphorylated lipovitellin 1 and PLCγ, respectively. Whether hormone-induced oocyte maturation involves Grb protein is not yet clear.

2.23 Heparin-binding and EGF-like growth factor (HB-EGF)

HB-EGF is a member of EGFR/Erb/HER ligand family, other members of which include EGF, transforming growth factor α, and heregulin. HB-EGF is initially expressed as a membrane-associated precursor and its mature form is secreted outside the cells is done by extracellular shedding as mediated by matrix metalloproteinases (MMPs). HB-EGF participates in several biological processes, including heart development and maintenance, skin wound healing, eyelid formation, progression of atherosclerosis and tumor formation (Miyamoto et al. 2006). In mammals, implantation of early embryos have been shown to involve the action of HB-EGF secreted from the surrounding epithelium as well as those autocrined (Lim and Dey 2009). In this system, HB-EGF exerts its biological functions through activation of intracellular Ca^{2+}-dependent pathways and MAPK cascade. Human trophoblast survival, where anti-apoptosis in low oxygen environment is a key event, has been shown to involve HB-EGF function (Armant et al. 2006). In other species such chicken and fish, expression of HB-EGF in oocytes is supposed to be required for ovarian follicle cell proliferation (Tse and Ge 2009; Wang et al. 2007).

2.24 Heterogenous nuclear ribonucleoprotein K (hnRNP K)

hnRNP K is a K homology (KH) domain-containing RNA-binding protein of the HnRNP family, other KH-containing RNA-binding proteins of which include hnRNP E1/E2 and Sam68 (Bomsztyk et al. 2004; Dreyfuss et al. 2002; Mattick 2004). hnRNP K binds to RNA through its three KH domains and serves multiple functions related to transcription and posttranscriptional regulation of mRNAs (e.g. splicing, translation). In *Xenopus* unfertilized eggs, hnRNP K is phosphorylated on serine and/or threonine residue(s). This phosphorylation seems to be done by MAPK, because a MAPKK inhibitor U0126, but not other inhibitors for MPF (Cdc2/cyclin B) and PKA, diminishes the signals. Consistently, fertilization results in a rapid decrease of the MAPK phosphorylation of hnRNP K. At the same time, hnRNP K becomes tyrosine-phosphorylated, most likely because of sperm-induced Src activation (Iwasaki et al. 2008). These MAPK and Src phosphorylation of hnRNP K has also been demonstrated in mammalian cell systems, in which RNA-binding property (i.e. inhibition of translation) of hnRNP K is up-regulated by MAPK and down-regulated by Src (Habelhah et al. 2001; Ostareck-Lederer et al. 2002). In *Xenopus* eggs and embryos (before mid-blastula transition, where zygotic transcription is activated), maternal mRNAs will be subjected to active protein synthesis to support embryonic development. Data obtained so far suggest that hnRNP K is involved in the suppression and release of specific subset of maternal mRNAs for its active translation (Iwasaki et al. 2008).

2.25 Heterotrimeric and monomeric GTP-binding proteins

G-proteins constitute a large family of proteins that includes small G-proteins and trimeric G-proteins, each of which act as a transducer for extracellular and/or intracellular signals (Gilman 1987; Kaziro et al. 1991). In the case of small G-proteins, a monomeric G-protein (e.g. Ras) is regulated by cell surface receptor-mediated modulation of GAP (GTPase-activating protein) and GEF (guanine nucleotide exchanging factor) activities, and the GTP-bound, active form interacts with effector molecules (e.g. Raf kinase) and regulates cellular functions. Trimeric G-proteins (e.g. Gi, Gs) consist of three subunits: α, β, and γ. Before activation, these three subunits containing GDP-bound form of a subunit are present in a tight complex. Upon activation of cognate cell surface receptors, they become dissociated and each of the subunit (GTP-bound form of α subunit and β/γ complex) exerts its cellular function. In some species, introduction of non-hydrolysable GTPγS or expression of G-protein-coupled cell surface receptor and its ligand activation, which promotes a constitutive activation of (mainly heterotrimeric) G-proteins, is shown to cause egg activation-like phenomena such as repetitive increase in intracellular Ca^{2+} concentration (in mammals) (Swann et al. 1989), cortical reactions (in *Xenopus*) (Kline et al. 1991), and DNA synthesis (in starfish) (Shilling et al. 1994). While involvement of some specific G-proteins (e.g. Gq) in the process of sperm-induced egg activation have been negatively evaluated (Runft et al. 1999; Williams et al. 1998), the fact that the *Xenopus* egg membrane-associated Src activity can be directly stimulated by GTPγS suggests that one or more unknown G-protein(s) serve as a signal transducer of gamete interaction (Sato et al. 2003; Shilling et al. 1994; Swann et al. 1989). Involvement of trimeric G-proteins in oocyte maturation is much more convincing in some species (Mehlmann 2005). Starfish and mouse oocyte meiotic arrest and/or maturation is shown to involve G-protein that directs PI3K-dependent or independent mechanism of Akt/MAPK/MPF/PKA activities (Han et al. 2006; Kalinowski et al. 2004; Kishimoto 2011; Mehlmann et al. 2004; Okumura et al. 2002). *Xenopus* oocyte maturation also seems to involve progesterone-induced membrane receptor activation that leads to modulation of G-protein (maybe Gs, not Gi)/adenylate cyclase pathway (Gallo et al. 1995; Kalinowski et al. 2003).

2.26 Histone H3

Histone is a family of basic polypeptides with ~130 amino acids and has been well characterized as DNA-binding proteins. Nucleosome, a complex of DNA-histones, is organized by an octamer of histone H2A, H2B, H3, and H4. Posttranslational modifications such as acetylation, methylation, and phosphorylation regulate the DNA-binding property of histones including H3. In some mammalian species, phosphorylation of H3 by aurora kinase and an adjacent dimethylated lysine residue are coordinately involved in chromosomal condensation during oocyte maturation (Bui et al. 2007; Ding et al. 2011; Eberlin et al. 2008; Gu et al. 2008; Jelinkova and Kubelka 2006; Maton et al. 2003; Swain et al. 2007; Wang et al. 2006).

2.27 Inositol trisphosphate receptor (IP3R)

Fertilization induces oscillation of inositol 1,4,5-trisphosphate receptor (**IP3R**)-dependent intracellular Ca^{2+} that is responsible for initiating oocyte maturation, egg activation and early embryogenesis. Three isoforms of IP3R have been detected. IP3R is dynamically regulated during meiotic maturation and is required for fertilization induced Ca^{2+} release in *Xenopus* (Kume et al. 1997; Runft et al. 1999). Developmentally regulated type 1 IP3R is up-regulated in oocytes at fertilization and down-regulated after fertilization and this down-regulation is mediated by degradation in proteasome pathway in mouse (Fissore et al. 1999; Jellerette et al. 2000; Parrington et al. 1998; Wakai et al. 2011) and bovine (Malcuit et al. 2005). IP3R1 is phosphorylated during both maturation and the first cell cycle mediated by M-phase kinases e.g. MAPK/ERK2 or polo-like kinase 1 and this is vital for IP3R function in optimum Ca^{2+} release at fertilization in *Xenopus*, mouse and pig (Ito et al. 2008; Ito et al. 2010; Lee et al. 2006; Sun et al. 2009; Vanderheyden et al. 2009). Type 1 IP3R is differentially distributed during human oocyte maturation through GV to MII stage and after fertilization in both peripheral and central in the zygotes and early 2-4-cell embryos and in perinuclear in the 6-8-cell embryos (Goud et al. 1999).

2.28 Insulin

Insulin is a peptide hormone and is crucial for follicular cell growth and development. The addition of insulin to the serum- and hormone-free maturation medium though does not improve the maturation but improves the fertilization rate of bovine oocytes in vitro (Matsui et al. 1995). Artificially induced impaired insulin secretion had a lower percentage of zygotes and a higher percentage of unfertilized and degenerated oocytes in mouse (Vesela et al. 1995). Mouse oocyte has the insulin receptor-beta and highly elevated insulin influences oocyte meiosis, chromatin remodeling, and embryonic developmental competence (Acevedo et al. 2007). Insulin did not activate MPF might be primarily due to the inability of the peptide to activate Ras and to stimulate Mos synthesis in *Xenopus* stage IV but successfully induced maturation of stage VI oocyte (Chesnel et al. 1997). Binding of insulin was revealed in oocytes, granulosa and theca internal cells of healthy pre-antral and antral follicles implying its function in these cells of swine (Quesnel 1999). Insulin increased the developmental potential of porcine oocytes and embryo (Lee et al. 2005). In insulin induced carp oocyte maturation, PI3K is an initial component of the signal transduction pathway, which proceeds, MAPK, and MPF activation (Paul et al. 2009).

