

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



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

A.K.M. Mahbub Hasan¹, Takashi Matsumoto²,
Shigeru Kihira², Junpei Yoshida² and Ken-ichi Sato^{2*}

¹*Laboratory of Gene Biology, Department of Biochemistry and Molecular Biology,
University of Dhaka, Dhaka,*

²*Laboratory of Cell Signaling and Development, Department of Molecular Biosciences,
Faculty of Life Sciences, Kyoto Sangyo University,
Kamigamo-Motoyama, Kita-ku, Kyoto*

¹Bangladesh

²Japan

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

* Corresponding Author

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; Tsafiriri 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; Niaux 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).

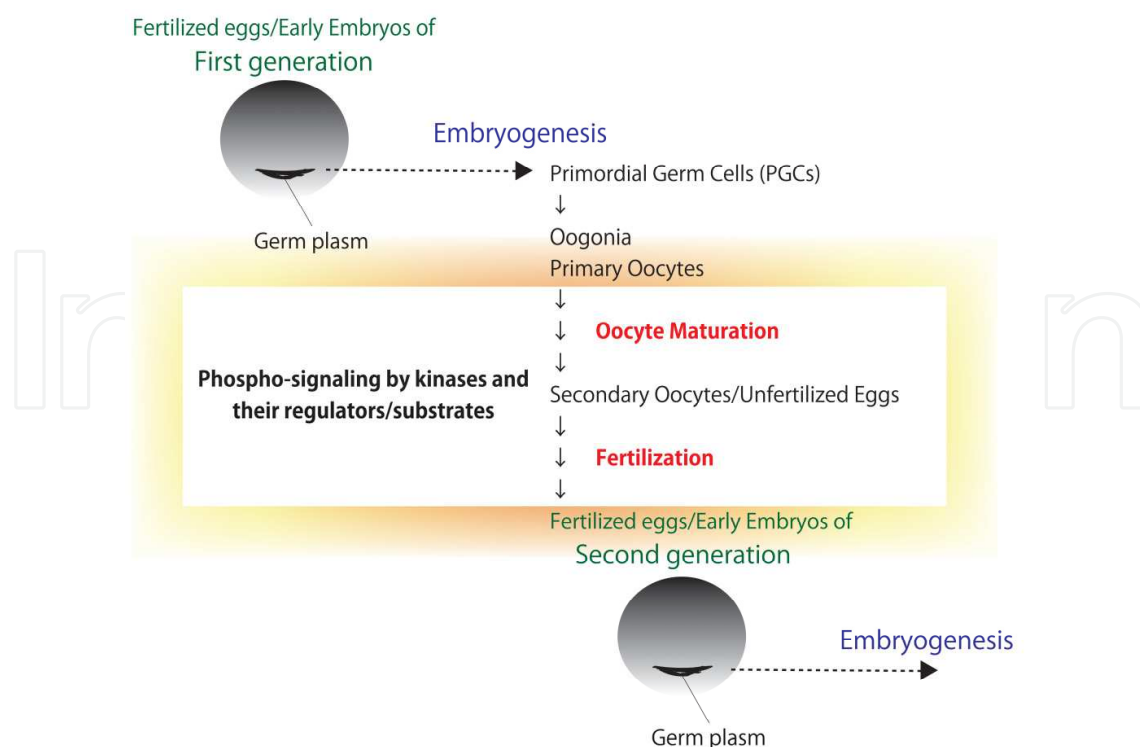


Fig. 1. Germline transmission from one generation to the next generation in sexual reproduction system. In most vertebrate species, the primary oocytes (or immature oocytes) in ovarian tissue pauses their cell cycle at prophase of the first meiosis, resumes the meiosis in response to hormonal signals, 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/lpl1p)

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; Karaïskou et al. 1998; Karaïskou 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 PLC γ .

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 C γ (PLC γ) plays an important role in inositol trisphosphate (IP $_3$)-induced Ca $^{2+}$ release. A similar tyrosine kinase-PLC γ 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 its 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 PLC γ , 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 granulosa 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)/Xp38 γ

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* p38 γ /SAPK3 is a major player in G2/M transition of immature oocytes induced by MKK6, a p38 activator. The activated p38 γ /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 G₂/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 G₂/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-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 granulosa 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 (PIP₃), a product of PI3K phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP₂) (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 Ca²⁺ 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 (Karaïskou et al. 2004). Plx1 acts as a direct inhibitory kinase of Myt1 in the mitotic cell cycles in *Xenopus* (Anger et al. 2004; Eckerd et al. 2009; Fan et al. 2003; Hansen et al. 2006; Inoue and Sagata 2005; Ito et al. 2008; Karaïskou 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 , $\beta\text{I}/\beta\text{II}$, 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 C γ (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-met}, a fused tyrosine kinase (Tpr-Met)

Tpr-met (p65^{tpr-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.

