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Phospho-Signaling at Oocyte Maturation and Fertilization: Set Up for Embryogenesis and Beyond Part I. Protein Kinases

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1. Introduction

In the field of developmental biology, day by day data are accumulated to describe the molecular mechanisms involved in gamete cell production (oogenesis and spermatogenesis) and the sperm-egg interaction/fusion (fertilization) leading the formation of zygote to embryo (embryogenesis) that ultimately develop into a complete body. Here, we will review how *oocyte maturation*, sperm mediated *egg activation/fertilization* and early steps of *embryogenesis* are accomplished and regulated through protein phosphorylation(s) highlighting the participating molecules (e.g. protein kinases) (**this chapter**) and their regulators and substrates (**another chapter entitled "Part II. Kinase Regulators and Substrates"**). Meiosis is the process by which diploid germ-line cell reduces their number of chromosomes in half to generate haploid gamete and combine with opposite sex haploid gamete to create a genetically new, diploid individual. Oocyte maturation, which undergoes two meiotic cell cycles that arrest at several stages, has been studied extensively in many species of vertebrates and invertebrates. A lot of review articles on oocyte meiotic maturation of different species have been written (Kang and Han 2011; Liang et al. 2007; Machaca 2007; Madgwick and Jones 2007; Schmitt and Nebreda 2002a; Tripathi et al. 2010). In almost all vertebrates, oocyte meiotic cell cycle starts during fetal life (at 4-5 weeks) but arrest at first in diplotene stage of first meiotic prophase (before the metaphase I or MI) that may last for several months or years in follicular microenvironment depending on the species (Mehlmann and Jaffe 2005; Sirard 2001; Trounson et al. 2001; Wassmann et al. 2003). The progression of meiotic cell cycle is also arrested, in many but not all species, at stages of second meiotic metaphase II (MII) and/or metaphase-like arrest (MIII). During oocyte

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maturation different kinds of molecules e.g. second messengers, protein kinases, protein phosphatases and their regulator and/or substrate proteins are involved. Here, the molecular mechanisms involved in the arrest and resumption of these stages will be discussed briefly.

MPF (maturation or M-phase promoting factor), a serine/threonine kinase, is composed of a catalytic subunit cyclin-dependent kinase 1 (Cdc2/CDK1), and a regulatory subunit, cyclin B; are the key components in the maintenance of diplotene arrest. In activated MPF, dephosphorylated CDK1 is associated with cyclin B and both cyclin B synthesis and degradation is required for MPF activity (Clarke and Karsenti 1991; Ledan et al. 2001). Cyclin B is accumulated in diplotene-arrested oocytes due to the presence of early mitotic inhibitor1 (Emi1) that inhibits anaphase promoting complex/cyclosome (APC/C), an ubiquitin ligase complex responsible for the destruction of cyclin B (Marangos et al. 2007). In oocyte, the level of cGMP and cAMP are very high and they are secreted from cumulus and granulosa cells surrounding the oocyte and are essential for the maintenance of meiotic arrest at diplotene stage (Norris et al. 2009; Sirard and Bilodeau 1990b; Sun et al. 2009; Vaccari et al. 2008). The increased level of cGMP inactivates phosphodiesterase 3A (PDE3A) and prevents hydrolysis of cAMP thus further increase its level (Mayes and Sirard 2002; Tsafriri et al. 1996; Vaccari et al. 2008). In diplotene-arrested oocytes, high concentrations of cAMP activate protein kinase A (PKA), and activated PKA phosphorylates two CDK1 regulators such as cell division cycle 25 homologue B (Cdc25B) phosphatase (Pirino et al. 2009) and Wee1/Myt1 (myelin transcription factor 1) kinase (Han and Conti 2006; Stanford and Ruderman 2005). The inactivation of Cdc25B and activation of Wee1/Myt1 kinase ultimately inactivate MPF activity for the maintenance of meiotic arrest at diplotene stage (Han and Conti 2006; Potapova et al. 2009; Solc et al. 2010). Luteinizing hormone (LH) released from surrounding granulosa cells act indirectly on oocytes to resume diplotene arrest at the onset of puberty (Mehlmann 2005; Zhang et al. 2009). LH mediated MAPK activation in granulosa cells interrupts the cells-oocytes communications and the result is the decrease of cAMP and cGMP level in oocytes (Liang et al. 2007; Mehlmann 2005; Norris et al. 2009). Reduced level of intraoocyte cGMP causes the activation of PDE3A activity that further reduces the intra oocyte cAMP level (Tornell et al. 1991; Wang et al. 2008). Net reduction of cAMP in oocytes inhibits PKA actions and dephospho-form of Cdc25B phosphatase remains active (Han and Conti 2006). On the other hand, dephospho-form of Wee1/Myt1 kinase remains inactive (Han and Conti 2006; Liang et al. 2007; Mehlmann et al. 2002; Solc et al. 2010) and finally resumes the diplotene arrest that is morphologically characterized by germinal vesicle breakdown (GVBD).

Getting release from diplotene arrest, activated MAPK through proper organization of metaphase spindle makes the progression of MI when homologous chromosomes are segregated (Sirard and Bilodeau 1990a). Oocytes are arrested at MI until the entire sister chromatids properly attached to the bipolar spindle and aligned at the metaphase plate where spindle assembly checkpoint (SAC) proteins e.g. Mad2 (metaphase arrest deficient 2), Bub1, and Bub3 (budding uninhibited by benzimidazole 1 and 3) act for all the required activities (Hupalowska et al. 2008; Li et al. 2009; Niault et al. 2007; Wassmann et al. 2003). The SAC proteins for accurate homologous chromosome segregation and to delay anaphase onset target APC/C (Brunet and Maro 2005; Homer 2011; Wassmann et al. 2003). Formation of functional spindle, spindle migration correlates with the progressive increase and

continuous MPF activity (Brunet and Maro 2005; Madgwick et al. 2004). Mos/MAPK activity is also important in microtubule reorganization and positioning of metaphase spindle to the oocyte cortex (Choi et al. 1996; Verlhac et al. 1996; Zhou et al. 1991). At the end of MI, MPF activity is declined and is characterized by first polar body extrusion. After completion of MI, oocytes undergo some cytoplasmic changes and progress to the arrest at MII with further high MPF activity until fertilization. Stabilization of MPF activity is maintained by CSF (cytostatic factor) activity, not a single molecule but a total activity (Madgwick and Jones 2007; Wu and Kornbluth 2008) and by Mos-mediated MAPK pathway (Perry and Verlhac 2008; Shoji et al. 2006). Emi1 and Emi2 are two members of Emi/Erp family of proteins that has also the CSF activity (Schmidt et al. 2006) and functions in MII arrest (Madgwick and Jones 2007; Schmidt et al. 2006; Shoji et al. 2006; Tang et al. 2008). Complex of dephosphorylated active Emi2 with Cdc20, inhibit APC/C for the maintenance of MII arrest (Shoji et al. 2006). Sperm mediated Ca^{2+} oscillation activates calcium/calmodulin-dependent protein kinase II (CaMKII) and Emi2 can be phosphorylated by activated CaMKII followed by further phosphorylation by polo-like kinase (Hansen et al. 2006; Madgwick and Jones 2007; Masui and Markert 1971; Shoji et al. 2006). Cdc20 is released from Emi2 and subsequently bind with APC/C that results an active APC/C complex (Liu et al. 2006). Activated APC/C induces the degradation of cyclin B and MPF activity is decreased with an exit of egg from MII arrest by a process of sperm-egg interaction and fusion called fertilization. Another mechanism of MII arrest is by Mos (pp39, serine/threonine kinase), a proto-oncogene product act in the upstream of MEK/MAPK pathway that ultimately activates ribosomal protein S6 kinase ($p90^{Rsk}$). $p90^{Rsk}$ induces SAC protein activation and thereby inhibition of APC/C (Madgwick and Jones 2007; Maller et al. 2001) to maintain MII arrest. At fertilization Mos is degraded while the MEK/MAPK/$p90^{Rsk}$ is shortly inactivated and release from MII arrest. To the end of this process the sister chromatids are segregated, second polar body is extruded and the first cleavage starts. Postovulatory oocytes mimic the action of egg activation due to aging, increases cytoplasmic Ca^{2+}, and induces exit from MII arrest but they do not progress further and get arrest again in a new metaphase-like stage called MIII in few vertebrate species though the mechanisms for MIII arrest is not well understood (Chaube et al. 2007; Galat et al. 2007; Vincent et al. 1992; Zernicka-Goetz 1991). In aged eggs insufficient Ca^{2+} release and sufficient CSF activity is still present to stabilize the residual or newly formed MPF activity results in MIII arrest (Kubiak et al. 1992; Vincent et al. 1992).

Sperm-induced release of MII of an egg is also termed as "egg activation" that is characterized by so many biochemical changes e.g. Ca^{2+} oscillations, cortical granules exocytosis to block polyspermy, the formation of polar body and male and female pronuclei, recruitment of maternal mRNAs, initiation of DNA synthesis for mitotic divisions to unveil the complete developmental program (Ducibella 1996; Ducibella and Fissore 2008; Schultz and Kopf 1995). The wave of Ca^{2+} initiates at the site of sperm binding/fusion and soon after a wave of intracellular Ca^{2+} traverses the entire volume of the egg (Gilkey et al. 1978; Miyazaki and Ito 2006; Runft et al. 2002; Steinhardt and Epel 1974; Stricker 1999; Whitaker 2006). It is interesting to note that the increase in Ca^{2+} was reported in lysates of sea urchin eggs more than quarter century ago (Mazia 1937). Several excellent review articles have been published describing how egg becomes active in fertilization dependent manner and unite with sperm nuclei to form a zygote (Ajduk et al. 2008; Ducibella and Fissore 2008; Horner and Wolfner 2008; Miyazaki and Ito 2006; Swann et al. 2006; Townley et al. 2006).