2.29 Insulin-like growth factor -1 (IGF-1)

Insulin-like growth factor-1 (**IGF-1**) is primarily synthesized in liver and secreted in circulation that mediate endocrine signal important for the early embryonic development. In *in vitro* reconstructed horse oocytes, IGF-1 induced a bigger accumulation of MAPK (especially ERK2) in the cytoplasm that undergoes nuclear remodeling like a normal embryo following somatic cell nuclear transfer (Li et al. 2004). IGF-1 acts differentially to induce oocyte maturation competence but not meiotic resumption by IGF-1 in white bass (Weber and Sullivan 2005) and white perch (Weber et al. 2007). IGF-1 as like insulin also mediates its action through the activity of IRS-1 in *Xenopus* oocyte maturation (Chuang et al. 1993b). IGF-1 induced mammalian oocyte maturation and subsequently the embryo development e.g. in bovine (Bonilla et al. 2011; Stefanello et al. 2006; Wasielak and Bogacki 2007), mouse (Inzunza et al. 2010) and even human (Coppola et al. 2009).

2.30 Insulin receptor substrate-1 (IRS-1)

Insulin and insulin-like growth factor-1 (IGF-1) receptors (IR and IGFR-1) possess tyrosine-kinase enzymatic activity that is essential for signal transduction to mediate the putative effects of these hormones on oocyte maturation, fetal growth and development. This causes rapid tyrosine phosphorylation of a high-molecular-weight substrate termed insulin receptor substrate-1 (**IRS-1**), a docking protein that can bind with Src homology 2 domain containing molecules e.g. PI 3-kinase, Grb2. Insulin-induced maturation of *Xenopus* oocytes involve the activation of IRS-1 and PI 3-kinase where activation of PI 3-kinase might act upstream of mitogen-activated protein kinase activation and p70 S6K activation (Chuang et al. 1994; Chuang et al. 1993a; Chuang et al. 1993b; Liu et al. 1995; Yamamoto-Honda et al. 1996). IRS-1 is expressed maternally and constantly during *Xenopus* embryogenesis and is important for eye development (Bugner et al. 2011).

2.31 Integrin β1

Integrins are a family of cell surface receptors that mediate cell-cell and cell-matrix interactions in different cellular systems. Variety of integrins is differentially expressed during development, consistent with diverse roles for integrins in embryogenesis. **Integrin β1** (this subunit can interact with α6) is present on the mouse egg surface that increases the rate of sperm attachment but does not alter the total number of sperm that can attach or fuse to the egg (Baessler et al. 2009; Tarone et al. 1993). Integrin α6β1 in association with tetraspanin CD151 and CD9 complex do function in human and mouse gamete fusion (Ziyyat et al. 2006). In *Xenopus*, integrin β1 is present on the oocyte membrane throughout oogenesis and during maturation it is localized in several membrane vesicles in the cytoplasm might be to provide the material source for the rapid membrane formation during cleavage (Muller et al. 1993). Even integrin α6β1 might serve as potential clinical marker for evaluating sperm quality in men (Reddy et al. 2003).

2.32 Interleukin-7 (IL-7)

Interleukin-7 (**IL-7**, pre-B-cell growth factor) is playing its role not only as immunomodulator but also in the beginning of development. IL-7 in together with IL-8 inhibited the gamete interaction of hamster egg and sperm (Lambert et al. 1992). The role of

IL-7 was tested in differentiation during embryonic development e.g. in mouse: development of thymus (Wiles et al. 1992) and lymph node (Coles et al. 2006). IL-7 could be also a good marker of the embryo quality for implantation (Achour-Frydman et al. 2010). In rat granulosa cell culture of early antral and preovulatory follicles, IL-7 stimulated the phosphorylation of AKT, glycogen synthase kinase (GSK3B), and STAT5 proteins in a time- and dose-dependent manner (Cheng et al. 2011). It is concluded that oocyte-derived IL-7 act on neighboring granulosa cells as a survival factor and promote the nuclear maturation of pre-ovulatory oocytes through activation of the PIK3/AKT pathway (Cheng et al. 2011).

2.33 Lipovitellin (LV)

LV1 and **LV2** are components of crystallized yolk platelet in vertebrate oocytes, eggs, and embryos. Precursor protein of LVs, vitellogenin, is synthesized in a highly phosphorylated form in liver of adult and transferred to ovarian tissue, where growing oocytes actively incorporate vitellogenin through the action of specific oocyte membrane receptors (Bergink and Wallace 1974). The incorporated vitellogenin is subjected to partial proteolysis so that LV2 and other fragments such as lipovitellin 1, phosvitin, and pp25 are formed (Finn 2007). A similar set of yolk-associated proteins is also found in invertebrates including insect (e.g. vitelline). It is well known that phosvitin and pp25 are highly serine/threonine-phosphorylated proteins that serve as an energy source of oogenesis and early embryogenesis. On the other hand, tyrosine phosphorylation of LV1 (Browaeys-Poly et al. 2007) and LV2 (Kushima et al. 2011) has recently been demonstrated in *Xenopus*. In particular, tyrosine phosphorylation of LV2 is unusually stable during oogenesis, oocyte maturation, and early embryogenesis until the removal of yolk-associated materials from swimming tadpole (Kushima et al. 2011). Possible function of tyrosine-phosphorylated form of *Xenopus* LV1 and LV2 so far suggested is oocyte maturation (Browaeys-Poly et al. 2007; Kushima et al. 2011), although it's upstream (liver or oocyte) kinase and downstream cellular function is uncertain.

2.34 Maskin/Cytoplasmic polyadenylation element (CPE)-binding protein (CPEB)/TACC3/p82

Maskin is a cytoplasmic polyadenylation element-binding protein-associated factor. Dormant state of maternal mRNAs in immature oocytes is maintained by an abortive interaction of this protein with the eukaryotic initiation factors 4E and 4G. Phosphorylation of maskin promotes the dissociation of this interaction, thereby allows the dormant mRNAs to be translated actively. Aurora phosphorylation of maskin is reported to be involved in protein synthesis in maturing clam and *Xenopus* oocytes and in centrosome-dependent microtubule assembly at mitosis (Kinoshita et al. 2005; Pascreau et al. 2005).

2.35 Myosin regulatory light chain (MRLC)

Myosin regulatory light chain (**MRLC**) or, in short, myosin light chain (MLC) is a component of myosin that regulates the function of actin and actin filaments (see above) through the binding to the actin molecule. Unfertilized eggs of sea urchin undergo cortical contraction in response to calyculin A, an inhibitor for protein phosphates. The results suggest that an egg protein(s), in its phosphorylated form(s), is capable of inducing cortical contraction in this system. As a candidate phosphoprotein for this phenomenon, MRLC has been identified (Asano and Mabuchi 2001). Further biochemical experiments have demonstrated that CK2 (casein kinase 2) is a responsible kinase for the phosphorylation of MRLC (Komaba et al. 2001). Phosphorylation of MRLC in sea urchin eggs occurs on Ser-19 and Thr-18 residues, both of which are stimulatory phosphorylation sites (Asano and Mabuchi 2001). On the other hand, MRLC has also been identified as a phosphoprotein in cell-free extracts prepared form sea urchin eggs. In this system, phosphorylation of MRLC occurs at mitotic phase of cell cycle on Ser-1/2 and Thr-9, all of which are canonical PKC sites, and it is suggested that MPF is the responsible kinase (Totsukawa et al. 1996). In *Drosophila*, phosphorylation of Ser-21 of MRLC-homologue (*sqh*, spaghetti squash gene product) has been implicated as an important event for oogenesis (Jordan and Karess 1997).