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.

5. References

- Abassi YA, Carroll DJ, Giusti AF, Belton RJ, Jr., Foltz KR. 2000. Evidence that Src-type tyrosine kinase activity is necessary for initiation of calcium release at fertilization in sea urchin eggs. *Dev Biol* 218(2):206-219.
- Abe Y, Matsumoto S, Kito K, Ueda N. 2000. Cloning and expression of a novel MAPKK-like protein kinase, lymphokine-activated killer T-cell-originated protein kinase, specifically expressed in the testis and activated lymphoid cells. *J Biol Chem* 275(28):21525-21531.
- Acevedo N, Ding J, Smith GD. 2007. Insulin signaling in mouse oocytes. *Biol Reprod* 77(5):872-879.
- Aegerter S, Jalabert B, Bobe J. 2004. Messenger RNA stockpile of cyclin B, insulin-like growth factor I, insulin-like growth factor II, insulin-like growth factor receptor Ib, and p53 in the rainbow trout oocyte in relation with developmental competence. *Mol Reprod Dev* 67(2):127-135.
- Ajduk A, Malagocki A, Maleszewski M. 2008. Cytoplasmic maturation of mammalian oocytes: development of a mechanism responsible for sperm-induced Ca^{2+} oscillations. *Reprod Biol* 8(1):3-22.
- Akabane H, Fan J, Zheng X, Zhu GZ. 2007. Protein kinase C activity in mouse eggs regulates gamete membrane interaction. *Mol Reprod Dev* 74(11):1465-1472.
- Anderson RG. 1998. The caveolae membrane system. *Annu Rev Biochem* 67:199-225.
- Andresson T, Ruderman JV. 1998. The kinase Eg2 is a component of the *Xenopus* oocyte progesterone-activated signaling pathway. *EMBO J* 17(19):5627-5637.
- Anger M, Klima J, Kubelka M, Prochazka R, Motlik J, Schultz RM. 2004. Timing of Plk1 and MPF activation during porcine oocyte maturation. *Mol Reprod Dev* 69(1):11-16.
- Arceci RJ, Pampfer S, Pollard JW. 1992. Expression of CSF-1/c-fms and SF/c-kit mRNA during preimplantation mouse development. *Dev Biol* 151(1):1-8.
- Arion D, Meijer L, Brizuela L, Beach D. 1988. cdc2 is a component of the M phase-specific histone H1 kinase: evidence for identity with MPF. *Cell* 55(2):371-378.
- Armant DR, Kilburn BA, Petkova A, Edwin SS, Duniec-Dmuchowski ZM, Edwards HJ, Romero R, Leach RE. 2006. Human trophoblast survival at low oxygen concentrations requires metalloproteinase-mediated shedding of heparin-binding EGF-like growth factor. *Development* 133(4):751-759.
- Astier A, Manie SN, Avraham H, Hirai H, Law SF, Zhang Y, Golemis EA, Fu Y, Druker BJ, Haghayeghi N, Freedman AS, Avraham S. 1997. The related adhesion focal tyrosine kinase differentially phosphorylates p130Cas and the Cas-like protein, p105HEF1. *J Biol Chem* 272(32):19719-19724.
- Bagowski CP, Xiong W, Ferrell JE, Jr. 2001. c-Jun N-terminal kinase activation in *Xenopus laevis* eggs and embryos. A possible non-genomic role for the JNK signaling pathway. *J Biol Chem* 276(2):1459-1465.