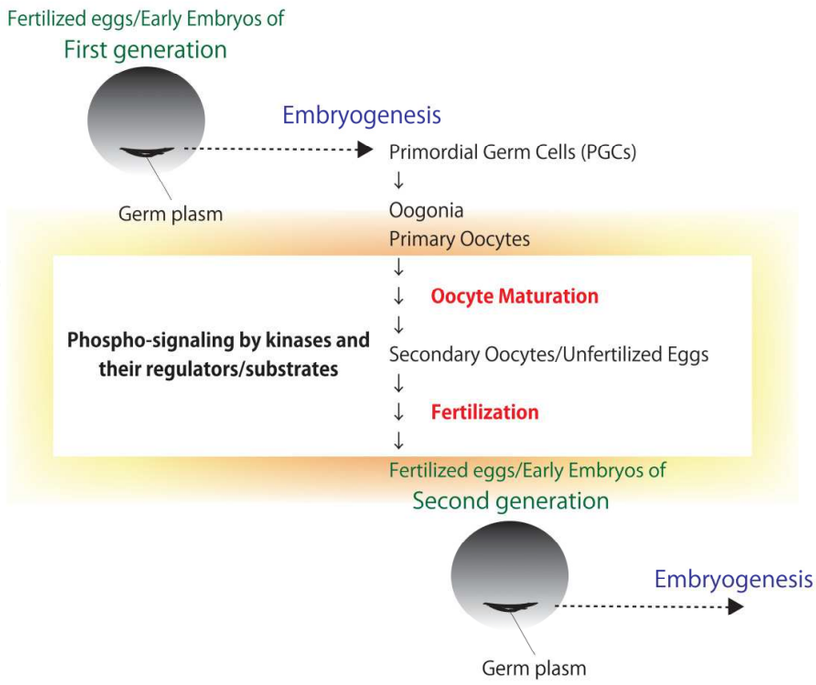

Fig. 1. Germline transmission from one generation to the next generation in sexual reproduction system. In most vertebrate species, the primary oocytes (or immature oocytes) in ovarian tissue pauses their cell cycle at prophase of the first meiosis, resumes the meiosis in response to hormonal signals, re-pauses at metaphase of the second meiotic cell cycle as the secondary oocytes (or mature oocytes), and are subject to ovulation and fertilization. Upon fertilization, eggs undergo a series of extracellular and intracellular reactions/changes, collectively called egg activation that triggers the initiation of development or early embryogenesis. A similar mechanism, although not identical in several species, has been shown to be involved in sexual reproduction system in a diverse array of animal species and maybe in some algae and plants.

Oocyte plasma membrane is surrounded by glycoprotein-rich extracellular matrix called the vitelline envelope (VE) or vitelline membrane (VM) in invertebrates and amphibians, and zona pellucida (ZP) in mammals. Upon fertilization this layer must be modified to prevent additional sperm to bind and fuse to block the polyspermy. Prevention of polyspermy is accomplished in part through Ca^{2+}-dependent cortical granule exocytosis (CGE) (Wessel et al. 2001; Wessel and Wong 2009). Upon egg activation, CGE fuse with the oocyte plasma membrane and release their contents into the perivitelline space that results the biochemical modification of the outer membrane. Ca^{2+}-mediated active CaMKII phosphorylate Emi2 that is further phosphorylated by polo-like kinase and this phosphorylated Emi2 is targeted by APC/C resulting in an active APC/C (Liu and Maller 2005; Rauh et al. 2005). Activated APC/C leads to the degradation of cyclin B that results the inactivation of Cdc2 and might also inactivate the function of Mos (Castro et al. 2001; Madgwick et al. 2006; Madgwick and Jones 2007). Thus, due to the absence of Cdc2/CDK1 activity, meiosis-specific host protein phosphorylations are reduced allowing eggs to exit M-phase. Src family tyrosine kinases (SFKs) are playing important roles in sperm-induced Ca^{2+} oscillation in several species e.g. in starfish (Abassi et al. 2000; Carroll et al. 1999; Giusti et al. 1999a, 1999b), Fyn kinase in sea

urchin eggs (Kinsey and Shen 2000) and in rat eggs (Talmor et al. 1998), and Src in frog eggs (Sato et al. 1996; Sato et al. 2006a). In mouse eggs though Src related tyrosine kinase (e.g. Lck, Src) has been reported (Mori et al. 1991) but it is not sufficient or required for fertilization-induced Ca^{2+} oscillation (Kurokawa et al. 2004). In mammals, PLC activity is high enough in sperm that's why even a single sperm equivalent PLC can generate sufficient IP_3 when introduced into the egg cytoplasm (Rice et al. 2000). ζ isoform of PLC present in sperm has been characterized as a soluble sperm factor that evokes Ca^{2+} oscillations in eggs of several mammals e.g. mouse, bovine and human (Malcuit et al. 2005; Rogers et al. 2004; Saunders et al. 2002). Thus upon successful fertilization, the newly formed zygote initiates the developmental program through early stages of embryogenesis until a full different born.

2. Kinases in oocyte maturation, fertilization and activation of development

2.1 Abelson tyrosine kinase (Abl)

Abl has been originally identified as the oncogene product (termed v-Abl) of Abelson murine leukemia virus (Wang et al. 1983). In human, the cellular homolog of v-Abl, c-Abl, is translocated to the Philadelphia chromosome in chronic myelocytic leukemia (so-called Philadelphia syndrome) (de Klein et al. 1982). Gleevec (STI-571), a well-known drug for chronic myeloid leukemia (CML) and some other cancers, has been designed to target the protein product of the CML transforming gene, Bcr (breakpoint cluster region)-Abl (Schindler et al. 2000). In the sea urchin, a 220-kDa Abl-related tyrosine kinase has been identified in the egg cortex. Immunoprecipitation studies demonstrated that it is activated within minutes of fertilization, suggesting a possible role for sperm-induced egg activation, and immunofluorescent studies showed its association with cortical cytoskeleton (Moore and Kinsey 1994; Walker et al. 1996; Wang et al. 1983). However, its mode of activation and physiological substrate has not yet been demonstrated.

2.2 Akt protein kinase (Akt)

The serine/threonine-specific protein kinase **Akt** has been identified first as the oncogene product of murine transforming retrovirus. Because of its structural homology in the catalytic domain to protein kinase A (PKA) and C (PKC), an alternative term "protein kinase B or PKB" is sometimes used. Akt is shown to be involved in several aspects of cellular functions, and most frequently, it is regarded as a kinase that promotes anti-apoptotic growth of cells (Hemmings 1997). Upstream kinases, such as phosphoinositide-dependent protein kinase 1 (PDK1) and mammalian target of rapamycin (mTOR), are responsible for phosphorylation and activation of Akt. Thus, Akt is regulated by metabolism of membrane-bound phosphoinositides as well as extracellular nutrient environments. Akt is shown to be involved in oocyte maturation in some species (e.g. starfish, mouse, and maybe *Xenopus*) (Deng et al. 2011; Feng et al. 2007; Han et al. 2006; Hoshino and Sato 2008; Hoshino et al. 2004; Kalous et al. 2009; Kalous et al. 2006; Mammadova et al. 2009; Okumura et al. 2002; Reddy et al. 2005; Tomek and Smiljakovic 2005; Zhang et al. 2010b). For example, Akt phosphorylation and down-regulation of Myt1, an MPF-inhibitory kinase, and PDE3, a cAMP-antagonizing enzyme, in maturing starfish and mouse oocytes have been demonstrated (Han et al. 2006a). On the other hand, fertilization promotes an activating phosphorylation (on Thr-308) of Akt in *Xenopus* (Mammadova et al. 2009), suggesting its possible role in initiation of development and/or suppression of cell death.

2.3 Adenosine 5'-monophosphate-dependent protein kinase (AMPK)

AMPK is a serine/threonine kinase that is activated in response to high AMP and/or low ATP levels in the cell. AMPK is composed of three subunits; one catalytic subunit and two regulatory subunits, all of which are evolutionary conserved in budding yeast as the SNF1 protein kinase complex (Hardie and Carling 1997). AMPK is phosphorylated and activated by an upstream AMPK kinase. Inhibitory effect of AMP and/or AMPK on oocyte maturation and/or meiotic resumption has been demonstrated in marine worm, starfish, and some mammalian species (Bilodeau-Goeseels et al. 2007; Chen and Downs 2008; Chen et al. 2006; LaRosa and Downs 2006; Stricker 2011; Stricker and Smythe 2006; Stricker et al. 2010b; Tosca et al. 2007). In marine worm, liver kinase B1 (LKB1)-like kinase is likely involved in up-regulation of AMPK (via phosphorylation of Thr-172), and thus suppresses the occurrence of oocyte maturation. On the other hand, MAPK and MPF are shown to simultaneously phosphorylate AMPK on two sites (Ser-485/491), and thereby inactivate the activity of AMPK. Physiological target of AMPK in this species is under investigation.

2.4 Aurora protein kinase (Aurora A/B/C/AIR-2/Eg2/IAK2/Ipl1p)

Aurora is a serine/threonine kinase that has been initially characterized as a protein that regulates proper chromosomal segregation and cytokinesis (Bischoff and Plowman 1999). In *C. elegans*, AIR-2 (homolog of aurora kinase) is involved in the release of chromosomal cohesion. In *Xenopus*, Eg2 (an alternative name of this kinase) has been shown as a component of progesterone-induced maturation of oocytes. H3 histone, a linker histone that regulates the integrity of nucleosome core, has been identified a substrate of aurora in mouse and porcine oocytes. Another substrate known to date includes cytoplasmic polyadenylation element-binding protein (CPEB) that regulates translation of mRNA for Mos, and maskin that regulates the assembly of microtubules. Analyses of cell-free extracts demonstrated that protein phosphatase 2A (PP2A) is responsible for suppression of MPF, which is an upstream activator for aurora kinase. In the meiotic and mitotic exit, aurora undergoes degradation under the control of APC/C interaction with the APC/C recognition domain of aurora kinase. Thus aurora kinase behaves like a component of cytostatic factor (e.g. cyclin, Mos) (Andresson and Ruderman 1998; Detivaud et al. 2003; Ding et al. 2011; Eckerdt et al. 2009; Frank-Vaillant et al. 2000; Hodgman et al. 2001; Jelinkova and Kubelka 2006; Kinoshita et al. 2005; Littlepage and Ruderman 2002; Littlepage et al. 2002; Ma et al. 2003; Maton et al. 2005; Maton et al. 2003; Mendez et al. 2000; Pascreau et al. 2005; Pascreau et al. 2008; Pascreau et al. 2009; Rogers et al. 2002; Roghi et al. 1998; Sardon et al. 2008; Yang et al. 2010b).