2.36 Na^+/H^+ antiporter/exchanger

On fertilization there are marked changes in the cytoplasmic ionic concentration e.g. Ca^{2+}, H^+, are necessary and sufficient to constitute the egg activation and beyond. A second messenger type substance that stimulates protein kinase C linked the activation of the Na^+/H^+ exchange to the calcium transient and ultimately the protein synthesis is increased and the cytoplasmic alkalinization occur in sea urchin eggs (Swann and Whitaker 1985). In sea urchin eggs, though the **Na^+/H^+ exchanger** is regulated by PKC or Ca^{2+}/CaMK activities but fertilization mediated activation of this exchanger is Ca^{2+}, CaM-dependent (Shen 1989). G proteins activated Na^+/H^+ antiporter mediated by PKA and/or PKC in *Xenopus* oocytes (Busch 1997; Busch et al. 1995). A typical Na^+/H^+ exchanger mediated increased intracellular pH though activate the surf clam oocytes but is neither sufficient nor required for GVBD (Dube and Eckberg 1997). The function of Na^+/H^+ exchanger has also been described even for later stage of development e.g. blastocyst of mouse (Barr et al. 1998), bovine embryos (Lane and Bavister 1999) and human pre-implantation embryos (Phillips et al. 2000).

2.37 OMA-1

In *C. elegans*, two CCCH-type zinc finger proteins **OMA-1** and OMA-2 are expressed specifically in maturing oocytes and are functionally redundant during maturation. Both Oma-1 and Oma-2 mutant oocytes arrest at a defined point in prophase I and the removal of Myt1-like kinase Wee-1.3 results the release of prophase I arrest (Detwiler et al. 2001). As WEE-1.3 functions as a negative regulator, OMA-1 and OMA-2 either function upstream of WEE-1.3 or in parallel with WEE-1.3 as positive regulators of prophase progression (Detwiler et al. 2001). OMA-1 protein is largely reduced because of rapid degradation after the first mitotic division and this is necessary for the early embryonic development by regulating the temporal degradation of maternal proteins in early *C. elegans* embryos (Lin 2003; Shimada et al. 2006; Shirayama et al. 2006). OMA-1 is directly phosphorylated (Thr-239) by DYRK kinase MBK-2 that facilitates subsequent phosphorylation (Thr-339) by another kinase GSK-3 and these precisely timed phosphorylation events are important for its function in 1-cell embryo and degradation after first mitosis (Nishi and Lin 2005).

2.38 p53

The **p53** protein family includes three transcription factors-p53, p63 and p73 that play roles in both cancer and normal development (Levine et al. 2011). Mostly stable p53 protein is synthesized during late oogenesis and stage VI oocyte and even after fertilization at least until the tadpole stage during *Xenopus* development (Tchang et al. 1993). After fertilization, part of the largely stored p53 is imported into the nucleus and associates both with decondensed DNA and the nuclear lamina envelope but not with any replication complexes during *Xenopus* early development (Tchang and Mechali 1999). In the absence of TPX2 (targeting protein for Xklp2), p53 can inhibit Aurora A, a serine/threonine kinase, activity (Eyers and Maller 2004). TPX2 is required for Aurora A activation and for p53 synthesis and phosphorylation during *Xenopus* oocyte maturation (Pascreau et al. 2009). The tumor suppressor protein p53 regulates the efficiency of human reproduction. The p53 allele encoding proline at 72 (Pro72) was found to be significantly higher (P=0.003) over the allele encoding arginine (Arg72) among women experiencing recurrent implantation failure (Kang et al. 2009; Kay et al. 2006; Levine et al. 2011)

2.39 p95

Several studies showed that in mammals, egg-specific extracellular matrix zona pellucida component ZP3 regulates an essential event in sperm function. Mouse zona pellucida glycoprotein ZP3 regulates acrosomal exocytosis by aggregating its corresponding receptors located in the mouse sperm plasma membrane e.g. a protein **p95** that might serve as a substrate for a tyrosine kinase in response to zona pellucida binding or itself act as tyrosine kinase (Saling 1991). A phosphotyrosine containing receptor tyrosine kinase was identified in human sperm that is similar to mouse sperm protein, p95, having tyrosine kinase activity and human ZP3 stimulate the tyrosine kinase activity of this protein (Burks et al. 1995; Naz and Ahmad 1994). Acrosome reaction was induced with increased tyrosine phosphorylation of p95 epitope only in capacitated human spermatozoa (Brewis et al. 1998).

2.40 Paxillin

Paxillin is a prominent focal adhesion docking protein that regulates somatic and germ cell signaling. Paxillin was shown as one of the major tyrosine kinase substrates during rat chick embryogenesis (Turner 1991) and regulator of Rho and Rac signaling during *Drosophila* development (Chen et al. 2005). It was described that paxillin is required for synthesis and activation of Mos (the germ cell Raf homolog), that promotes MEK and subsequently Erk signaling and then possibly Erk mediate the phosphorylation of paxillin required for steroid (testosterone)-induced *Xenopus* oocyte maturation (Rasar et al. 2006). In prostate cancer cell, EGFR-induced Erk activation requires Src-mediated phosphorylation of paxillin but paxillin was not involved in PKC-induced Erk signal (Sen et al. 2010). Erk-mediated phosphorylation of paxillin was necessary for both EGFR- and PKC-mediated cellular proliferation indicate that paxillin serves as a specific upstream regulator of Erk in response to receptor-tyrosine kinase activity but as a general regulator of downstream Erk actions regardless of agonist (Sen et al. 2010).

2.41 Peptidylarginine deiminase (PAD)

Peptidylarginine deiminase (PAD) catalyzes the post-translational modification of protein converting the arginine to citrulline in the presence of calcium ions. PAD is present in the cortical granules of mouse oocytes, is released extracellularly during the cortical reaction, and remains associated as a peripheral membrane protein until the blastocyst stage (Liu et al. 2005). In mouse peptidylarginine deiminase-like protein termed ePAD (p75) was expressed in immature oocyte, mature egg, and until the blastocyst stage of embryonic development (Wright et al. 2003). Peptidylarginine deiminase 6 (PAD6) is uniquely expressed in male and female germ cells but the inactivation of PAD6 gene leads to female infertility whereas male fertility is not affected (Esposito et al. 2007) and its transcript is detectable at embryonic day 16.5 in mouse (Choi et al. 2010). Mouse oocyte cytoplasmic sheet-associated PADI6 undergoes developmental change in phosphorylation that might be linked to interaction between PAD16-YWHA during oocyte maturation (Snow et al. 2008). PADI6-deficient mice are also infertile might be due to disruption of development beyond the two-cell stage (Snow et al. 2008).

2.42 Phosphodiesterase 3A (PDE3A)

Intracellular concentration of the second messenger cAMP is the key signaling molecules in the control of oocyte meiotic resumption mediated by the activity of phosphodiesterases (**PDEs**). cAMP blocks meiotic maturation of oocytes of a broad spectrum of species and cyclic nucleotide phosphodiesterase 3A (PDE3A) is primarily responsible for oocyte cAMP hydrolysis. The PDE3A activity in the regulation of oocyte maturation of several species has been studied extensively e.g. in rodent (Wiersma et al. 1998), rat (Richard et al. 2001), mouse (Masciarelli et al. 2004; Nogueira et al. 2003b; Nogueira et al. 2005), monkey (Jensen et al. 2005), porcine (Sasseville et al. 2006; Sasseville et al. 2007), bovine (Mayes and Sirard 2002; Thomas et al. 2002), and human (Nogueira et al. 2003a). Various PDE3 inhibitors were used like org9935, cilostamide, or milrinone. PDE3 activity is required for insulin/insulin-like growth factor-1 stimulation of *Xenopus* oocyte meiotic resumption. It should be note that the activation of PDE3A by PKB/Akt-mediated phosphorylation potentiates the *Xenopus* and mouse oocytes maturation (Han et al. 2006).

2.43 pp25 and phosvitin

Functions of multiple vitellogenin (VgA, VgB, and VgC)-derived yolk products, e.g. lipovitellin/**phosvitin** were described during oocyte maturation and early embryos in various species, e.g. barfin flounder, *Verasper moseri*, a marine teleost (Matsubara et al. 1999; Sawaguchi et al. 2006), red seabream (*Pagrus major*), another marine teleost and gray mullet (*Mugil cephalus*) (Amano et al. 2008). A substrate **pp25** for protein serine/threonine kinases was derived from the precursor of pp43 that is consisting of a portion of the *Xenopus* VgB1 protein (Xi et al. 2003). pp25 may have a role as an inhibitory modulator of some protein phosphorylation mediated by CKII and PKC in *Xenopus* oocytes and embryos (Sugimoto and Hashimoto 2006). A differentially distributed pp25 was shown to localize at the surface just below the plasma membrane in oocyte and in embryogenesis a transition from beneath the outer surface of each germ layer to endoderm during tail budding from where it gradually decreased and disappeared at the tadpole stage in *Xenopus* (Nakamura et al. 2007).