- Balamurugan K, Haider S. 1998. Partial purification of maturation-promoting factor from catfish, *Clarias batrachus*: identification as the histone H1 kinase and its periodic activation. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol* 120(3):329-342.
- Baluch DP, Capco DG. 2008. GSK3 beta mediates acentromeric spindle stabilization by activated PKC zeta. *Dev Biol* 317(1):46-58.
- Baluch DP, Koeneman BA, Hatch KR, McGaughey RW, Capco DG. 2004. PKC isotypes in post-activated and fertilized mouse eggs: association with the meiotic spindle. *Dev Biol* 274(1):45-55.
- Barrett CB, Erikson E, Maller JL. 1992. A purified S6 kinase kinase from *Xenopus* eggs activates S6 kinase II and autophosphorylates on serine, threonine, and tyrosine residues. *J Biol Chem* 267(7):4408-4415.
- Becker W. 2011. Recent insights into the function of DYRK1A. *FEBS J* 278(2):222.
- Becker W, Sippl W. 2011. Activation, regulation, and inhibition of DYRK1A. *FEBS J* 278(2):246-256.
- Belton RJ, Jr., Adams NL, Foltz KR. 2001. Isolation and characterization of sea urchin egg lipid rafts and their possible function during fertilization. *Mol Reprod Dev* 59(3):294-305.
- Bilodeau-Goeseels S, Sasseville M, Guillemette C, Richard FJ. 2007. Effects of adenosine monophosphate-activated kinase activators on bovine oocyte nuclear maturation in vitro. *Mol Reprod Dev* 74(8):1021-1034.
- Bischoff JR, Plowman GD. 1999. The Aurora/Ipl1p kinase family: regulators of chromosome segregation and cytokinesis. *Trends Cell Biol* 9(11):454-459.
- Bokoch GM. 2003. Biology of the p21-activated kinases. *Annu Rev Biochem* 72:743-781.
- Bornslaeger EA, Mattei P, Schultz RM. 1986. Involvement of cAMP-dependent protein kinase and protein phosphorylation in regulation of mouse oocyte maturation. *Dev Biol* 114(2):453-462.
- Brown MR, Clark KD, Gulia M, Zhao Z, Garczynski SF, Crim JW, Suderman RJ, Strand MR. 2008. An insulin-like peptide regulates egg maturation and metabolism in the mosquito *Aedes aegypti*. *Proc Natl Acad Sci U S A* 105(15):5716-5721.
- Brown MT, Cooper JA. 1996. Regulation, substrates and functions of src. *Biochim Biophys Acta* 1287(2-3):121-149.
- Browne CL, Bower WA, Palazzo RE, Rebhun LI. 1990. Inhibition of mitosis in fertilized sea urchin eggs by inhibition of the cyclic AMP-dependent protein kinase. *Exp Cell Res* 188(1):122-128.
- Brunet S, Maro B. 2005. Cytoskeleton and cell cycle control during meiotic maturation of the mouse oocyte: integrating time and space. *Reproduction* 130(6):801-811.
- Burrows AE, Scurman BK, Kosinski ME, Richie CT, Sadler PL, Schumacher JM, Golden A. 2006. The *C. elegans* Myt1 ortholog is required for the proper timing of oocyte maturation. *Development* 133(4):697-709.
- Byun HM, Kang SG, Kang HM. 2002. Cloning of ribosomal protein S6 kinase cDNA and its involvement in meiotic maturation in *Rana dybowskii* oocytes. *Mol Cells* 14(1):16-23.
- Cailliau K, Le Marcis V, Bereziat V, Perdureau D, Cariou B, Vilain JP, Burnol AF, Browaeys-Poly E. 2003. Inhibition of FGF receptor signalling in *Xenopus* oocytes: differential effect of Grb7, Grb10 and Grb14. *FEBS Lett* 548(1-3):43-48.
- Capco DG. 2001. Molecular and biochemical regulation of early mammalian development. *Int Rev Cytol* 207:195-235.