2.5 Calmodulin-dependent protein kinase II (CaMKII)

CaMKII is a serine/threonine-specific kinase that is regulated by the intracellular concentration of Ca^{2+} ions. Biochemical analyses demonstrated that the binding of Ca^{2+}/calmodulin to the catalytic core of the kinase as well as the release of an autoinhibitory region from the kinase domain coordinately activates the enzyme (Ishida and Fujisawa 1995). Gene targeting analyses have demonstrated that this kinase is involved in synaptic plasticity such as the long-term potentiation in hippocampus (Silva et al. 1992a; Silva et al. 1992b). In mammalian oocytes and cell-free extracts prepared from *Xenopus* unfertilized eggs, the kinase activity of CaMKII oscillates in response to sperm-induced Ca^{2+} oscillations,

well-known phenomenon that is required for the meiotic exit and initiation of embryonic development. The activated CaMKII is believed to be involved in the initiation of signaling cascade involving cyclin/Mos degradation and calcineurin/Rsk activation, both of which leads to the inactivation of Emi2, a suppressor of meiotic exit (Ducibella and Fissore 2008; Hansen et al. 2006; Hudmon et al. 2005; Liu and Maller 2005; Madgwick et al. 2005; Nishiyama et al. 2007b; Nutt et al. 2005).

2.6 Casein kinase II (CKII/CK2)

CKII is a family of serine/threonine-specific kinases that are ubiquitously expressed in eukaryotic organisms including budding yeast (Glover 1998). In the oocyte of *Xenopus*, CKII is shown to localize to the nucleus and transcription factor IIIA has been identified as a substrate of CKII (Leiva et al. 1987; Sanghera et al. 1992; Westmark et al. 2002). CKII can be regulated by PKC and other serine/threonine kinases, and therefore it may be involved in sperm-induced egg activation as well. In this respect, the fact that CKII phosphorylates a serine/threonine residue in the cytoplasmic sequence of uroplakin IIIa (UPIIIa) in uropathological bacteria-infected human urinary bladder cells is interesting. As UPIIIa in *Xenopus* eggs has been suggested to be important for sperm-egg interaction and subsequent phospho-signaling for egg activation (see below) (Mahbub Hasan et al. 2011), CKII may also be an important player in the same system through the phosphorylation of UPIIIa.

2.7 Cyclic AMP-dependent protein kinase (cAPK/PKA)

Inactive **PKA** is a tetrameric protein that is composed of two catalytic subunits and two regulatory (or inhibitory) subunits, latter of which, when cAMP binds, is released from the catalytic subunits. The discovery of AMP as well as PKA as intracellular mediators of several extracellular signal-dependent cellular functions has opened firstly a window of the research field of "phospho-signal transduction" (Robison et al. 1968), followed by discoveries of other important factors such as PKC, receptor/kinase and Src. In vertebrate oocytes, activity of PKA is shown to decrease by phosphodiesterase (PDE)-mediated decrease of intracellular cAMP and then re-increase upon meiotic maturation, and its active state is maintained until fertilization. Upon fertilization, PKA undergoes a rapid decline in its activity. Transition from mitotic phase to interphase in fertilized egg requires MPF-dependent PKA activity. In mammals, maturing oocytes involves PKA phosphorylation of Cdc25B tyrosine phosphatase that leads to up-regulation of MPF activity. In marine worm, AMPK activity has been implicated in oocyte maturation, suggesting that intracellular balance of cAMP and AMP concentrations, as regulated by PDE and adenylate cyclase, is important for oocyte functions (Bornslaeger et al. 1986; Browne et al. 1990; Daar et al. 1993; Faure et al. 1998; Faure et al. 1999; Grieco et al. 1994; Grieco et al. 1996; Matten et al. 1994; Meijer et al. 1989b; Newhall et al. 2006; Pirino et al. 2009; Schmitt and Nebreda 2002a, 2002b; Stricker and Smythe 2006; Stricker et al. 2010b; Wang and Liu 2004; Webb et al. 2008; Yu et al. 2005; Zhang et al. 2008).

2.8 Cyclin-dependent protein kinase (Cdc2/CDK/MPF)

The term "cdc" refers *cell division cycle* and has originally been coined in the study of yeast genetics. While the genetic background as well as biochemical and molecular biological

identifications of key regulators for cell division cycle (i.e. several **cdc/CDK** kinases and cyclins) have firstly been demonstrated in the studies of such model organisms as yeast, sea urchin, and clam (Hartwell 1991; Minshull et al. 1989; Nurse 1990), early studies with use of frog oocytes has also contributed to arise a concept of **MPF** (maturation/mitosis-promoting factor) (Masui 1992). It is well known that cdc/CDK kinases are mainly responsible for meiotic cell cycle progression in maturing oocytes, and thereafter acts as an essential component of mitotic cell cycles. Regulatory mechanism of cdc/CDK kinases involves a complex combination of phosphorylation/dephosphorylation on a threonine and tyrosine residues in the ATP-binding pocket (e.g. Wee1, Myt1, Cdc25, PP2A) and a threonine residue in the catalytic domain of cdc/CDK kinase (i.e. CAK kinase), and protein level of activator proteins (e.g. cyclin and RINGO/speedy) and inhibitor proteins (e.g. p16 and p21). Kinase activity of cdc/CDK/MPF has been sometimes regarded as "histone H1 kinase (H1K or HH1K)" because of its in vitro evaluation. Cellular targets of cdc/CDK kinases include aurora kinase and Emi2, which are implicated in chromosomal integrity and meiotic arrest, respectively (Anger et al. 2004; Castilho et al. 2009; Culp and Musci 1999; Eckberg 1997; Edgecombe et al. 1991; Ferrell 1999; Ferrell et al. 1991; Gavin et al. 1999; Grieco et al. 1996; Gutierrez et al. 2006; Karaiskou et al. 1998; Karaiskou et al. 2004; Katsu et al. 1999; Kume et al. 2007; Kuo et al. 2011; Lohka et al. 1988; Masui 2000; Maton et al. 2005; Maton et al. 2003; Meijer et al. 1989a; Meijer et al. 1991; Meijer et al. 1989b; Palmer et al. 1998; Qian et al. 2001; Rime et al. 1994; Ruiz et al. 2008; Sakamoto et al. 1998; Tang et al. 2008; Tokmakov et al. 2005; Wu et al. 2007b; Yu et al. 2005; Yu et al. 2004).

2.9 Dual-specificity tyrosine-regulated kinase 1A/2 (DYRK)/Minibrain-related kinase (Mirk)/MBK-2/Nuclear kinase

DYRK is a dual-specificity protein kinase, whose expression in a wide variety of animal species (e.g. Yak1 in yeast, Mnb in fly, Dyrk1~4 in mammals) has been reported. Tyrosine autophosphorylation in the activation loop is important for enzyme activation of DYRK as a serine/threonine kinase. A similar scheme of kinase regulation has been shown in some other kinases including MAPK, so DYRK is regarded as a member of the MAPK superfamily (Miyata and Nishida 1999). DYRK has been implicated in neurobiological disease such as Down syndrome, cell proliferation and anti-apoptosis in cancer cells, and cell cycle control (Becker 2011; Becker and Sippl 2011). In nematode oocytes, DYRK2/MBK2, a member of DYRK, in cooperation with CDK1 (this kinase catalyses activating phosphorylation of MBK-2 on Ser-68) (Cheng et al. 2009), GSK3, and Kin-19, phosphorylates and promotes degradation of OMA-1 that regulates oocyte-to-embryo transition (Nishi and Lin 2005; Qu et al. 2006; Qu et al. 2007; Stitzel et al. 2007; Stitzel et al. 2006). In *Xenopus* oocytes, Ras-dependent oocyte maturation involves the function of DYRK1A (Qu et al. 2006; Qu et al. 2007).

2.10 Epidermal growth factor receptor (EGFR/HER1)

EGFR is a prototype of the cell surface receptor/kinase that consists of an extracellular ligand -binding domain, a transmembrane hydrophobic sequence, and a cytoplasmic kinase domain that is followed by a non-catalytic sequence, which contains some tyrosine residues to be autophosphorylated in activated molecules. Normally, EGFR is activated by EGF-dependent dimerization (activation as tyrosine kinase) and autophosphorylation (activation

as phosphotyrosine-dependent docking protein). Its oncogenic counterpart has been found in avian sarcoma virus that encodes v-erbB, whose protein product lacks entirely the extracellular domain so that the kinase activity is constitutively elevated irrespective of the presence of EGF. While a variety of cellular functions (e.g. normal and malignant growth in several kinds of cells and tissues) have been shown to involve EGF and EGFR, its contribution to oocyte maturation and fertilization remains unclear. In *Xenopus* eggs, ectopically expressed EGFR is capable of inducing egg activation in an EGF-dependent manner (Yim et al. 1994). This could be explained as that active tyrosine kinase can mediate the process of egg activation in this system. In fact, it has been shown that *Xenopus* eggs employ an endogenous tyrosine kinase-dependent egg activation system involving Src and PLCγ.

2.11 ErbB4/HER4

ErbB4 is a member of the EGFR (ErbB1/HER1)/HER family of receptor/tyrosine kinases. Although its involvement in oocyte maturation and fertilization has not yet been shown, implantation of mammalian early embryos involves the actions of ErbB4 and its cognate ligand heparin-binding EGF-like growth factor (HB-EGF) (Chobotova et al. 2002). In this system, metalloproteinase-dependent extracellular shedding of HB-EGF is required for survival of trophoblasts at low oxygen conditions (Armant et al. 2006; Jessmon et al. 2009), one of pro-apoptotic pressures in the embryogenic microenvironment at early stages of pregnancy.

2.12 Focal adhesion kinase (FAK)

FAK is a cytoplasmic tyrosine kinase, whose activity is stimulated by integrin-dependent cell-extracellular matrix (ECM) interactions. Namely, in response to heterodimeric interaction with the ECM-activated integrin α and β subunits, FAK undergoes autophosphorylation and then phosphorylated by Src on tyrosine residues. The activated FAK undergoes a number of molecular interactions with cytoskeletal and signaling proteins, including Src, phosphatidylinositol 3-kinase (PI3K), Grb2, $p130^{Cas}$ and paxillin (Cary and Guan 1999). Recent studies also highlight the interaction of FAK with cell cycle control system (e.g. CDK5), pro-apoptotic system (e.g. p53), and cadherin-dependent cell-cell communications (Golubovskaya and Cance 2010; Quadri 2011; Xie et al. 2003). On the other hand, roles of FAK in gamete interaction and gametogenesis have not yet been fully documented. Developmental expression of FAK in porcine oocytes (Okamura et al. 2001) and in *Xenopus* oocytes and early embryos (Hens and DeSimone 1995; Zhang et al. 1995) have only been reported.