2.44 Protein methyl transferase 5 (PRMT5)

Distinct protein/DNA methylation patterns were observed in developmental stages during genomic reorganization. The protein methylase activity was measured at mesenchymal blastula and at young gastrula of sea urchin embryonic development and lysine of histones H3 and H4 are the main target (Branno et al. 1983). A Janus-2 (JAK-2) binding protein, JBP1, acts as an arginine methyl transferase and is now designated as **PRMT5**. In *Xenopus* oocytes, PRMT5 inhibited the oncogenic/transformed $p21^{Ras}$ mediated maturation but not the insulin mediated maturation that involve the wild-type $p21^{Ras}$ (Chie et al. 2003). Decreased level of methylated H3K79 was observed soon after fertilization and the hypomethylated state was maintained at interphase (before the blastocyst stage) and variation in methylation was observed at M phase (Ooga et al. 2008) in mouse. DNA methyltransferase-1 might work during the late stage of oocyte differentiation, maturation and early embryonic development in mammals e.g. cow (Lodde et al. 2009).

2.45 Proline-rich inositol phosphate 5-phosphatase (PIPP)

Different types of inositol polyphosphate 5-phosphatases (IPP) selectively remove the phosphate from the 5-position of the inositol ring from both soluble and lipid substrates, i.e., inositol 1,4,5-trisphosphate, inositol 1,3,4,5-tetrakisphosphate, phosphatidylinositol 4,5-bisphosphate or phosphatidylinositol 3,4,5-trisphosphate and they have various protein modules probably responsible for specific cell organelle localization or recruitment e.g. SH2 domain, SH3-binding motif, proline-rich sequences, etc. (Erneux et al. 1998; Kong et al. 2000; Mochizuki and Takenawa 1999). They demonstrate the restricted substrate specificity and act downstream of various receptors by removing a phosphate. Proline-rich IPP (**PIPP**) had been studied in PI3K pathway for early development of fertilized mouse eggs. PIPP might affect development of fertilized mouse eggs by inhibition of level of phosphorylated Akt at Ser-473 and subsequent inhibition of downstream signal cascades resulting reduced cleavage rate of fertilized mouse eggs (Deng et al. 2011). In embryonic day 15.5 mice, SHIP2 a homologue of SHIP1 was strongly expressed in the liver, specific regions of the central nervous system, the thymus, the lung, and the cartilage perichondrium (Schurmans et al. 1999).

2.46 Protein phosphatase 1/2A (PP1/PP2A)

Numerous protein kinases and phosphatases have important functions during mitosis and meiosis. Protein phosphatase (PP) 1 (**PP1**) and 2A (**PP2A**) that preferentially dephosphorylate the β- and α-subunit of phosphorylase kinase had been identified in starfish oocyte (Pondaven and Cohen 1987). With the similar mechanism involved in mammals and *Drosophila*, PP4, a centrosomal protein, involved in the recruitment of pericentriolar material components to the centrosome from prophase to telophase, but not during interphase, and is essential for the activation of microtubule nucleation that promote spindle formation in *C. elegans* (Sumiyoshi et al. 2002). When the normal physiological function of PP1 and PP2A was blocked, premature separation of sister chromatids during meiosis I and aneuploidy in mouse oocytes was observed (Mailhes et al. 2003). In *Xenopus* oocyte, PP2A negatively regulates Cdc2 activation whereas Aurora-A activation is indirectly controlled by Cdc2 activity independent of either PP1 or PP2A activity (Maton et al. 2005). Constant cyclin B levels are maintained during a CSF arrest through the regulation of Emi2 activity that inhibits the anaphase-promoting complex (APC), an E3 ubiquitin ligase that targets cyclin B for degradation in vertebrates like *Xenopus* (Wu et al. 2007b). Rsk or Cdc2-mediated phosphorylation of Emi2 was antagonized by PP2A, which could bind to Emi2 and promote Emi2-APC interactions results CSF arrest (Wu et al. 2007a; Wu et al. 2007b). Cdk1/cyclin B (MPF) induced active Gwl promotes PP2A (B55 is the regulatory subunit) inhibition to enter and maintenance the M phase that would otherwise remove MPF-driven phosphorylations (Castilho et al. 2009; Vigneron et al. 2009).

2.47 Protein tyrosine phosphatase (PTP)

In the early steps of embryogenesis both the protein tyrosine phosphorylation and the protein tyrosine phosphatase (**PTP**) regulated activities are involved. In *Xenopus* MPF and progesterone but not insulin-induced oocyte maturation was retarded by PTPase 1B action (Tonks et al. 1990) whereas non receptor PTP13 activate the oocyte maturation (Nedachi and Conti 2004). PTP exert its role by different mechanism for example, PTP regulate the oocyte maturation in pig (Kim et al. 1999a), receptor-type PTP regulate Fyn in zebrafish egg fertilization (Wu and Kinsey 2002), Src homology-2 domain containing PTP (SHP2) regulate normal human trophoblast proliferation (Forbes et al. 2009), and pseudo-PTP (lack at least one key residue in the catalytic site) regulate oocyte-embryo transition in nematode (Heighington and Kipreos 2009) and antagonist of PTP reduced GVBD and MAPK/MPF activities in sea water treated marine nemertean worms oocytes (Stricker and Smythe 2006). Receptor type PTP and PTP are essential for convergence and extension cell movements to shape the body axis during vertebrate gastrulation e.g. for zebrafish in a signaling pathway parallel to non-canonical Wnt and upstream of Fyn, Yes and RhoA (van Eekelen et al. 2010).

2.48 Pumilio1/2

In *Xenopus*, the cytoplasmic polyadenylation element (CPE) in the 3′-untranslated region (UTR) of cyclin B1 mRNA is responsible for both the translational repression (masking) and activation (unmasking) of the mRNA where CPE is bound by a CPE-binding (CPEB) protein (Hake and Richter 1994; Hodgman et al. 2001; Mendez and Richter 2001). *Xenopus* **pumilio** (Pum) in coordination with CPEB-maskin complex acts as a specific regulator for timing translational activation of cyclin B1 mRNA first as repressor in mature oocyte by binding and as activator by its release from phosphorylated CPEB during oocyte maturation (Nakahata et al. 2003). Usually nemo-like kinase (NLK) that acts downstream of Mos, phosphorylate Pum1, Pum2 and CPEB and this phosphorylation is proceeded with translational activation of cyclin B1 mRNA stored in oocytes for maturation (Ota et al. 2011a; Ota et al. 2011b).

2.49 $p21^{Ras}$

In *Xenopus* oocytes, transformed/active **$p21^{Ras}$** increased the level of total cell protein phosphorylation that culminated with germinal vesicle breakdown (GVBD) in the absence of protein synthesis and the same pattern of phosphorylation was observed by hormone either progesterone or insulin treatment (Nebreda et al. 1993). Activated $p21^{Ras}$ and GTPase-activating protein (GAP) complex may promote MAPK activity by tyrosine phosphorylation followed by the activation of S6-kinase II (Nebreda et al. 1993; Pomerance et al. 1992). Later it was shown that Ras-GAP activity is required for Cdc2 activation and Mos induction independent of MAPK activation (Pomerance et al. 1996). It should be note that active Ras increased MAPK and S6K activities and sensitized the oocytes to insulin-stimulated maturation via IRS-1 (Chuang et al. 1994). T-Cell Origin protein Kinase (TOPK) and the nuclear kinase, DYRK1A are attractive candidates in insulin mediated wild-type $p21^{Ras}$-induced oocyte maturation independent of MAPK (Qu et al. 2006; Qu et al. 2007). Phospholipase D (PLD) activity induced MAPK and S6K II activity might constitute a relevant step in Ras-induced GVBD in *Xenopus* oocytes was also reported (Carnero and Lacal 1995). $p21^{Ras}$ did not appear to be ubiquitous in the rat conceptus prior to gastrulation but was found in embryos from 6.5 to 12 days of age (Brewer and Brown 1992).