- Capco DG, Tutnick JM, Bement WM. 1992. The role of protein kinase C in reorganization of the cortical cytoskeleton during the transition from oocyte to fertilization-competent egg. *J Exp Zool* 264(4):395-405.
- Carroll DJ, Albay DT, Terasaki M, Jaffe LA, Foltz KR. 1999. Identification of PLCgamma-dependent and -independent events during fertilization of sea urchin eggs. *Dev Biol* 206(2):232-247.
- Cary LA, Guan JL. 1999. Focal adhesion kinase in integrin-mediated signaling. *Front Biosci* 4:D102-113.
- Castilho PV, Williams BC, Mochida S, Zhao Y, Goldberg ML. 2009. The M phase kinase Greatwall (Gwl) promotes inactivation of PP2A/B55delta, a phosphatase directed against CDK phosphosites. *Mol Biol Cell* 20(22):4777-4789.
- Castro A, Peter M, Magnaghi-Jaulin L, Vigneron S, Galas S, Lorca T, Labbe JC. 2001. Cyclin B/cdc2 induces c-Mos stability by direct phosphorylation in *Xenopus* oocytes. *Mol Biol Cell* 12(9):2660-2671.
- Charlesworth A, Welk J, MacNicol AM. 2000. The temporal control of Wee1 mRNA translation during *Xenopus* oocyte maturation is regulated by cytoplasmic polyadenylation elements within the 3'-untranslated region. *Dev Biol* 227(2):706-719.
- Chaube SK, Dubey PK, Mishra SK, Shrivastav TG. 2007. Verapamil reversibly inhibits spontaneous parthenogenetic activation in aged rat eggs cultured in vitro. *Cloning Stem Cells* 9(4):608-617.
- Chen J, Downs SM. 2008. AMP-activated protein kinase is involved in hormone-induced mouse oocyte meiotic maturation in vitro. *Dev Biol* 313(1):47-57.
- Chen J, Hudson E, Chi MM, Chang AS, Moley KH, Hardie DG, Downs SM. 2006. AMPK regulation of mouse oocyte meiotic resumption in vitro. *Dev Biol* 291(2):227-238.
- Cheng KC, Klancer R, Singson A, Seydoux G. 2009. Regulation of MBK-2/DYRK by CDK-1 and the pseudophosphatases EGG-4 and EGG-5 during the oocyte-to-embryo transition. *Cell* 139(3):560-572.
- Chesnel F, Bonnet G, Tardivel A, Boujard D. 1997. Comparative effects of insulin on the activation of the Raf/Mos-dependent MAP kinase cascade in vitellogenic versus postvitellogenic *Xenopus* oocytes. *Dev Biol* 188(1):122-133.
- Chie L, Amar S, Kung HF, Lin MC, Chen H, Chung DL, Adler V, Ronai Z, Friedman FK, Robinson RC, Kovac C, Brandt-Rauf PW, Yamaizumi Z, Michl J, Pincus MR. 2000. Induction of oocyte maturation by jun-N-terminal kinase (JNK) on the oncogenic ras-p21 pathway is dependent on the raf-MEK signal transduction pathway. *Cancer Chemother Pharmacol* 45(6):441-449.
- Chieffi P, Barchi M, Di Agostino S, Rossi P, Tramontano D, Geremia R. 2003. Prolin-rich tyrosine kinase 2 (PYK2) expression and localization in mouse testis. *Mol Reprod Dev* 65(3):330-335.
- Chobotova K, Spyropoulou I, Carver J, Manek S, Heath JK, Gullick WJ, Barlow DH, Sargent IL, Mardon HJ. 2002. Heparin-binding epidermal growth factor and its receptor ErbB4 mediate implantation of the human blastocyst. *Mech Dev* 119(2):137-144.
- Choi T, Rulong S, Resau J, Fukasawa K, Matten W, Kuriyama R, Mansour S, Ahn N, Vande Woude GF. 1996. Mos/mitogen-activated protein kinase can induce early meiotic phenotypes in the absence of maturation-promoting factor: a novel system for analyzing spindle formation during meiosis I. *Proc Natl Acad Sci U S A* 93(10):4730-4735.