2.13 Fer tyrosine kinase (Fer)

DNA microarray analysis demonstrates that Feline encephalitis virus (FES)-related tyrosine kinase protein, named **FER**, is highly expressed in oocytes of the mouse (McGinnis et al. 2011a). It shows a uniform distribution in the ooplasm of small oocytes, but becomes concentrated in the germinal vesicle (GV) during oocyte growth. Association of FER with spindle bodies is seen after GV breakdown (GVBD), suggesting that it is involved in the control of cell cycle and/or chromosomal dynamics (McGinnis et al. 2011b). In support with

this, siRNA-mediated knockdown of FER causes the failure of the oocytes to undergo GVBD or during MI (McGinnis et al. 2011b). While upstream and downstream mediators of FER regulation and functions have not yet been shown, other cell systems so far analyzed demonstrate that phospholipase D (PLD)-phosphatidic acid (PA) pathway is capable of stimulating FER activity (Itoh et al. 2009), and that TATA-element modulatory protein is a substrate of nuclear-localized FER (Schwartz et al. 1998). The former fact is of interest because, in amphibian (*Rana pipiens*) oocytes, progesterone-induced oocyte maturation involves a rapid activation of PLD (Kostellow et al. 1996).

2.14 Fibroblast growth factor receptor-1/-2 (FGFR1/2)

To date, 22 members of FGF family of growth factors and 4 members of **FGFR** family of receptor/tyrosine kinase have been identified in human. The FGF-FGFR system is activated in concert with heparin and heparan sulfate proteoglycan on the cell surface, and phosphorylates a number of intracellular substrate to promote a variety of cellular functions (Eswarakumar et al. 2005). In *Xenopus* maturing oocytes, translational activation of FGFR1 has been demonstrated. In the same system, overexpressed FGFR by itself can promote oocyte maturation in response to FGF stimulation, through interaction and/or phosphorylation of the SNT1/FRS2 adaptor protein. In bovine oocytes, FGF10 is shown to enhance the maturation and developmental competence (Zhang et al. 2010a), suggesting that oocytes contain the endogenous and functional FGFR. Developmental expression of FGFR has also been demonstrated in *Xenopus* and zebrafish. However, its involvement in fertilization has not yet been shown (Cailliau et al. 2003; Culp and Musci 1998; Culp and Musci 1999; Mood et al. 2002; Rappolee et al. 1998; Robbie et al. 1995; Tonou-Fujimori et al. 2002).

2.15 Fyn tyrosine kinase (Fyn)

Fyn, 59-kDa protein, is a member of Src family of non-receptor tyrosine kinases (SFKs). Like Src and Yes, another kind of SFK, Fyn is ubiquitously expressed in human tissues and its pleiotropic contribution to cellular functions (e.g. T-lymphocyte activation, spatial learning, and alcohol sensitivity) has been well documented (Palacios and Weiss 2004; Resh 1998; Trepanier et al. 2011). Oocyte-expressing Fyn and Fyn-related protein have been characterized extensively not only in vertebrates (e.g. mammals and fish) but also in sea invertebrates (sea urchin). In sea urchin, sperm-induced tyrosine phosphorylation of oocyte/egg proteins is mainly due to the activated Fyn and Src (and maybe Abl). In this species, tyrosine phosphorylation of phospholipase Cγ (PLCγ) plays an important role in inositol trisphosphate (IP_3)-induced Ca^{2+} release. A similar tyrosine kinase-PLCγ pathway also operates in starfish, ascidian, fish, and frog. In mice and rats, Fyn is shown to interact with tubulin and involve in cleavage furrow ingression during meiosis and mitosis. Another report demonstrates that Fyn contributes to establish and maintain polarity of the egg cortex. Further, knockdown of FYN kinase by siRNA resulted in an approximately 50% reduction in progression to metaphase II similar to what was observed in oocytes isolated from Fyn-knockout mice matured in vitro. These results clearly demonstrate that involvement of Fyn in oocyte and egg functions vary among species (Eliyahu et al. 2002; Kierszenbaum et al. 2009; Kinsey 1995; Kinsey 1996; Kinsey and Shen 2000; Kinsey et al. 2003; Levi et al. 2010; Luo et al. 2009; McGinnis et al. 2009;

Rongish and Kinsey 2000; Sette et al. 2002; Sharma and Kinsey 2006; Sharma and Kinsey 2008; Steele et al. 1990; Talmor et al. 1998; Talmor-Cohen et al. 2004b; Wu and Kinsey 2000; Wu and Kinsey 2002; Wu and Kinsey 2004).

2.16 Flagellar protein-tyrosine kinase (Flagellar PTK)

Fertilization in the biflagellated green algae, *Chlamydomonas*, is initiated by flagellar adhesion between gametes of opposite mating types: plus (mt+) and minus (mt-). Flagellar adhesion is followed by an increase in cytoplasmic cAMP concentration that is required for gamete fusion. Pharmacological and biochemical studies have demonstrated that a tyrosine kinase activity, named **flagellar PTK**, which acts upstream of the cAMP elevation, is present in adhering bisexual gametes but not in non-adhering, unisexual gametes. A 105-kDa protein has been identified as a substrate of the flagellar PTK. Analyses of temperature-sensitive mutants have shown that kinesin II is an essential component that connects flagellar adhesion and activation of the tyrosine kinase activity (Kurvari and Snell 1996; Kurvari et al. 1996; Wang and Snell 2003).

2.17 Flagellar p48 protein kinase (SksC)

On the contrary to flagellar PTK, another protein kinase activity is shown to decrease rapidly after gamete adhesion in *Chlamydomonas*. The kinase, named **SksC**, is a 48-kDa protein that is capable of autophosphorylating on serine and tyrosine residues, indicating that it is a dual-specificity kinase. Although it's physiological substrate other than SksC by itself has not yet been identified, adhesion-induced SksC down-regulation and flagellar PTK up-regulation may play important roles simultaneously in gamete fusion and activation of embryogenesis (Pan and Snell 2000; Zhang et al. 1996). In this species, a rapid degradation of two gamete-specific proteins, FUS1 and HAP1, occur upon gamete fusion (Liu et al. 2010). This event is required for polyspermy block. However, its relationship to the aforementioned phospho-signaling is not known.

2.18 Fms-like tyrosine kinase/vascular endothelial growth factor receptor (FLT/Colony-stimulating factor receptor-like/VEGFR)

FLT/VEGFR is a receptor/tyrosine kinase, whose extracellular ligand is VEGF (de Vries et al. 1992). The term FLT is coined because it is structurally related to c-fms/macrophage colony-stimulating factor-1 receptor/kinase. The viral counterpart of c-fms in a feline sarcoma virus (McDonough and HZ-5 strain) arises as a result of alterations in receptor coding sequences that affect its activity as a tyrosine kinase (Sherr et al. 1988). Pleiotropic functions of FLT/VEGFR have been well documented and, most of all, its involvement in angiogenesis in normal as well as cancerous cell conditions has been of clinical interest (Shibuya 1995). In bovine cumulus-oocyte complexes and porcine ovary, expression and physiological impact of VEGF and/or FLT/VEGFR have been investigated. The results so far obtained suggest that VEGF-FLA/VEGFR pathway is involved in viability of oocytes (Einspanier et al. 2002; Okamura et al. 2001).

2.19 Glycogen synthase kinase 3 (GSK3/shaggy/GSK3-B)

GSK3, a serine/threonine protein kinase, have the two isoforms GSK3 (p51) and GSK3 (p47) is known to play roles in many biological processes. Mouse eggs contain centrosomal

spindle poles when arrested at meiotic metaphase II. Phosphorylated PKC (p-PKC) and GSK3 are enriched at both centrosomal spindle poles and the kinetochore region (Baluch and Capco 2008). p-PKC phosphorylates GSK3 on the Ser-9 position to inactivate GSK3 and consequently maintaining spindle stability during meiotic metaphase arrest (Baluch and Capco 2008). Similarly, in mouse oocytes, p-GSK3 was increased and phospho-MAPK3/MAPK1 was decreased before GVBD and oocytes were mainly arrested at MI (Uzbekova et al. 2009). GSK3 might be also involved in the local activation of Aurora A kinase that controls MI/MII transition (Uzbekova et al. 2009). GSK3/shaggy along with other downstream components of the Wnt pathway mediate patterning along the primary animal-vegetal axis of the sea urchin embryo (Emily-Fenouil et al. 1998) and along the dorsal-ventral axis in *Xenopus*, suggesting a conserved basis for axial patterning between invertebrate and vertebrate. Double phosphorylation (Thr-239 by DYRK kinase MBK-2 and Thr-339 by GSK-3) on OMA-1 is essential for correctly timed degradation of OMA-1 and ensures a normal oocyte-to-embryo transition in *C. elegans* (Nishi and Lin 2005). Even the conserved function of GSK3 is observed in hydra embryogenesis (Rentzsch et al. 2005), and in zebrafish cardiogenesis (Emily-Fenouil et al. 1998; Lee et al. 2007; Liu et al. 2007; Nishi and Lin 2005; Uzbekova et al. 2009).

2.20 Greatwall kinase (Gwl/GWK)

The balance between Cdc2 kinase/cyclin B also known as M-phase-promoting factor (Arceci et al. 1992), and protein phosphatase 2A (PP2A) is crucial to enable in time mitotic entry and exit. Greatwall (Gwl) kinase (**GWK**) has been identified as a key element in M phase initiation and maintenance in *Drosophila*, *Xenopus* oocytes/eggs, and mammalian cells. GWK is activated by cdk1/cyclin B (Arceci et al. 1992), and promotes the inhibition of protein phosphatase 2A (PP2A) that works on the phosphorylated substrate mediated by CDKs. Activated GWK negatively regulates a crucial phosphatase and thus induce inhibiting phosphorylations of Cdc25 to inhibits M phase induction (Zhao et al. 2008). Thus, mitotic entry and maintenance is not only mediated by the activation of Cdc2 kinase/cyclin B but also by the regulation of PP2A by GWK in *Xenopus* oocytes/eggs (Castilho et al. 2009; Mochida et al. 2010; Vigneron et al. 2009; Yamamoto et al. 2011).