2.50 Phosphatidylinositol 3-kinase (PI3K)

PI3K is a lipid kinase that phosphorylates 3′-position in the inositol ling structure of inositol phospholipids (e.g. phosphatidylinositol 4,5-bisphosphate). Inactive PI3K consists of a heterodimer of one catalytic subunit (e.g. p110) and one regulatory subunit (e.g. p85), a latter of which is known to be tyrosine-phosphorylated in response to a variety of extracellular signals (Vanhaesebroeck et al. 1997). The tyrosine-phosphorylated regulatory subunit releases the catalytic subunit so that PI3K becomes enzymatically active. Involvement of PI3K in oocyte maturation and fertilization has been examined with the use of specific inhibitors such as LY294002 and Wortmannin as well as expression of native or mutant PI3K proteins (Chuang et al. 1993a; Hoshino and Sato 2008; Hoshino et al. 2004; Mammadova et al. 2009). In starfish oocyte, 1-methyladenine-induced oocyte maturation involves a sequential activation of the hormone receptor on the cell surface, G-proteins attached to the receptor, and PI3K. The activated PI3K promotes Akt kinase activation through the production of PIP_3 and stimulation of PIP_3-dependent protein kinase PDK1 (Kishimoto 2011). In oocytes of *Xenopus* or other frog species, PI3K is suggested to be a component of progesterone-induced oocyte maturation (Bagowski et al. 2001; Ota et al. 2008). However, wortmannin promotes oocyte maturation in the absence of hormonal signal (Carnero and Lacal 1998), suggesting the possibility that this drug targets unknown factor(s) other than PI3K or that, as opposed to the case in starfish, PI3K is negative regulator of oocyte maturation. On the other hand, LY294002 has been shown to block sperm-induced egg activation (Mammadova et al. 2009). LY294002 also blocks sperm-induced Src activation and Ca^{2+} release, suggesting that PIP_3 production by PI3K plays a role in fertilization. Interestingly, however, tyrosine phosphorylation of p85 subunit of PI3K is not detected, suggesting that alternative pathway for PI3K activation (e.g. recruitment to membrane microdomains) is working in this system.

2.51 Phospholipase Cγ (PLCγ)

PLCγ is a member of PLC family proteins (other members are PLCβ, PLCδ, PLCε, PLCζ etc.) that hydrolyzes phosphatidylinositol 4,5-bisphosphate into DG and IP_3, both of which are second messenger to promote PKC activation and intracellular Ca^{2+} mobilization, respectively (Rhee 2001). PLCγ is the first example of non-tyrosine kinase protein, whose structure contains SH2 and SH3 domains (Stahl et al. 1988). PLCγ is also unique in its regulatory mechanism, where tyrosine phosphorylation of the protein can up-regulate the enzyme activity. Under this background, function of PLCγ in oocyte maturation and fertilization has been analyzed extensively in relation to tyrosine kinase signaling. In fact, tyrosine kinase-dependent activation of PLCγ at fertilization has been demonstrated in some vertebrate (e.g. fish, frog) and invertebrate species (e.g. ascidian, sea urchin, starfish) (Carroll et al. 1999; Carroll et al. 1997; Giusti et al. 1999; Giusti et al. 2000; Mehlmann et al. 1998; Runft et al. 2004; Runft and Jaffe 2000; Runft et al. 2002; Runft et al. 1999; Sato et al. 2002a; Sato et al. 2001; Sato et al. 2003; Sato et al. 2000b; Shearer et al. 1999; Tokmakov et al. 2002). It should be noted that Src-dependent activation of PLCγ involves a new function of PLCγ as GEF for small G-protein Ras (Bivona et al. 2003), suggesting that other means of cellular function contributes to egg activation in these species. On the other hand, Ca^{2+} release associated with mammalian fertilization does not seem to involve tyrosine kinase activity and PLCγ activation, probably because sperm-derived PLCζ activity is necessary and sufficient for sperm-induced Ca^{2+} release in these species (Kurokawa et al. 2004; Parrington et al. 2002; Saunders et al. 2002).

2.52 RNA polymerase II large subunit

RNA polymerase II (also called RNAP II or Pol II), a complex of twelve subunits (p550) is an enzyme that catalyzes the transcription of DNA to synthesize precursors of mRNA and most snRNA and microRNA (Kornberg 1999; Sims et al. 2004). A large subunit of RNAPII (p220) was shown to be phosphorylated at the onset of wheat germination that moderately increase the RNA polymerase activity (Mazus et al. 1980). In *C. elegans*, embryonically transcribed gene products are required for gastrulation initiation where a large subunit of RNAPII is involved (Powell-Coffman et al. 1996). In *Xenopus*, the largest subunit of RNA polymerase II (RPB1) accumulates in large quantities from previtellogenic early diplotene oocytes up to fully grown oocytes where the C-terminal domain (CTD) was essentially hypophosphorylated in growing oocytes from stage IV to VI (Bellier et al. 1997). Upon maturation, RPB1 is hyperphosphorylated dramatically and abruptly but dephosphorylated within 1 h after fertilization (Bellier et al. 1997). Metaphase II-arrested oocytes showed a much stronger CTD kinase activity than that of prophase stage VI and this kinase activity were attributed to the activated MAPK i.e. RPB1 could be a substrate of MAPKs (e.g. p42) during *Xenopus* oocyte maturation (Bellier et al. 1997).

2.53 Receptor for activated C kinase (RACK)

PKC, serine/threonine kinase, is a pivotal enzyme in a variety of signal transduction pathways that includes the maturation through actin cytoskeleton rearrangement and cortical granules exocytosis (CGE) to early stages of embryogenesis. The translocation of PKC is facilitated by receptor for activated C kinase (**RACK**). Activation of PKC exposes the RACK-binding site, enabling the association of the enzyme with its anchoring RACK (Ron and Mochly-Rosen 1995). Inhibition of binding the PKC to RACK blocks the function of PKC (Ron et al. 1995). During the activation of MII eggs, PKCα, βII and γ individually and RACK1 together with both PKCα and PKCβII translocate to the egg cortex (Haberman et al. 2011). The association of PKC and actin with RACK1 is known to be involved in CGE. Upon egg activation, increased level of RACK1 shuttles activated PKCs to the egg cortex, thus facilitating CGE (Haberman et al. 2011). The phytohormone abscisic acid promoted the expression level of RACK that is regulated by Gα-protein and plays an important role in a basic cellular process as well as in rice embryogenesis and germination (Komatsu et al. 2005).

2.54 Rho

The **Rho** family of small GTPases is known to organize and maintain the actin filament-dependent cytoskeleton, and rho is involved in the control mechanism of cytokinesis. Actin-depolymerizing factor (ADF)/coffilin, a key regulator for actin dynamics during cytokinesis, is suppressed and reactivated by phosphorylation and dephosphorylation respectively. Rho-induced dephosphorylation of ADF/coffilin is dependent on the XSSH (*Xenopus* homologue of Slingshot phosphatase) activation that is caused by increase in the amount of F-actin induced by Rho signaling (Tanaka et al. 2005). XSSH may reorganize actin filaments through dephosphorylation and reactivation of ADF/coffilin at early stage of contractile ring formation during *Xenopus* cleavage (Tanaka et al. 2005). In sea urchin egg, Rho is synthesized early in oogenesis in soluble form, associates with cortical granules in the end of maturation and after insemination secreted by cortical granules exocytosis and retained in the fertilization membrane indicate the involvement of Rho in Ca^{2+}-regulated exocytosis or actin reorganization that accompany the egg activation (Covian-Nares et al. 2004; Cuellar-Mata et al. 2000; Manzo et al. 2003). In ascidians Rho proteins are involved in egg deformation, ooplasmic segregation and cytokinesis downstream of the Ca^{2+} transients (Yoshida et al. 2003).