- Chuang LM, Hausdorff SF, Myers MG, Jr., White MF, Birnbaum MJ, Kahn CR. 1994. Interactive roles of Ras, insulin receptor substrate-1, and proteins with Src homology-2 domains in insulin signaling in *Xenopus* oocytes. *J Biol Chem* 269(44):27645-27649.
- Chuang LM, Myers MG, Jr., Backer JM, Shoelson SE, White MF, Birnbaum MJ, Kahn CR. 1993. Insulin-stimulated oocyte maturation requires insulin receptor substrate 1 and interaction with the SH2 domains of phosphatidylinositol 3-kinase. *Mol Cell Biol* 13(11):6653-6660.
- Chung J, Pelech SL, Blenis J. 1991. Mitogen-activated Swiss mouse 3T3 RSK kinases I and II are related to pp44mpk from sea star oocytes and participate in the regulation of pp90rsk activity. *Proc Natl Acad Sci U S A* 88(11):4981-4985.
- Ciemerych MA, Tarkowski AK, Kubiak JZ. 1998. Autonomous activation of histone H1 kinase, cortical activity and microtubule organization in one- and two-cell mouse embryos. *Biol Cell* 90(8):557-564.
- Clarke PR, Karsenti E. 1991. Regulation of p34cdc2 protein kinase: new insights into protein phosphorylation and the cell cycle. *J Cell Sci* 100 (Pt 3):409-414.
- Collas P, Sullivan EJ, Barnes FL. 1993. Histone H1 kinase activity in bovine oocytes following calcium stimulation. *Mol Reprod Dev* 34(2):224-231.
- Culp PA, Musci TJ. 1998. Translational activation and cytoplasmic polyadenylation of FGF receptor-1 are independently regulated during *Xenopus* oocyte maturation. *Dev Biol* 193(1):63-76.
- Culp PA, Musci TJ. 1999. c-mos and cdc2 cooperate in the translational activation of fibroblast growth factor receptor-1 during *Xenopus* oocyte maturation. *Mol Biol Cell* 10(11):3567-3581.
- Daar I, Yew N, Vande Woude GF. 1993. Inhibition of mos-induced oocyte maturation by protein kinase A. *J Cell Biol* 120(5):1197-1202.
- Daar IO, White GA, Schuh SM, Ferris DK, Vande Woude GF. 1991. tpr-met oncogene product induces maturation-producing factor activation in *Xenopus* oocytes. *Mol Cell Biol* 11(12):5985-5991.
- Dasgupta JD, Garbers DL. 1983. Tyrosine protein kinase activity during embryogenesis. *J Biol Chem* 258(10):6174-6178.
- de Barry J, Kawahara S, Takamura K, Janoshazi A, Kirino Y, Olds JL, Lester DS, Alkon DL, Yoshioka T. 1997. Time-resolved imaging of protein kinase C activation during sea urchin egg fertilization. *Exp Cell Res* 234(1):115-124.
- de Klein A, van Kessel AG, Grosveld G, Bartram CR, Hagemeijer A, Bootsma D, Spurr NK, Heisterkamp N, Groffen J, Stephenson JR. 1982. A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukaemia. *Nature* 300(5894):765-767.
- de Vries C, Escobedo JA, Ueno H, Houck K, Ferrara N, Williams LT. 1992. The fms-like tyrosine kinase, a receptor for vascular endothelial growth factor. *Science* 255(5047):989-991.
- Deng X, Feng C, Wang EH, Zhu YQ, Cui C, Zong ZH, Li GS, Liu C, Meng J, Yu BZ. 2011. Influence of proline-rich inositol polyphosphate 5-phosphatase, on early development of fertilized mouse eggs, via inhibition of phosphorylation of Akt. *Cell Prolif* 44(2):156-165.
- Detivaud L, Pascreau G, Karaïskou A, Osborne HB, Kubiak JZ. 2003. Regulation of EDEN-dependent deadenylation of Aurora A/Eg2-derived mRNA via phosphorylation

- and dephosphorylation in *Xenopus laevis* egg extracts. *J Cell Sci* 116(Pt 13):2697-2705.
- Diaz-Meco MT, Lozano J, Municio MM, Berra E, Frutos S, Sanz L, Moscat J. 1994. Evidence for the in vitro and in vivo interaction of Ras with protein kinase C zeta. *J Biol Chem* 269(50):31706-31710.
- Ding J, Swain JE, Smith GD. 2011. Aurora kinase-A regulates microtubule organizing center (MTOC) localization, chromosome dynamics, and histone-H3 phosphorylation in mouse oocytes. *Mol Reprod Dev* 78(2):80-90.
- Dodson GS, Guarnieri DJ, Simon MA. 1998. Src64 is required for ovarian ring canal morphogenesis during *Drosophila* oogenesis. *Development* 125(15):2883-2892.
- Ducibella T. 1996. The cortical reaction and development of activation competence in mammalian oocytes. *Hum Reprod Update* 2(1):29-42.
- Ducibella T, Fissore R. 2008. The roles of Ca²⁺, downstream protein kinases, and oscillatory signaling in regulating fertilization and the activation of development. *Dev Biol* 315(2):257-279.
- Ducibella T, LeFevre L. 1997. Study of protein kinase C antagonists on cortical granule exocytosis and cell-cycle resumption in fertilized mouse eggs. *Mol Reprod Dev* 46(2):216-226.
- Dumont J, Umbhauer M, Rassinier P, Hanauer A, Verlhac MH. 2005. p90Rsk is not involved in cytostatic factor arrest in mouse oocytes. *J Cell Biol* 169(2):227-231.
- Duncan MJ, Li G, Shin JS, Carson JL, Abraham SN. 2004. Bacterial penetration of bladder epithelium through lipid rafts. *J Biol Chem* 279(18):18944-18951.
- Duncan PI, Pollet N, Niehrs C, Nigg EA. 2001. Cloning and characterization of Plx2 and Plx3, two additional Polo-like kinases from *Xenopus laevis*. *Exp Cell Res* 270(1):78-87.
- Eckberg WR. 1997. MAP and cdc2 kinase activities at germinal vesicle breakdown in *Chaetopterus*. *Dev Biol* 191(2):182-190.
- Eckerdt F, Pascreau G, Phistry M, Lewellyn AL, DePaoli-Roach AA, Maller JL. 2009. Phosphorylation of TPX2 by Plx1 enhances activation of Aurora A. *Cell Cycle* 8(15):2413-2419.
- Edgecombe M, Patel R, Whitaker M. 1991. A cyclin-abundance cycle-independent p34cdc2 tyrosine phosphorylation cycle in early sea urchin embryos. *EMBO J* 10(12):3769-3775.
- Einspanier R, Schonfelder M, Muller K, Stojkovic M, Kosmann M, Wolf E, Schams D. 2002. Expression of the vascular endothelial growth factor and its receptors and effects of VEGF during in vitro maturation of bovine cumulus-oocyte complexes (COC). *Mol Reprod Dev* 62(1):29-36.
- El-Etr M, Schorderet-Slatkine S, Baulieu EE. 1979. Meiotic maturation in *Xenopus laevis* oocytes initiated by insulin. *Science* 205(4413):1397-1399.
- Eliyahu E, Kaplan-Kraicer R, Shalgi R. 2001. PKC in eggs and embryos. *Front Biosci* 6:D785-791.
- Eliyahu E, Shalgi R. 2002. A role for protein kinase C during rat egg activation. *Biol Reprod* 67(1):189-195.
- Eliyahu E, Talmor-Cohen A, Shalgi R. 2002. Signaling through protein kinases during egg activation. *J Reprod Immunol* 53(1-2):161-169.
- Eliyahu E, Tsaadon A, Shtraizent N, Shalgi R. 2005. The involvement of protein kinase C and actin filaments in cortical granule exocytosis in the rat. *Reproduction* 129(2):161-170.