2.21 Histone H1 kinase (HH1K/H1K)

Maturation promoting factor (Arceci et al. 1992) is universally recognized as the biological entity responsible for driving the cell cycle from G2- to M-phase. Histone H1 kinase (**HH1K**) activity is widely accepted as a biochemical indicator of p34Cdc2 protein kinase complex activity and therefore MPF activity. In spontaneously maturing oocytes, HH1K activity increases before GVBD in mouse (Gavin et al. 1994). HH1K activity being higher in the first than in the second cell cycle in mouse embryogenesis that reaches to the basal level (Ciemerych et al. 1998; Fulka et al. 1992). Inhibition of protein phosphatases are correlated with HH1K activity and is sufficient to induce the entry into M-phase during the first cell cycle of the mouse parthenogenetic activated oocyte (Rime and Ozon 1990). In fertilized sea urchin eggs the activity of HH1K oscillates during the cell division cycle and there is a striking temporal correlation between HH1K activation and the accumulation of a phosphorylated form of cyclin (Meijer et al. 1989a; Meijer and Pondaven 1988; Tosuji et al. 2003). HH1K activity correlation with the oocyte maturation and after fertilization were

carried out in other species e.g. bovine (Collas et al. 1993), cat fish (Balamurugan and Haider 1998), fish (Yamashita et al. 1992), goldfish (Pati et al. 2000), pig (Kikuchi et al. 1995), rabbit (Jelinkova et al. 1994) and sea star (Arion et al. 1988; Pelech et al. 1987).

2.22 Insulin-like growth factor 1 receptor/kinase (IGF-1R/IGFR)

In somatic cell insulin-like growth factor (IGF) receptor (**IGFR**) has the ability to phosphorylate the overall cellular substrates, in particular PLCγ, annexin II and to activate phosphatidylinositol 3-kinase via insulin receptor substrate 1 (Jiang et al. 1996). *Xenopus* oocytes bear both the IGFR-1 and IGFR-2, where IGFR-1, a tyrosine kinase, has the capability of autophosphorylation (Janicot et al. 1991; Nissley et al. 1985). IGF-1-induced oocyte maturation required IGFR-1-mediated endocytosis in *Xenopus* (Taghon and Sadler 1994). IGFR-1 in *Xenopus* ovarian follicle cells somehow supports the IGF-1-stimulated oocyte maturation (Sadler et al. 2010). Expression of IGFR has been shown in the oocytes of rat (Zhao et al. 2001), in bovine (Nuttinck et al. 2004) and in rainbow trout positively correlated with embryonic survival (Aegerter et al. 2004).

2.23 Insulin receptor/kinase (IR)

Insulin/insulin-like growth factor (IGF)-1 receptor (**IR/IGF1R**), a tyrosine kinase, exerts its cellular functions by the phosphorylation of insulin receptor substrate-1 (IRS-1). Tyrosine phosphorylated form of IRS-1 binds to specific Src homology-2 (SH2) domain-containing proteins including the p85 subunit of phosphatidylinositol (PI) 3-kinase and GRB2, a molecule believed to link IRS-1 to the Ras pathway in *Xenopus* oocyte maturation (Chuang et al. 1994; Chuang et al. 1993; El-Etr et al. 1979; Grigorescu et al. 1994). Insulin through IR has influences on oocyte maturation and embryonic development in mouse (Acevedo et al. 2007). Recently, it has been shown that IR and IGF1R are not required for oocyte growth, differentiation, and maturation in mice using genetically ablated mouse (Pitetti et al. 2009). It was shown that IR is the components of sea urchin eggs plasma membrane (Jeanmart et al. 1976) and insulin like peptide 3 acts through mosquito IR in mosquito egg production (Brown et al. 2008).

2.24 c-Jun N-terminal kinase (JNK)

The c-Jun N-terminal kinase (**JNK**) is member of the mitogen-activated protein kinase family that plays critical roles in stress responses and apoptosis. JNK is activated just prior to germinal vesicle breakdown during *Xenopus* oocyte maturation and remains active until the early gastrula stage of embryogenesis (Bagowski et al. 2001). JNK was activated after the microinjection of Mos (Bagowski et al. 2001). Progesterone mediated *Xenopus* oocyte maturation might involve JNK activation both through the raf/MEK (MAPKK)/p42 MAPK-dependent pathway (Bagowski et al. 2001; Chie et al. 2000) and through MEK/p42 MAPK-independent pathways (Bagowski et al. 2001). JNK2 plays an important role in spindle assembly and first polar body extrusion during mouse oocyte meiotic maturation (Huang et al. 2011). JNK mRNA was detected in mouse eggs and pre-implantation embryos (Zhong et al. 2004).

2.25 c-Kit tyrosine kinase (c-Kit)

The proto-oncogene product **c-Kit**, a transmembrane tyrosine kinase, acts as a receptor in mouse oocytes to communicate with the surrounding granulose cells and for its maturation.

Stem cell factor (SCF), a ligand for c-Kit is required for the production of the mature gametes e.g. the growth and maturation of the oocytes in response to gonadotropic hormones (Sette et al. 2000). The level of c-Kit increases during the maturation of mouse oocytes and following fertilization, it decreases rapidly until the early 2-cell stage but it is not detected in the embryos of 4-cell, 8-cell, and morula stages (Arceci et al. 1992; Horie et al. 1991). It is suggested that Kit-PI3K-Akt-GSK-3 pathway might work in the regulation of mouse oocytes growth (Liu et al. 2007).

2.26 Lck tyrosine kinase (Lck)

Lck, a 56-kDa protein, has originally been characterized as a Src-related tyrosine kinase that is specifically expressed in lymphocytes (Lck is named after lymphocyte kinase). In T-cells, Lck associates with CD4/CD8 cell surface receptor for major histocompatibility complex and, upon interaction with antigen-presenting cells, it will be activated by dephosphorylation in the carboxyl-terminal tyrosine residue, as catalyzed by CD45 phosphatase. In murine eggs, it has been reported that CD4-like structures on the vitelline membranes are involved in gamete interaction, and that Lck-like protein could have been detected in association with those CD4-like structures (Mori et al. 2000; Mori et al. 1991). While these studies have been done with the use of specific monoclonal antibodies (e.g. immunofluorescent and immunochemical approaches), biochemical and molecular biological identifications have not yet been demonstrated.

2.27 p38 MAPK/Mipk/Stress-activated protein kinase (SAPK)/Xp38γ

p38/SAPK, which has initially been identified as a stress-activated protein kinase, belongs to the MAPK superfamily (Miyata and Nishida 1999). In the sea star, a p38-related kinase Mipk (meiosis-inhibited protein kinase) has been identified and characterized. Before oocyte maturation, Mipk is highly phosphorylated on tyrosine residues, and during oocyte maturation and some hours after fertilization, it becomes tyrosine-dephosphorylated and enzymatically inactive, suggesting that inhibition of Mipk is related to cell cycle progression during meiosis (Morrison et al. 2000). However, knockdown of Mipk by antisense oligonucleotide is not effective in inducing oocyte maturation. On the other hand, *Xenopus* p38γ/SAPK3 is a major player in G2/M transition of immature oocytes induced by MKK6, a p38 activator. The activated p38γ/SAPK3 is also shown to phosphorylate Ser-205 of and activate Cdc25C phosphatase (Perdiguero et al. 2003). One another interesting feature of p38 in oocyte/egg system is that it may contribute to apoptotic process in starfish eggs left unfertilized for a long time. In this system, inactivation of MAPK is pre-requisite for inducing activation of caspase, a pro-apoptotic protease. p38 has been shown to activate after the MAPK inactivation and seems to be responsible for apoptotic body formation (Morrison et al. 2000; Perdiguero et al. 2003; Sasaki and Chiba 2004).

2.28 Mitogen-activated protein kinase (p42/p44MAPK/ERK)

MAPK is a serine/threonine kinase that has been originally identified as a microtubule-associated protein 2 (MAP2) kinase (this is also termed "MAPK" or "MAP2 kinase") and then well recognized as a mitogen-activated protein kinase (Maller 1990). MAPK is a component of the MAPK kinase, which consists of at least three steps of phospho-dependent

activation of kinases that include MAPK (e.g. Erk, p38, JNK), MAPK kinase (MAPKK: e.g. MEK), and MAPKK kinase (MAPKKK: e.g. Mos, Raf). The MAPK cascade is evolutionarily conserved in a variety of unicellular and multicellular organisms and serves as a trigger of multiple cellular functions such as differentiation, nutrition signals, proliferation, and stress responses. In maturing oocytes of several organisms, stoichiometric activation of MAPK will occur (all-or-none signaling of MAPK activation) (Ferrell and Machleder 1998). This MAPK activation seems to be required for maintaining the maturing oocytes to arrest at the metaphase of second meiosis (in mammals and frog), rather than oocyte maturation itself. This is a so-called cytostatic factor's function. MAPK activation can be evaluated by the phosphorylation of a threonine and tyrosine residues in the MAPK molecule, both of which are catalyzed by an upstream dual-specificity kinase, MAPKK. Fertilization promotes Ca^{2+}-dependent degradation and/or inactivation of upstream kinases Mos and MAPKK, and triggers a rapid dephosphorylation/inactivation of all MAPK (inactivation of cytostatic factor). In the actively dividing embryos, a fraction of MAPK will be transiently activated at mitotic phase, and thereafter serves as a component of checkpoint (Chesnel et al. 1997; Chung et al. 1991; Eckberg 1997; Fabian et al. 1993; Ferrell 1999; Ferrell et al. 1991; Gavin et al. 1999; Git et al. 2009; Gross et al. 2000; Huo et al. 2004; Ito et al. 2010; Iwasaki et al. 2008; Katsu et al. 1999; Keady et al. 2007; Kosako et al. 1992; Lee et al. 2006; Lu et al. 2002; Palmer et al. 1998; Philipova and Whitaker 1998; Sackton et al. 2007; Sadler et al. 2004; Sasaki and Chiba 2004; Sato et al. 2001; Sato et al. 2003; Sato et al. 2000; Shibuya et al. 1992; Shibuya et al. 1996; Stricker 2009; Sun et al. 1999; Tokmakov et al. 2005; Verlhac et al. 1996; Zhang et al. 2006).