2.55 Ribosomal S6

In *Xenopus* oocytes 40S ribosomal protein **S6** becomes phosphorylated by S6K on serine residues in response to hormones or growth factors and following microinjection of the tyrosine-specific protein kinases associated with Rous sarcoma virus or Abelson murine leukemia virus. S6 is minimally phosphorylated in unstimulated oocytes and in progesterone induced *Xenopus* oocyte maturation: phosphorylation of S6 precedes germinal vesicle breakdown (GVBD) and is maximal at the time when 50% of the oocytes have undergone GVBD (Erikson and Maller 1985; Hanocq-Quertier and Baltus 1981; Nielsen et al. 1982). In *Xenopus* oocytes, Ras (p21, have GTPase activity) proteins activate the pathway linked to S6 phosphorylation and that PKC has a synergistic effect on the Ras-mediated pathway (Kamata and Kung 1990). Microinjection of purified pp60$^{v\text{-}Src}$ into *Xenopus* caused the phosphorylation of S6 and accelerated the time course of progesterone-induced oocyte maturation (Spivack et al. 1984).

2.56 RINGO

RINGO/Speedy (Rapid Inducer of G2/M transition in Oocytes) proteins can bind to and directly stimulate CDKs (CDK1 and CDK2) that regulate cell cycle transition although they do not have amino acid sequence homology with cyclins. In *Xenopus* oocytes RINGO (XRINGO) accumulates transiently during meiosis I entry and this process is directly stimulated by several kinases, including PKA and GSK3β, and contributes to the maintenance of G2 arrest (Gutierrez et al. 2006). Later XRINGO is down-regulated/degraded after meiosis I that is mediated by the ubiquitin ligase Siah-2, which probably requires phosphorylation of XRINGO on Ser-243 and important for the omission of S phase at the meiosis-I-meiosis-II transition in *Xenopus* oocytes and finally trigger G2/M progression (Gutierrez et al. 2006; Karaiskou et al. 2001). p42 MAPK (ERK2) activity and RINGO accumulation are also required for activating phosphorylation of CPEB by Cdk1.

RINGO/Speedy, is necessary for CPEB-directed polyadenylation-induced translation of Mos and cyclin B1 mRNAs in maturing *Xenopus* oocytes (Padmanabhan and Richter 2006). Recently, it was shown that XGef (a Rho family guanine nucleotide exchange factor) is involved in XRINGO/CDK1-mediated activation of CPEB and that an XGef/XRINGO/ERK2/CPEB complex forms in ovo to facilitate the maturation process (Kuo et al. 2011). In mammals for example in porcine RINGO A2 (SPDYA2) speed up the oocyte maturation (Kume et al. 2007) and in mouse RINGO efficiently triggers meiosis resumption of oocytes and induces cell cycle arrest in embryos (Terret et al. 2001).

2.57 Sam68 adaptor protein (Sam68)

Sam68 is a KH domain-containing, STAR (signal transduction and activation of RNA) family RNA-binding protein that has been originally identified as a mitosis-specific Src-phosphorylated protein of 68 kDa (Taylor et al. 1995; Taylor and Shalloway 1994). Sam68 has also a proline-rich sequence that would interact with SH3 domain-containing proteins, linking its possible function to Src-dependent signal transduction pathways. The RNA-binding ability of Sam68 contributes to, like hnRNP K, another KH-containing RNA-binding protein, posttranscriptional regulation of mRNAs (e.g. splicing, translation). While its physiological function in spermatogenesis has been well known to date (Sette et al. 2010), roles of Sam68 in the oocyte and/or egg system have just recently been shown in mammalian species: Sam68-deficient female mice are severely subfertile (Bianchi et al. 2010). Further studies demonstrated that Sam68 directly binds the mRNAs for the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH) receptors (FSHR and LHR) and is involved in proper expression of these transcripts in pre-ovulatory follicles in adult ovary. Whether these Sam68 functions involve phosphorylation of Sam68 is not known.

2.58 Separase

The cysteine protease named **separase** is widely expressed in unicellular and multicellular organisms and is involved in a timely cleavage of the sister chromatid protein cohesins/SCC1 so that the separation of sister chromatids is made possible in the anaphase. The activity of separase can be negatively regulated by two mechanisms: one is the binding of securin, and the other is Cdc2-dependent phosphorylation on Ser-1126 and subsequent phospho-dependent binding of cyclin B (Nagao and Yanagida 2002; Nasmyth et al. 2000; Stemmann et al. 2001). In meiotic cell cycles in *Xenopus* oocytes, phospho-dependent inhibition of separase seems to occur: progesterone-induced oocyte maturation promotes firstly an accumulation of *Xenopus* homolog of securin, and then it undergoes degradation at the meiotic anaphase I and II in an APC/C-dependent manner (Fan et al. 2006; Holland and Taylor 2006). Mutation studies of the phosphorylation site in separase demonstrated that phospho-dependent regulation of this enzyme also works in germ cell developmental stages and early embryonic (8-cell and 16-cell) stages (Huang et al. 2009).

2.59 SHB

The adaptor protein **SHB** (Src homology 2 domain-containing adapter protein B) mediates certain responses in platelet-derived growth factor (PDGF) receptor-, fibroblast growth factor (FGF) receptor-, neural growth factor (NGF) receptor-, T cell (TC) receptor-, interleukin-2 (IL-2) receptor- and focal adhesion kinase- (FAK) signaling where in some cells the Src-like Fyn-related kinase (FRK/RAK) act upstream of SHB (Cross et al. 2002; Karlsson et al. 1998; Karlsson et al. 1995; Welsh et al. 1998).The absence of SHB enhanced ERK (extracellular-signal regulated kinase) and RSK (ribosomal S6K) signaling in mouse oocytes increasing the ribosomal protein S6 phosphorylation and activation (Calounova et al. 2010). SHB regulates normal oocyte and follicle development and that perturbation of SHB signaling causes defective meiosis I and early embryo development in mouse (Calounova et al. 2010). The SHB protein is required for normal maturation of mesoderm and efficient multilineage differentiation during in vitro differentiation of embryonic stem cells (Kriz et al. 2006; Kriz et al. 2003).

2.60 Shc adaptor protein (Shc)

Src homology and collagen (**Shc**) is an SH2-containing adaptor protein that has been identified as a mammalian proto-oncogene, whose overexpression in fibroblast cells leads to the malignant transformation (McGlade et al. 1992; Pelicci et al. 1992; Rozakis-Adcock et al. 1992). Shc consists of three isoforms (i.e. p46, p52, and p66) produced by alternative transcription and translation from one transcript and all isoforms also have an additional phosphotyrosine-binding domain in its amino-terminal region, named PTB domain. In some receptor/tyrosine kinase-mediated signal transduction pathway, Shc is recruited to the phosphotyrosine clusters of the activated receptor proteins, phosphorylated on its tyrosine residues (e.g. in mammals, Tyr-239/240 for Myc activation, Tyr-317 for MAPK/Fos activation), and recruit other SH2 and/or SH3-containing proteins (e.g. Grb2) to elicit downstream signaling cascade. In *Xenopus*, insulin-dependent oocyte maturation and egg fertilization seem to involve tyrosine kinase-dependent function of Shc (Aoto et al. 1999; Chesnel et al. 2003). Because two of three isoforms of Shc (p52 and p66) has been shown to be a direct activator of Src tyrosine kinase (Sato et al. 2002b), it is interesting to examine whether Shc-dependent Src activity contributes to these physiological events.

2.61 SNT/FRS2

Membrane anchored adaptor protein Suc1-associated neurotrophic target-1 or -2/fibroblast growth factor receptor substrate-2 or (**SNT**-1 or -2/FRS2), is implicated in the transmission of extracellular signals from several growth factor receptors e.g. fibroblast growth factor receptors (FGFRs) and neurotrophin receptors (Trks) through their N-terminal phosphotyrosine binding (PTB) domains to the mitogen-activated protein (MAP) kinase signaling cascade during embryogenesis. SNT-1 physically associates with the Src-like kinase Laloo, and SNT-1 activity is required for mesoderm induction by Laloo in *Xenopus* (Akagi et al. 2002; Hama et al. 2001). Activated FGFR and FRS2 induced Mek/MAPK activity for germinal vesicle breakdown (GVBD) and substantial H1 kinase activity might be through PI3 kinase activation for *Xenopus* oocyte maturation but not by progesterone (Mood et al. 2002). During progesterone-induced oocyte maturation Mek/MAPK activity is critical for the induction and/or maintenance of H1 kinase activity (Mood et al. 2002).