- Emily-Fenouil F, Ghiglione C, Lhomond G, Lepage T, Gache C. 1998. GSK3 β /shaggy mediates patterning along the animal-vegetal axis of the sea urchin embryo. *Development* 125(13):2489-2498.
- Erikson E, Maller JL. 1988. Substrate specificity of ribosomal protein S6 kinase II from *Xenopus* eggs. *Second Messengers Phosphoproteins* 12(2-3):135-143.
- Erikson E, Stefanovic D, Blenis J, Erikson RL, Maller JL. 1987. Antibodies to *Xenopus* egg S6 kinase II recognize S6 kinase from progesterone- and insulin-stimulated *Xenopus* oocytes and from proliferating chicken embryo fibroblasts. *Mol Cell Biol* 7(9):3147-3155.
- Eswarakumar VP, Lax I, Schlessinger J. 2005. Cellular signaling by fibroblast growth factor receptors. *Cytokine Growth Factor Rev* 16(2):139-149.
- Fabian JR, Morrison DK, Daar IO. 1993. Requirement for Raf and MAP kinase function during the meiotic maturation of *Xenopus* oocytes. *J Cell Biol* 122(3):645-652.
- Fan HY, Tong C, Li MY, Lian L, Chen DY, Schatten H, Sun QY. 2002. Translocation of the classic protein kinase C isoforms in porcine oocytes: implications of protein kinase C involvement in the regulation of nuclear activity and cortical granule exocytosis. *Exp Cell Res* 277(2):183-191.
- Fan HY, Tong C, Teng CB, Lian L, Li SW, Yang ZM, Chen DY, Schatten H, Sun QY. 2003. Characterization of Polo-like kinase-1 in rat oocytes and early embryos implies its functional roles in the regulation of meiotic maturation, fertilization, and cleavage. *Mol Reprod Dev* 65(3):318-329.
- Farhi J, Ao A, Fisch B, Zhang XY, Garor R, Abir R. 2010. Glial cell line-derived neurotrophic factor (GDNF) and its receptors in human ovaries from fetuses, girls, and women. *Fertil Steril* 93(8):2565-2571.
- Faure S, Morin N, Doree M. 1998. Inactivation of protein kinase A is not required for c-mos translation during meiotic maturation of *Xenopus* oocytes. *Oncogene* 17(10):1215-1221.
- Faure S, Vigneron S, Doree M, Morin N. 1997. A member of the Ste20/PAK family of protein kinases is involved in both arrest of *Xenopus* oocytes at G2/prophase of the first meiotic cell cycle and in prevention of apoptosis. *EMBO J* 16(18):5550-5561.
- Faure S, Vigneron S, Galas S, Brassac T, Delsert C, Morin N. 1999. Control of G2/M transition in *Xenopus* by a member of the p21-activated kinase (PAK) family: a link between protein kinase A and PAK signaling pathways? *J Biol Chem* 274(6):3573-3579.
- Feng C, Yu A, Liu Y, Zhang J, Zong Z, Su W, Zhang Z, Yu D, Sun QY, Yu B. 2007. Involvement of protein kinase B/AKT in early development of mouse fertilized eggs. *Biol Reprod* 77(3):560-568.
- Ferrell JE, Jr. 1999. *Xenopus* oocyte maturation: new lessons from a good egg. *Bioessays* 21(10):833-842.
- Ferrell JE, Jr., Machleder EM. 1998. The biochemical basis of an all-or-none cell fate switch in *Xenopus* oocytes. *Science* 280(5365):895-898.
- Ferrell JE, Jr., Wu M, Gerhart JC, Martin GS. 1991. Cell cycle tyrosine phosphorylation of p34cdc2 and a microtubule-associated protein kinase homolog in *Xenopus* oocytes and eggs. *Mol Cell Biol* 11(4):1965-1971.
- Frank-Vaillant M, Haccard O, Thibier C, Ozon R, Arlot-Bonnemains Y, Prigent C, Jessus C. 2000. Progesterone regulates the accumulation and the activation of Eg2 kinase in *Xenopus* oocytes. *J Cell Sci* 113 (Pt 7):1127-1138.