2.29 MAPK kinase (MAPKK/MEK)

MAPKK is a serine/threonine kinase that will be activated by MAPKKK phosphorylation of its serine residues in the catalytic domain. The activated MAPKK is capable of phosphorylating threonine and tyrosine residues in the catalytic domain of a downstream kinase MAPK, thus MAPKK is a dual-specificity kinase. MAPKK is well known as a mediator of Mos-dependent activation of MAPK cascade in maturing oocytes (Kosako et al. 1992; Xiong et al. 2008).

2.30 Meiosis inhibited protein kinase (MIPK)

p38 type of MAPK is a member of the mitogen-activated protein kinase (MAPK) is usually activated in response to cytokines and various stresses and plays a role in the inhibition of cell proliferation and tumor progression, but its role in oocyte maturation is described recently. In *Xenopus* oocytes, p38MAPK phosphorylated Cdc25C for the meiotic G_2/M progression and this required neither protein synthesis nor activation of p42MAPK-$p90^{Rsk}$ pathway (Perdiguero et al. 2003). The function of p38MAPK in accurate chromosome segregation during mouse oocyte meiotic maturation has also been described (Ou et al. 2010). In porcine oocytes, active phosphorylated p38MAPK accumulated in the nucleus before GVBD and remained active through MI to MII (Villa-Diaz and Miyano 2004). A p38MAPK homolog **Mipk** (meiosis-inhibited protein kinase) was highly tyrosine phosphorylated in immature sea star oocytes and subsequently dephosphorylated during the arrest at the G_2/M transition of meiosis I (Morrison et al. 2000). Dephosphorylated Mipk was maintained until the maturation of oocytes and the early mitotic cell divisions but was

re-phosphorylated at the time of differentiation and acquisition of G phases in the developing embryos (Morrison et al. 2000).

2.31 Mos protein kinase (Mos)

Mos, a mitogen-activated protein (MAP) kinase kinase kinase that activates the MAPK pathway, is normally expressed only in vertebrate oocytes and take part in their maturation. Cytoplasmic polyadenylation element binding (CPEB) factor is essential for the polyadenylation of c-Mos mRNA and its subsequent translation (Mendez et al. 2000). Early phosphorylation of CPEB is catalyzed by Eg2, a member of the Aurora family of serine/threonine protein kinases (Mendez et al. 2000). Mos in coordination with Cdc2 regulate the translational activation of a maternal FGF receptor-1 (FGFR) mRNA during *Xenopus* oocyte maturation (Culp and Musci 1999). Mos contribute in the first cycle of *Xenopus* embryogenesis (Murakami and Vande Woude 1998) and act like Mos/Raf-1/MAPK pathway (Muslin et al. 1993) or without Raf like Mos/MAPK pathway both in *Xenopus* (Shibuya et al. 1996) and mouse (Verlhac et al. 1996). Mos is also involved in MAPK cascade in the control of microtubule and chromatin organization during meiosis in mouse oocytes (Chesnel et al. 1997; Culp and Musci 1999; Daar et al. 1993; Faure et al. 1998; Mendez et al. 2000; Murakami and Vande Woude 1998; Muslin et al. 1993; Shibuya et al. 1992; Shibuya et al. 1996; Tang et al. 2008; Verlhac et al. 1996; Wu et al. 2007a).

2.32 Myelin basic protein kinase (MBPK)

MBPK is present during maturation and early embryogenesis of the sea star. A meiosis-activated MBP kinase (MBPK) was purified from maturing oocytes of the sea star that rapidly undergo autophosphorylation on serine/threonine residues (Sanghera et al. 1990). MBPK remained highly active until 12 h post-fertilization (Arceci et al. 1992), after which it declined (Lefebvre et al. 1999). During maturation of sea star oocytes, MBPK-II (p110) was fully activated at the time of GVBD, whereas peak activation of MBPK-I (p45) occurred after this event (Pelech et al. 1988). Inhibiting an upstream phosphorylation event in the MBPK activation pathway the sea urchin embryo mitotic cycle at metaphase can be blocked (Pesando et al. 1999). The MBPK activity was at approximately the same high level in all categories (medium, small and tiny) of bovine oocytes after 24 h of culture and remained stable until 40 h (Pavlok et al. 1997; Pelech et al. 1988; Sanghera et al. 1990).

2.33 Myt1 protein kinase (Myt1)

Activation of MPF (composed of cyclin B and Cdc2 kinase) is required to entry into M-phase in all animals. The inhibitory kinase **Myt1**, a member of Wee1 family phosphorylates Cdc2 kinase to keep MPF in an inactive state. During *Xenopus* oocyte maturation MAPK phosphorylates and activates $p90^{Rsk}$ and that $p90^{Rsk}$ in turn down-regulates Myt1 by phosphorylation, leading to the activation of Cdc2 kinase/cyclin B (Palmer et al. 1998; Ruiz et al. 2010). Alternatively, Mos triggers Myt1 phosphorylation, even in the absence of MAPK activation in a mechanism that directly activates MPF in *Xenopus* oocytes (Peter et al. 2002). Recent model is that up-regulation of cyclin B synthesis causes rapid inactivating phosphorylation of Myt1, mediated by Cdc2 and without any significant contribution of Mos/MAPK or Plx1 (Gaffre et al. 2011). Non-cyclin proteins RINGO/Speedy can

phosphorylate Ser residue in the regulatory domain of Myt1 and lead the activation of CDK during G2/M transition in *Xenopus* oocytes (Burrows et al. 2006; Inoue and Sagata 2005; Oh et al. 2010; Palmer et al. 1998; Ruiz et al. 2008).

2.34 Nemo-like kinase 1 (NLK1)

NLK Nemo-like kinase (NLK) is an evolutionary conserved MAPK-like kinase, an atypical MAPK that phosphorylates several transcription factors and is known to function in multiple developmental processes in vertebrates and invertebrates (Ota et al. 2011a; Ota et al. 2011b). Activated NLK directly phosphorylates microtubule-associated protein-1B (MAP1B) and the focal adhesion adaptor protein, paxillin (Ishitani et al. 2009). Inactive NLK1 in immature *Xenopus* oocytes becomes active during maturation depending on Mos protein synthesis but not on p42 MAPK activation (Ota et al. 2011b). NLK1 acts as a kinase downstream of Mos and catalyzes the phosphorylation of Pumilio 1 (Pum1), Pum2, and cytoplasmic polyadenylation element-binding protein (CPEB) to regulate the translation of mRNAs, including cyclin B1 mRNA, stored in oocytes (Ota et al. 2011b). NLK may play a role in neural development together with Sox11 during early *Xenopus* embryogenesis (Hyodo-Miura et al. 2002). NLK appears to function as a positive regulator of Wnt signaling during early zebrafish development (Thorpe and Moon 2004).

2.35 Nerve growth factor receptor (NGFR/TrkA/TrkB)

NGFR, the nerve growth factor (NGF) receptor (NGFR), an integral single membrane protein that is phosphorylated and heavily glycosylated in *Xenopus* oocytes and potentiates the ability of progesterone to induce maturation (Sehgal et al. 1988). NGF treatment on *Xenopus* oocytes results the tyrosine phosphorylation of ectopically expressed human Trk, a proto-oncogene product ($p140^{proto\text{-}Trk}$), and meiotic maturation, as determined by germinal vesicle breakdown and the activation of MPF (Nebreda et al. 1991). Thus, the Trk proto-oncogene product can act as a receptor for NGF (Nebreda et al. 1991). In human ovaries, NGF and TrkA (NGF's high-affinity receptor) were detected in granulose cells of preantral and antral follicles and in thecal cells of antral follicles (Salas et al. 2006). NGF/TrkA is present in bovine sperm and might have roles in regulation of sperm physiology relevant to male fertility and infertility (Li et al. 2010).

2.36 Neu tyrosine kinase

$p185^{Neu}$, the protein product of the neu gene, is a tyrosine kinase receptor that has the structural similarity to EGFR. The transformed/activated form of $p185^{Neu}$ tyrosine kinase (Val664Glu) facilitates the oocyte maturation events reducing the half-life from approximately 9 h to 5 h that are elicited by some steroids (e.g. progesterone) (Narasimhan et al. 1992). However, the activated $p185^{Neu}$ tyrosine kinases are not able to mimic the EGF-stimulated EGF receptor tyrosine kinase in triggering oocyte maturation, which suggests that the EGF receptor and the $p185^{Neu}$ tyrosine kinase do not work in the same pathways in *Xenopus* oocytes (Narasimhan et al. 1992). But in mouse embryo culture cells, it was shown that mutationally activated Neu protein can substitute the ligand-activated EGF receptor activity to reflect the structural similarity and EGF induced phosphorylation and regulation of $p185^{Neu}$ (Kokai et al. 1988; Shirahata et al. 1990).

2.37 p21-activated protein kinase (PAK)

PAK is a serine/threonine kinase that will be activated by its interaction with a small GTP-binding protein (e.g. Rac, Cdc42) and has been implicated in cytoskeletal dynamics and cell motility, transcription through MAPK cascades, death and survival signaling, and cell-cycle progression (Bokoch 2003). In *Xenopus* oocytes, microinjection of catalytically inactive mutant of PAK-related kinase (X-PAK) accelerates cell cycle progression from GV through MII stages. On the other hand, catalytically active mutant of X-PAK is shown to suppress progesterone-induced Mos accumulation and MAPK activation. These data suggest that the endogenous PAK activity is involved in the cell cycle arrest before maturation (Faure et al. 1997; Faure et al. 1999). An inhibitory effect of X-PAK on oocyte maturation seems to be due to a PKA-like mechanism of suppression of the PLK-induced activation of Cdc25 phosphatase, which is a trigger of the activation of Cdc2/cyclin complex (i.e. MPF) (Faure et al. 1999).

2.38 Phosphoinositide-dependent protein kinase 1 (PDK1)

PDK is a serine/threonine kinase that is regulated by a lipid activator phosphatidylinositol 3,4,5-trisphosphate (PIP_3), a product of PI3K phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP_2) (Toker and Newton 2000). In general, PDK consists of two distinct gene products, PDK1 and PDK2. In 1-methyladenine (1-MA)-dependent maturing starfish oocytes, Akt kinase is responsible for activation of MPF. Akt kinase is, as described above, regulated by upstream kinases such as PDK and mTOR. In fact, starfish PDK1, but not PDK2, is required for 1-MA-induced Akt activation and cell cycle progression (Hiraoka et al. 2004). PI3K-PDK-Akt axis has also been shown in other organisms such as nematode *C. elegans* (Hertweck et al. 2004), however, their involvement in oocyte and egg functions is not yet known.