2.62 Sperm receptor/p350

During fertilization, sperm must first bind in a species-specific manner to the eggs thick extracellular coat, the zona pellucida or vitelline envelope and then undergo a form of cellular exocytosis, the acrosome reaction. Little is known about sperm-binding proteins in egg envelope of vertebrate/invertebrate species. In sea urchin the sperm receptor is phosphorylated by an egg cortical tyrosine kinase in response to sperm or purified ligand (bindin) binding within 20 sec (Abassi and Foltz 1994). In sea urchin egg, a protein (**p350**) was isolated as sperm receptor with the egg plasma membrane-vitelline layer complexes (Giusti et al. 1997) and another report have shown that EBR1 gene product serves a species-specific sperm-interacting protein on the egg vitelline envelope (Kamei and Glabe 2003). In Ascidians (*Halocynthia roretzi*), the sperm-egg binding is mediated by the molecular interaction between HrUrabin, a glycosylphosphatidylinositol-anchored CRISP (cysteine-rich secretory protein)-like protein on the sperm surface and HrVC70 on the polymorphic vitelline coat, but that HrUrabin per se is unlikely to be a direct allorecognition protein (Urayama et al. 2008). In *Xenopus* egg, gp69/64 glycoproteins are two glycoforms in the vitelline envelope and have the same number of N-linked oligosaccharide chains but differ in the extent of O-glycosylation, might serve as sperm receptor (Tian et al. 1999). In *bufo*, gp75 is expressed by previtellogenic oocytes and follicle cells and can be considered as a sperm receptor that undergoes N-terminal proteolysis during fertilization (Scarpeci et al. 2008). mZP3, a zona pellucida glycoprotein that serve as sperm receptor is unique to mammalian eggs, from mice to humans, although related glycoproteins are found in vitelline envelopes of a variety of non-mammalian eggs, from fish to birds (Wassarman and Litscher 2001).

2.63 STAT1/3

Signal transducer and activator of transcription (**STAT**) proteins are transcription factors that play the important roles in fertility and early embryonic development. STAT1 and STAT3 are known to interact with each other and the heterodimer complex enters the nucleus and controls the expression of specific genes. Several studies have reported the association of JAK/STAT signaling pathway with fertility traits in cattle. Genotype combinations of STAT1 and STAT3 are found to promote fertilization and embryonic survival in Holstein cattle (Khatib et al. 2009). Leptin that is secreted from granulosa and follicular cells through the binding of leptin receptor can trigger the phosphorylation of STAT3 during mouse oocyte maturation (Matsuoka et al. 1999). JAK-STAT signaling crucially contributes to early embryonic patterning (Baumer et al. 2011). It was reported that *Drosophila* STAT (STAT92E) in conjunction with Zelda (Zld; Zinc-finger early *Drosophila* activator), plays an important role in the transcription of the zygotic genome at the onset of embryonic development (Tsurumi et al. 2011).

2.64 Stomatin-like protein-2 (SLP-2/STML-2)

Stomatin is an integral membrane protein, which is widely expressed in many cell types. **Stomatin-like protein-2** (SLP-2; p42), a novel and unusual stomatin homologue, has been implicated in interaction with erythrocyte cytoskeleton and presumably with other integral membrane proteins. SLP-2 is overexpressed in human esophageal squamous cell carcinoma, lung cancer, laryngeal cancer, and endometrial adenocarcinoma (Zhang et al. 2006). SLP-2 is a mitochondrial protein, interact with the mitochondrial fusion mediator mitofusin 2 (Mfn2) and might be participate in mitochondrial fusion (Hajek et al. 2007). On the other hand, human erythrocytes and T-cells express plasma membrane-associated SLP-2, where it seems to act as a transmembrane signaling involving protein phosphorylation (Kirchhof et al. 2008; Wang and Morrow 2000). In *Xenopus* eggs, a 40-kDa SLP-2-like protein has been identified as a membrane microdomain-associated protein that becomes tyrosine-phosphorylated by Src in vitro and in vivo (our unpublished results), suggesting that it is a component of sperm-induced tyrosine kinase signaling at fertilization.

2.65 Transcription factor IIIA

In *Xenopus* oocytes, transcription factor IIIA (**TFIIIA**), was isolated from the cytoplasmic 7 S ribonucleoprotein complex and is phosphorylated on Ser by CKII (Westmark et al. 2002). Expression of the TFIIIA gene is differentially regulated in oogenesis, early embryos and in somatic cells in *Xenopus*. The incorporation of histone H1 into chromatin during *Xenopus* embryogenesis directs the specific repression of the TFIIIA-activated transcription of 5S rRNA genes (Bouvet et al. 1994). Phospho-form of TFIIIA may allow the factor to act as repressor for oocyte-type 5S rRNA genes (Ghose et al. 2004). TFIIIA favorably binds to the somatic nucleosome whereas H1 preferentially binds to the oocyte nucleosome, excluding TFIIIA binding in *Xenopus* oocyte (Panetta et al. 1998).

2.66 TPX2

TPX2, targeting protein for *Xenopus* kinesin-like protein (Xklp2), has multiple functions during mitosis, including microtubule nucleation around the chromosomes and the targeting of Xklp2 and Aurora A, a serine/threonine kinase, to the spindle. At the physiological conditions, TPX2 is essential for microtubule nucleation around chromatin (Brunet et al. 2004). TPX2 is required for spindle assembly and spindle pole integrity in mouse oocyte maturation (Brunet et al. 2008). In *Xenopus* oocyte, activation of the centrosomal Aurora A by TPX2 is required during spindle assembly (Sardon et al. 2008). Localized Aurora A kinase activity is required to target the factors involved in microtubule (MT) nucleation and stabilization to the centrosome, therefore promoting the formation of a MT aster (Sardon et al. 2008). In *Xenopus*, TPX2 is required for nearly all Aurora A activation and for full p53 synthesis and phosphorylation during oocyte maturation (Pascreau et al. 2009).

2.67 Tr-kit

The c-kit, a tyrosine kinase receptor, is consists of an extracellular ligand binding domain and an intracellular kinase domain. With the onset of meiosis c-kit expression ceases, but a truncated c-kit product, **Tr-kit**, is specifically expressed in post-meiotic stages of spermatogenesis, and is accumulated in mature spermatozoa (Rossi et al. 2000). Fyn is localized in the cortex region underneath the plasma membrane in mouse oocytes. The interaction of Tr-kit with Fyn, make the Fyn active and that phosphorylate PLCγ1 with the result of Ca^{2+} oscillation (Sette et al. 2002). The truncated c-kit protein is present in primary tumors and shows a correlation between Tr-kit expression and activation of the Src pathway in the advanced stages of human prostate cancer (Paronetto et al. 2004). Recently it was shown that Tr-kit is present in the equatorial region of human spermatozoa, which are the first sperm components that enter into the oocyte cytoplasm after fusion with the egg (Muciaccia et al. 2010).

2.68 Tubulin β

Several studies were carried out to reveal the function of **tubulin** in some species oocytes to embryo because the spindle of vertebrate eggs must remain stable and well organized during the second meiotic arrest. The transition of tubulin from the quiescent oocyte state to that competent to form spindle microtubules may involve the changes in the availability of microtubule and qualitative changes in tubulin mRNAs occurred between the early blastula and hatched blastula stages in sea urchin embryos (Alexandraki and Ruderman 1985). Tubulin β1 mRNA is evenly distributed during early embryogenesis but in later stages of embryogenesis is predominantly expressed in neural derivatives whereas tubulin β3 mRNA is restricted to the mesoderm in *Drosophila* (Gasch et al. 1988). Vg1 RBP is associated with microtubules and co-precipitated by heterologous, polymerized tubulin in *Xenopus* oocytes (Elisha et al. 1995). It was shown recently that Fyn and tubulin are closely associated where Fyn can phosphorylate tubulin and thus SFKs mediate significant functions during the organization of the MII spindle that involves possibly microtubules in rat eggs (Talmor-Cohen et al. 2004). Similarly, well-organized microtubule formation increased the GVBD and MII development in mouse oocytes (Mohammadi Roushandeh and Habibi Roudkenar 2009).