- Fujibuchi T, Abe Y, Takeuchi T, Ueda N, Shigemoto K, Yamamoto H, Kito K. 2005. Expression and phosphorylation of TOPK during spermatogenesis. *Dev Growth Differ* 47(9):637-644.
- Fulka J, Jr., Jung T, Moor RM. 1992. The fall of biological maturation promoting factor (MPF) and histone H1 kinase activity during anaphase and telophase in mouse oocytes. *Mol Reprod Dev* 32(4):378-382.
- Gaffre M, Martoriati A, Belhachemi N, Chambon JP, Houliston E, Jessus C, Karaïskou A. 2011. A critical balance between Cyclin B synthesis and Myt1 activity controls meiosis entry in *Xenopus* oocytes. *Development* 138(17):3735-3744.
- Galat V, Zhou Y, Taborn G, Garton R, Iannaccone P. 2007. Overcoming MIII arrest from spontaneous activation in cultured rat oocytes. *Cloning Stem Cells* 9(3):303-314.
- Gallicano GI, McGaughey RW, Capco DG. 1995. Protein kinase M, the cytosolic counterpart of protein kinase C, remodels the internal cytoskeleton of the mammalian egg during activation. *Dev Biol* 167(2):482-501.
- Gallicano GI, McGaughey RW, Capco DG. 1997. Activation of protein kinase C after fertilization is required for remodeling the mouse egg into the zygote. *Mol Reprod Dev* 46(4):587-601.
- Gavin AC, Cavadore JC, Schorderet-Slatkine S. 1994. Histone H1 kinase activity, germinal vesicle breakdown and M phase entry in mouse oocytes. *J Cell Sci* 107 (Pt 1):275-283.
- Gavin AC, Ni Ainle A, Chierici E, Jones M, Nebreda AR. 1999. A p90(rsk) mutant constitutively interacting with MAP kinase uncouples MAP kinase from p34(cdc2)/cyclin B activation in *Xenopus* oocytes. *Mol Biol Cell* 10(9):2971-2986.
- Gilkey JC, Jaffe LF, Ridgway EB, Reynolds GT. 1978. A free calcium wave traverses the activating egg of the medaka, *Oryzias latipes*. *J Cell Biol* 76(2):448-466.
- Git A, Allison R, Perdiguero E, Nebreda AR, Houliston E, Standart N. 2009. Vg1RBP phosphorylation by Erk2 MAP kinase correlates with the cortical release of Vg1 mRNA during meiotic maturation of *Xenopus* oocytes. *RNA* 15(6):1121-1133.
- Giusti AF, Carroll DJ, Abassi YA, Foltz KR. 1999a. Evidence that a starfish egg Src family tyrosine kinase associates with PLC-gamma1 SH2 domains at fertilization. *Dev Biol* 208(1):189-199.
- Giusti AF, Carroll DJ, Abassi YA, Terasaki M, Foltz KR, Jaffe LA. 1999b. Requirement of a Src family kinase for initiating calcium release at fertilization in starfish eggs. *J Biol Chem* 274(41):29318-29322.
- Giusti AF, Foltz KR, Jaffe LA. 2000a. The role of Src family kinases in starfish egg fertilisation. *Zygote* 8 Suppl 1:S16-17.
- Giusti AF, O'Neill FJ, Yamasu K, Foltz KR, Jaffe LA. 2003. Function of a sea urchin egg Src family kinase in initiating Ca²⁺ release at fertilization. *Dev Biol* 256(2):367-378.
- Giusti AF, Xu W, Hinkle B, Terasaki M, Jaffe LA. 2000b. Evidence that fertilization activates starfish eggs by sequential activation of a Src-like kinase and phospholipase cgamma. *J Biol Chem* 275(22):16788-16794.
- Glahn D, Mark SD, Behr RK, Nuccitelli R. 1999. Tyrosine kinase inhibitors block sperm-induced egg activation in *Xenopus laevis*. *Dev Biol* 205(1):171-180.
- Glover CV, 3rd. 1998. On the physiological role of casein kinase II in *Saccharomyces cerevisiae*. *Prog Nucleic Acid Res Mol Biol* 59:95-133.
- Golubovskaya VM, Cance W. 2010. Focal adhesion kinase and p53 signal transduction pathways in cancer. *Front Biosci* 15:901-912.