2.39 Polo-like protein kinase-1 (Plk/1PLK-1/Plx1)

PLK, polo-like kinase, a serine/threonine kinase, is implicated in the regulation of cell cycle progression in all eukaryotes (Sumara et al. 2002). Polo-like kinase type 1 (plk1) is present during meiotic maturation, fertilization, and early embryo cleavage in mouse (Pahlavan et al. 2000; Tong et al. 2002; Xiong et al. 2008), rat (Fan et al. 2003), porcine (Anger et al. 2004; Yao et al. 2003) and parasite trematode oocytes (Long et al. 2010). Though all three *Xenopus* type Plk (Plx); Plx1, Plx2 and Plx3 are observed in oocytes and unfertilized eggs but Plx2 and Plx3 in embryos strongly suggests that individual Plk family members perform distinct functions at later stages of development (Duncan et al. 2001). Plx1 is required for activation of the phosphatase Cdc25C and cyclin B-Cdc2 in *Xenopus* oocytes (Liu and Maller 2005; Qian et al. 2001). The APC/C inhibitor Emi2 or XErp1, a pivotal CSF component, required to maintain metaphase II arrest and rapidly destroyed in response to Ca^{2+} signaling through phosphorylation by Plx1 (Hansen et al. 2006). Interestingly, Plx1 kinase that is required for Cdc25 activation and MPF auto-amplification in fully-grown oocytes is not expressed at the protein level in small stage IV oocytes (Karaiskou et al. 2004). Plx1 acts as a direct inhibitory kinase of Myt1 in the mitotic cell cycles in *Xenopus* (Anger et al. 2004; Eckerdt et al. 2009; Fan et al. 2003; Hansen et al. 2006; Inoue and Sagata 2005; Ito et al. 2008; Karaiskou et al. 2004; Liu and Maller 2005; Pahlavan et al. 2000; Qian et al. 2001; Sumara et al. 2002; Tong et al. 2002; Wianny et al. 1998; Xiong et al. 2008; Yao et al. 2003).

2.40 Protein kinase C (PKC)

PKC is a family of serine/threonine kinase that is primarily regulated by diacylglycerol (DG), a phospholipase C-hydrolyzed product of PIP_2, and intracellular Ca^{2+} (Nishizuka 1984; Nishizuka 1986; Nishizuka 1988). Classical or typical PKCs (α, βI/βII, γ) are also known as an intracellular receptor for phorbol ester, a tumor promoter. Other subfamily members of PKC (atypical or novel types: e.g. δ, ε, ζ) have other mechanisms of enzyme regulation such as tyrosine phosphorylation. Live cell imaging studies demonstrated that spatial distribution of PKCs, which differ in both PKC subfamily members and cellular environments, is crucial for PKC activation and its access to substrates. In eggs/oocytes of several organisms (e.g. mammals, marine worms, frog, and sea urchin), activation and PKC(s) and its contribution to oocyte maturation, fertilization, and initiation of development have been well documented. Cellular functions regulated by PKC(s) include the onset of anaphase I, sperm-induced activation of respiratory burst oxidase, MAPK inactivation, reorganization of cytoskeleton, exocytosis of cortical granules, and pronucleus formation (Akabane et al. 2007; Baluch et al. 2004; Capco 2001; Capco et al. 1992; de Barry et al. 1997; Diaz-Meco et al. 1994; Ducibella and LeFevre 1997; Eliyahu et al. 2001; Eliyahu and Shalgi 2002; Eliyahu et al. 2002; Eliyahu et al. 2005; Fan et al. 2002; Gallicano et al. 1995; Gallicano et al. 1997; Haberman et al. 2011; Halet 2004; Heinecke et al. 1990; Kalive et al. 2010; Lu et al. 2002; Luria et al. 2000; Madgwick et al. 2005; Nakaya et al. 2000; Olds et al. 1995; Pauken and Capco 2000; Quan et al. 2003; Sakuma et al. 1997; Sanghera et al. 1992; Shen and Buck 1990; Stricker 2009; Swann et al. 1989; Tatone et al. 2003; Viveiros et al. 2004; Viveiros et al. 2003; Yang et al. 2004; Yu et al. 2004; Yu et al. 2008). In rat eggs, PKC interaction and phosphorylation of RACK (receptor for C-kinase) has been suggested (Haberman et al. 2011). In *Xenopus* oocytes, hormone-induced maturation is accompanied by polarized localization and interaction of atypical PKC(s) and ASIP/PAR-3, a cell polarity regulator, suggesting their involvement in establishing animal-vegetal asymmetry before fertilization (Nakaya et al. 2000).

2.41 Protein kinase M (PKM)

PKM is a catalytic fragment of PKC, produced by a limited proteolysis (probably by calpain, a Ca^{2+}-dependent protease) of the molecule. It has been shown that PKM contributes to the remodeling of cytoskeleton during egg activation in the mouse (Gallicano et al. 1995). Its physiological target (i.e. substrate) is not yet known.

2.42 Proline-rich tyrosine kinase2 (Pyk2)

Pyk2 is a non-receptor tyrosine kinase related to the focal adhesion kinase (FAK; p125) that is rapidly phosphorylated on tyrosine residues in response to various stimuli that elevate the intracellular calcium ion concentration (Lev et al. 1995). Pyk2 is up-regulated in various types of tumors like hepatocellular carcinoma (HCC) (Sun et al. 2011; Sun et al. 2007) and small cell lung cancer (SCLC) (Roelle et al. 2008). Activation of Pyk2 leads to the activation of the MAPK signaling pathways. PYK2 is present in mouse spermatocytes and spermatids (Chieffi et al. 2003). Pyk2 plays a dynamic role during rat oocyte meiotic maturation by regulating the organization of actin filaments (microfilaments) from GV stage to telophase (Meng et al. 2006). Pyk2 has ligand sequences for Src homology 2 and 3 (SH2 and SH3), and has binding sites for paxillin (Li and Earp 1997) and $p130^{Cas}$ (Astier et al. 1997).

2.43 Raf protein kinase (A-Raf/B-Raf/Raf-1)

Raf is a serine/threonine kinase that has been originally identified as an oncogene that acts in concert with Myc transcription factor. Raf can be activated by PKC phosphorylation, and the activated Raf acts as a MAPKKK that activates MAPKK-MAPK pathway. Therefore, Raf is a mediator of transmembrane signaling involving hydrolysis of phospholipids and subsequent cytoplasmic kinase cascade. In *Xenopus* oocytes, Raf-1 is shown to act downstream of Mos, another kind of MAPKKK specific to oocyte maturation system, to promote MAPK activation and rearrangement of intracellular pH (from 7.2 to 7.7) in response to progesterone or insulin. The latter phenomenon involves phospho-dependent regulation of Na^+/H^+ exchanger. Whether Raf is responsible for this phosphorylation is unknown (Chesnel et al. 1997; Fabian et al. 1993; Kang et al. 1998; MacNicol et al. 1995; Muslin et al. 1993; Shibuya et al. 1996). Developmental expression of Raf has also been demonstrated in *Xenopus*; however, its role in fertilization has not yet been shown (MacNicol et al. 1995).

2.44 RET tyrosine kinase (Ret)

Receptor tyrosine kinase are rearranged during transfection (**RET**) for activation and about 15 RET gene rearrangement was identified in papillary thyroid carcinoma (PTC) among which RET/PTC1 and RET/PTC3 are the most common type (Marotta et al. 2011). RET was detected in mammalian (human) oocytes (Farhi et al. 2010) and are expressed in embryos throughout the early development with an increase after the early blastocyst stage (Kawamura et al. 2008). Glial cell line-derived neurotrophic factor (GDNF) and both its co-receptors, GDNF family receptor alpha-1 (GFR alpha-1) and RET receptor affect porcine oocyte maturation and pre-implantation embryo developmental competence in a follicular stage-dependent manner (Linher et al. 2007). Receptor tyrosine kinase (RTK1) that is highly similar to RET kinase was not detected in sea urchin unfertilized eggs and was activated after blastula stage (Sakuma et al. 1997).

2.45 S6 kinase (S6K)/ Rsk protein kinase I/II (Rsk)

Several 40S ribosomal protein kinases in vertebrate/frog oocyte stage 6 (**S6K**) are directly phosphorylated and activated by MAPK in order to activate MPF (Barrett et al. 1992; Erikson and Maller 1988). Some S6Ks have been identified and characterized for example in progesterone- and insulin-treated *Xenopus* eggs termed S6K II (S6K II, p92) different from S6K I (Erikson et al. 1987), differential role in *Xenopus* embryogenesis (S6K; p70) (Schwab et al. 1999), in *Rana* oocytes (S6K; p83) (Byun et al. 2002), in porcine oocytes (Sugiura et al. 2002), and G1 phase after completion of meiosis II in starfish unfertilized eggs (Mori et al. 2006) but not in mouse oocytes (Dumont et al. 2005). S6K ($p90^{Rsk}$) inhibits the degradation of cyclin B by anaphase-promoting complex/cyclosome (APC/C) and results the second meiotic metaphase arrest (Maller et al. 2001). S6K phosphorylates and activates the Bub1 protein kinase, which may cause metaphase arrest due to the inhibition of APC (Maller et al. 2001). Mos-dependent phosphorylation of Erp1 by $p90^{Rsk}$ at Thr-336, Ser-342 and Ser-344 is crucial for both stabilizing Erp1 that inhibits cyclin B degradation by binding the APC/C and establishing CSF arrest in meiosis II of *Xenopus* oocytes (Nishiyama et al. 2007a).