2.69 Ubiquitin-proteasome pathway

The **ubiquitin-proteasome** pathway (Schonfelder et al. 2006) is involved in the degradation of proteins e.g. cyclin B, a regulatory subunit of MPF that are related to oocyte meiotic maturation, fertilization and embryogenesis. Proteasome (26S) catalyzes the ATP- and ubiquitin-dependent degradation of Mos in an early stage of meiotic maturation of *Xenopus* oocytes and egg activation (Aizawa et al. 1996; Ishida et al. 1993). *Xenopus* RINGO/Speedy, a direct activator of Cdk1 and Cdk2, is limitedly processed by UPP to maintenance of G2 arrest and fully degraded by the ubiquitin ligase Siah-2 during MI-MII transition (Gutierrez et al. 2006). UPP is important for oocyte meiotic maturation, fertilization, and early embryonic mitosis and may play its roles by regulating cyclin B1 degradation and MAPK/$p90^{Rsk}$ phosphorylation in pig (Huo et al. 2004a; Sun et al. 2004) and in mouse (Huo et al. 2004b; Karabinova et al. 2011; Tan et al. 2005a). UPP is required for meiotic maturation of rat oocyte (Tan et al. 2005b). In gold fish, cyclin B degradation is initiated by the ATP-dependent and ubiquitin-independent proteolytic activity of 26S proteasome and then the cyclin to be ubiquitinated for further destruction by ubiquitin-dependent activity of the 26S proteasome that leads to MPF inactivation (Tokumoto et al. 1997).

2.70 Uroplakin Ib/III (UPIb/UPIII)

Uroplakins (UP; UPIa, UPIb, UPII, UPIIIa and UPIIIb) were first identified in highly differentiated somatic cells plasma membrane called asymmetric unit membrane (AUM), which is believed to play a protective role. Recently, they were identified in genital tract (Kalma et al. 2009; Shapiro et al. 2000) and germ cells and their function has been described in *Xenopus* fertilization (Mahbub Hasan et al. 2011; Sakakibara et al. 2005; Sato et al. 2006), pathogen infection (Thumbikat et al. 2009a; Thumbikat et al. 2009b) and cancer (Matsumoto et al. 2008). In *Xenopus*, UPIIIa a single transmembrane protein is tyrosine phosphorylated transiently in the cytosolic domain by a tyrosine kinase Src and this tyrosine phosphorylation is required for sperm mediated egg activation. UPIIIa was shaded in the extracellular domain by cathepsin B like activity that is present in sperm and this activity are essential for egg activation and fertilization (Mahbub Hasan et al. 2005; Mizote et al. 1999). UPIIIa can serve as sperm receptor as the antibody against the extracellular domain of UPIIIa inhibited the fertilization (Sakakibara et al. 2005). UPIIIa is an interactive partner of UPIb, a tetraspanin and their interaction is required to negatively regulate the Src activity (Mahbub Hasan et al. 2007).

2.71 Vg1RBP

Xenopus **Vg1RBP** (RNA binding protein), also known as Vera or IMP3, is a member of the highly conserved IMP family of four KH (hnRNP K-homologous)-domain RNA binding proteins, with roles in RNA localization, translational control, RNA stability, and cell motility. *Xenopus* Vg1 mRNA is localized to the vegetal cortex during oogenesis for the regulation of germ layer formation and germ cell development where proteins e.g. Vg1RBP/Vera that specifically recognize the vegetal localization element (VLE) within the 3' untranslated region. It is reported that multiple KH domains are important in mediating RNA-protein and protein-protein interactions in the formation of a stable complex of Vg1RBP and Vg1 mRNA (Git and Standart 2002). PTB/hnRNP I (ribonucleo protein) is required for remodeling of the interaction between Vg1 mRNA and Vg1RBP/Vera in *Xenopus* oocytes (Lewis et al. 2008). Vg1RBP undergoes regulated phosphorylation by Erk2 MAPK during meiotic maturation in *Xenopus* (Git et al. 2009).

2.72 XEEK

The PAR-4 and PAR-1 kinases are necessary for the formation of the anterior-posterior (A-P) axis in *C. elegans*. The *Drosophila* PAR-4 homologue, LKB1, is required for the early A-P polarity of the oocyte, and for the repolarization of the oocyte cytoskeleton that defines the embryonic A-P axis in *Drosophila* (Martin and St Johnston 2003) and in mouse (Szczepanska and Maleszewski 2005). PKA phosphorylates *Drosophila* LKB1 on a conserved site that is important for its activity(Martin and St Johnston 2003). **LKB1/XEEK1** (*Xenopus* egg and embryo kinase 1) is found to exist in a complex with GSK3 and PKC, a known kinase for GSK3 and to regulate GSK3 phosphorylation resulting in increased Wnt-catenin signal in *Xenopus* embryonic development and mammalian cells (Clements and Kimelman 2003; Ossipova et al. 2003).

2.73 Xp95

In *Xenopus* oocytes, a protein X**p95** is tyrosine-phosphorylated from the first through the second meiotic divisions during progesterone-induced oocyte maturation. The Xp95 protein sequence exhibited homology to mouse Rhophilin, budding yeast Bro1, and *Aspergillus* PalA, all of which are important in signal transduction (Che et al. 1999). Src kinase mediated phosphorylation of Xp95 was increased during oocyte maturation (Che et al. 1999). Xp95 is phosphorylated at multiple sites within the N-terminal half of the proline-rich domain (PRD) during *Xenopus* oocyte maturation and the phosphorylation may both positively and negatively modulate their interaction with partner proteins at different stage of cell cycle (Dejournett et al. 2007). Human homologue of Xp95, termed Hp95, induces G1 phase arrest in confluent HeLa cells when overexpressed (Wu et al. 2001).

2.74 Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (YWHA)/14-3-3

The tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein family (**YWHA**; also known as 14-3-3) are involved in the regulation of many intracellular processes. PKB, PKC and JNK target 14-3-3 to phosphorylate at different sites (Aitken 2006). YWHA might play the role regulating peptidylarginine deiminase type VI (PADI6), that undergo a dramatic developmental change in phosphorylation during mouse oocyte maturation until two cell stage (Snow et al. 2008). 14-3-3 protein binds to Cdc25C and inhibits dephosphorylation of Ser-287 by PP2A, allowing the arrest in the meiotic metaphase II in *Xenopus* oocytes (Hutchins et al. 2002). If 14-3-3 binding to Cdc25 is prevented while nuclear export is inhibited, the coordinate nuclear accumulation of Cdc25 that dephosphorylates Cdc2-cyclin B1 to make it active, which promotes oocyte maturation (Yang et al. 1999).

3. Conclusion

Since the discovery in the late 1800's of the gamete membrane interaction and fusion as an initial and indispensable process for the beginning of life, i.e. fertilization, a number of research have dealt with the molecular and cellular basis of fertilization. In this chapter, we have reviewed the structure and function of key molecules likely involved in the phospho-signaling at oocyte maturation, sperm-egg interaction and subsequent events for activation of development, collectively called "egg activation". This work is an updated version of the review paper that we published in 2000 (Sato et al. 2000a), and thus a special focus point in this chapter is the kinases (both tyrosine kinases and serine/threonine kinases, total number of 53) and their regulators and/or substrates expressed in oocytes/eggs and/or early embryos of animal species (including some algae, total number of 74). We have compiled the currently available knowledge in the molecular level to explore the general as well as the species-specific features of oocyte maturation and fertilization, which is widely employed as an only-one strategy to give rise to a newborn in the bisexual reproduction system. It seems that number of kinases and their regulators/substrates will still be growing from day to day, and we may miss some important molecules in this chapter: we would continue to update that information not cited here in a future. Although the phospho-signaling system is just one kind of the post-translational modifications of cellular proteins, other kinds of steps e.g. transcriptional regulations or post-transcriptional modifications would also contribute to oocyte maturation and fertilization. We hope that this chapter could be helpful and enthusiastic for the readers in any kind of research field that deals with molecular (in particular, cellular proteins') network involved in physiological and/or pathological features of biological system.

4. Acknowledgements

We apologize to those whose work was not cited or insufficiently cited. This work is supported by a Grant-in-Aid on Innovative Areas (22112522), and a grant for Private University Strategic Research Foundation Support Program (S0801060) from the Ministry of Education, Culture, Sports, Science and Technology, Japan to K.S.

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ISBN 978-953-51-0466-7
Hard cover, 652 pages
Publisher InTech
Published online 20, April, 2012
Published in print edition April, 2012