2.46 Src tyrosine kinase (Src)

Src has been firstly identified as an oncogene of Rous sarcoma virus and thereafter discovered as a normal cellular gene that encodes a 60-kDa protein-tyrosine kinase (Brown and Cooper 1996; Jove and Hanafusa 1987; Thomas and Brugge 1997) that is distributed in a wide range of animal species from a unicellular organism (i.e. *Monosiga ovata*) through multicellular organisms including human (Segawa et al. 2006). In human, Src is ubiquitously expressed in several tissues and seems to be involved in several cellular functions as well (e.g. lymphocyte activation, neuronal signal transduction). In some sea invertebrates (sea urchin, starfish, ascidian, and others) (Abassi et al. 2000; Belton et al. 2001; Dasgupta and Garbers 1983; Giusti et al. 1999a; Giusti et al. 1999b; Giusti et al. 2000a; Giusti et al. 2003; Giusti et al. 2000b; Kamel et al. 1986; O'Neill et al. 2004; Runft et al. 2004; Runft and Jaffe 2000; Runft et al. 2002; Sakuma et al. 1997; Shen et al. 1999; Shilling et al. 1994; Stricker et al. 2010a; Townley et al. 2006; Townley et al. 2009), fish (zebrafish) (in this case, Fyn tyrosine kinase) and frog (African clawed frog) (Glahn et al. 1999; Iwasaki et al. 2008; Iwasaki et al. 2006; Kushima et al. 2011; Mahbub Hasan et al. 2011; Mahbub Hasan et al. 2007; Mahbub Hasan et al. 2005; Mammadova et al. 2009; Sakakibara et al. 2005; Sato et al. 1996; Sato et al. 2006a; Sato et al. 1999; Sato et al. 2004; Sato et al. 2002; Sato et al. 2001; Sato et al. 2003; Sato et al. 2000; Sato et al. 2006b; Steele 1985; Steele et al. 1989b; Tokmakov et al. 2002), the oocyte-expressing Src is suggested to be involved in the initiation of sperm-induced egg activation through the phosphorylation and activation of oocyte proteins such as phospholipase Cγ (thereby promoting IP_3-dependent Ca^{2+} release). Progesterone-induced oocyte maturation in *Xenopus* also seems to involve the activity of Src (Tokmakov et al. 2005). In mammalian species (i.e. mouse and rat), chromosomal dynamics, rather than sperm-induced Ca^{2+} release (Kurokawa et al. 2004b; McGinnis et al. 2007; Mehlmann and Jaffe 2005; Reut et al. 2007; Tomashov-Matar et al. 2008), seems to be regulated by Src and/or other Src-related kinases (e.g. Fyn) in fertilized oocytes.

2.47 Src64/DSrc

Src64 is a *Drosophila* homolog of the tyrosine kinase Src and is required for ovarian ring canal morphogenesis during oogenesis. Tec29 tyrosine kinase interacts with Src64 and contributes to ring canal development. The Src64-Tec29 axis is also involved in microfilament contraction during cellularization, a *Drosophila*-specific phenomenon. Although the cellular target of Src64 phosphorylation is not yet clearly shown, its upstream regulators such as csk homolog-mediated phosphorylation and phosphoinositide-dependent activation mechanism have been demonstrated (Dodson et al. 1998; Lu et al. 2004; O'Reilly et al. 2006).

2.48 Stigmatic S receptor kinase (SRK)

SRK is a transmembrane receptor/kinase that works as a female determinant for self-incompatibility/self-sterility to prevent inbreeding in *Brassica*, a flowering plant. Upon self-pollination, the pollen-borne ligand S locus protein 11/SCR interacts with SRK expressed in stigma, which in turn autophosphorylates and promotes Ca^{2+}-dependent signal transduction that culminates in self-pollen rejection (Murase et al. 2004). Another protein kinase, named M locus protein kinase, has also been identified as a cytoplasmic mediator

of self-incompatibility in this species (Kakita et al. 2007). This is the first example that explains how self-incompatibility, in other words, allogenic authentication, is made possible in sexual reproduction of hermaphrodite organism. More recent studies have demonstrated that a similar system of the allogenic authentication (that utilizes gamete coat/membrane-associated proteins) is also present in animal hermaphrodite organisms (e.g. ascidian) (Harada et al. 2008). Whether such animal system involves protein kinase signaling is unknown.

2.49 T-Cell Origin Protein Kinase/ T-LAK cell-originated protein kinase (TOPK)

TOPK (T-LAK cell-originated protein kinase) is distributed in lymphokine-activated killer T (T-LAK) cell, testis, activated lymphoid cells, and lymphoid tumors, and is related to the dual specific mitogen-activated protein kinase kinase (MAPKK) (Abe et al. 2000). TOPK protein is expressed mainly in the cytosol of spermatocytes and spermatids to support the testicular functions (Fujibuchi et al. 2005). During mitosis, TOPK-Thr-9 was phosphorylated by cdk1/cyclin B and TOPK significantly associates with mitotic spindles (Matsumoto et al. 2004). Insulin-matured *Xenopus* oocytes showed much higher expression of TOPK and nuclear kinase (DYRK1A) but neither of these kinases activates or is activated by MAPK and is therefore unique to insulin-activated wild-type $p21^{Ras}$-induced oocyte maturation via the activation of Raf (Qu et al. 2006; Qu et al. 2007). The functions of insulin-activated wild-type $p21^{Ras}$ do not depend on the two classic Raf targets, MEK and MAPK (MAPK or ERK) (Qu et al. 2006; Qu et al. 2007).

2.50 $p65^{tpr\text{-}met}$, a fused tyrosine kinase (Tpr-Met)

Tpr-met ($p65^{tpr\text{-}met}$, a fused tyrosine kinase) efficiently induced meiotic maturation in *Xenopus* oocytes and activate MPF through a Mos-dependent pathway (Daar et al. 1991; Park et al. 1986). During *Xenopus* oocyte maturation, receptor tyrosine kinase (RTK) pathway including tpr-met takes part in the activation of MPF that requires activation of Raf and MAPK (Fabian et al. 1993). Aberrant or activated expression of Met receptor (Tpr-Met) in *Xenopus* embryonic system induces ectopic morphogenetic structures during *Xenopus* embryogenesis where recruitment of either the Grb2 or the Shc adaptor protein is sufficient to induce ectopic structures and anterior reduction but the role of PI 3-kinase and PLC recruitment are unclear (Ishimura et al. 2006). Grb2-associated binder 1 (Gab1) when overexpressed in *Xenopus* oocyte is crucial for Tpr-Met-mediated morphological transformation (Mood et al. 2006). Thus, to induce such structure Ras/Raf/MAPK pathway is important.

2.51 Vaccinia-related kinase 1 (VRK1)/*Drosophila* NHK-1

VRK1, a member of the casein kinase I (Minshull et al. 1989) family is a serine/threonine kinase related to vaccinia virus B1R serine/threonine kinase (Klerkx et al. 2009), has been identified as an early response gene required for cyclin D1 expression. VRK1 controls cell survival by phosphorylation of p53, chromatin condensation by phosphorylation of histone, and nuclear envelope assembly by phosphorylation of BANF1 (Valbuena et al. 2011). It is also involved in fragmentation of Golgi apparatus in the G2 phase-cell cycle. In *Drosophila* oocytes, nucleosomal histone kinase-1 (*Drosophila* homolog of VRK1) regulates

chromosome-nuclear envelope association via phosphorylation of BAF protein (barrier to auto-integration factor), thereby supports the meiotic progression (karyosome formation) (Lancaster et al. 2007). In the mouse, target disruption of VRK1 causes a delay in meiotic progression and results in the appearance of lagging chromosomes during formation of the metaphase plate (Schober et al. 2011), suggesting that function of VRK1 is evolutionarily conserved, although its substrate has not yet been demonstrated.

2.52 Wee1 protein kinase (Wee1)

Wee1, a protein tyrosine kinase, is the key regulator of cell cycle progression by phosphorylating and inhibiting Cdc2. Wee1, an inhibitor of Cdc2/cyclin B kinase, is decreased for mammalian oocytes meiotic competence (Mitra and Schultz 1996). Wee1 activity is necessary for the control of the first embryonic cell cycle following the fertilization of meiotically mature *Xenopus* oocytes where the protein accumulation is regulated at the level of mRNA translation (Charlesworth et al. 2000). p42 MAPK was found to phosphorylate and activate Wee1 activity towards Cdc2, thus Wee1 might work in the downstream of Mos/MEK/p42 MAPK (Walter et al. 2000). Basically in *Xenopus*, eukaryotic Wee1 homologue, termed Wee1A functions in pre-gastrula embryos with rapid cell cycle and zygotic isoform Wee1B functions post-gastrula embryos where Wee1B inhibits Cdc2 activity and oocyte maturation much more strongly than Wee1A (Okamoto et al. 2002). PKA also involved in the inactive state of Cdc2/cyclin B kinase by regulating Wee1 kinase (Han and Conti 2006).

2.53 Yes tyrosine kinase (Yes/c-Yes)

The egg cortex is known to be rich in cortical structures such as actin cytoskeleton forming microfilaments and cortical vesicles and they are important in many dynamic events in mammalian egg maturation and fertilization, such as sperm incorporation, cortical granule exocytosis, polar body emission, etc. SFKs have been shown to be associated with a wide range of cytoskeletal components and/or to phosphorylate them (Thomas and Brugge 1997). It has demonstrated that Fyn, **c-Yes** and c-Src are distributed throughout the rat egg cytoplasm, but Fyn and c-Yes are tend to concentrate at the egg cortex whereas only Fyn is localized to the spindle (Talmor-Cohen et al. 2004a). Localization of c-Src, c-Yes and Fyn to different compartments within the egg indicates that these proteins may have different functions within the egg. No change in the subcellular distribution of the three kinases has been observed throughout the stages of the fertilization process, or after parthenogenetic activation (Talmor-Cohen et al. 2004a). Though Yes kinase activity was decreased at fertilization in Zebra fish but it was concentrated in blastoderm cells and maintained the high activity throughout the gastrulation (Tsai et al. 2005). It is possible that the intracellular distribution of c-Src, c-Yes and Fyn imply their association with the cytoskeleton. The involvement of SFKs in reorganization of the cytoskeleton might be involved in egg fertilization. (Steele et al. 1989a; Tsai et al. 2005)

3. Conclusion

For conclusion, please refer to the section 3 of the chapter entitled “Phospho-signaling at Oocyte Maturation and Fertilization: Set Up for Embryogenesis and Beyond Part II. Kinase Regulators and Substrates” by Mahbub Hasan et al.

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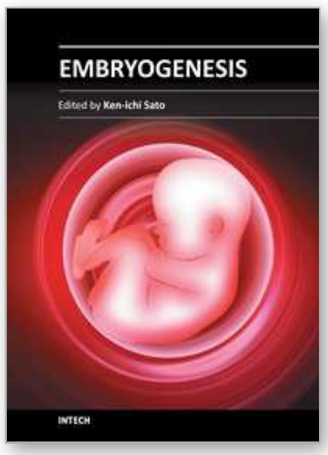

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