- Grieco D, Avvedimento EV, Gottesman ME. 1994. A role for cAMP-dependent protein kinase in early embryonic divisions. *Proc Natl Acad Sci U S A* 91(21):9896-9900.
- Grieco D, Porcellini A, Avvedimento EV, Gottesman ME. 1996. Requirement for cAMP-PKA pathway activation by M phase-promoting factor in the transition from mitosis to interphase. *Science* 271(5256):1718-1723.
- Grigorescu F, Baccara MT, Rouard M, Renard E. 1994. Insulin and IGF-1 signaling in oocyte maturation. *Horm Res* 42(1-2):55-61.
- Gross SD, Schwab MS, Taieb FE, Lewellyn AL, Qian YW, Maller JL. 2000. The critical role of the MAP kinase pathway in meiosis II in *Xenopus* oocytes is mediated by p90(Rsk). *Curr Biol* 10(8):430-438.
- Gutierrez GJ, Vogtlin A, Castro A, Ferby I, Salvagiotto G, Ronai Z, Lorca T, Nebreda AR. 2006. Meiotic regulation of the CDK activator RINGO/Speedy by ubiquitin-proteasome-mediated processing and degradation. *Nat Cell Biol* 8(10):1084-1094.
- Haberman Y, Alon LT, Eliyahu E, Shalgi R. 2011. Receptor for activated C kinase (RACK) and protein kinase C (PKC) in egg activation. *Theriogenology* 75(1):80-89.
- Halet G. 2004. PKC signaling at fertilization in mammalian eggs. *Biochim Biophys Acta* 1742(1-3):185-189.
- Han SJ, Conti M. 2006. New pathways from PKA to the Cdc2/cyclin B complex in oocytes: Wee1B as a potential PKA substrate. *Cell Cycle* 5(3):227-231.
- Han SJ, Vaccari S, Nedachi T, Andersen CB, Kovacina KS, Roth RA, Conti M. 2006a. Protein kinase B/Akt phosphorylation of PDE3A and its role in mammalian oocyte maturation. *EMBO J* 25(24):5716-5725.
- Hansen DV, Tung JJ, Jackson PK. 2006. CaMKII and polo-like kinase 1 sequentially phosphorylate the cytostatic factor Emi2/XErp1 to trigger its destruction and meiotic exit. *Proc Natl Acad Sci U S A* 103(3):608-613.
- Harada Y, Takagaki Y, Sunagawa M, Saito T, Yamada L, Taniguchi H, Shoguchi E, Sawada H. 2008. Mechanism of self-sterility in a hermaphroditic chordate. *Science* 320(5875):548-550.
- Hardie DG, Carling D. 1997. The AMP-activated protein kinase--fuel gauge of the mammalian cell? *Eur J Biochem* 246(2):259-273.
- Hartwell LH. 1991. Twenty-five years of cell cycle genetics. *Genetics* 129(4):975-980.
- Heinecke JW, Meier KE, Lorenzen JA, Shapiro BM. 1990. A specific requirement for protein kinase C in activation of the respiratory burst oxidase of fertilization. *J Biol Chem* 265(14):7717-7720.
- Hemmings BA. 1997. Akt signaling: linking membrane events to life and death decisions. *Science* 275(5300):628-630.
- Hens MD, DeSimone DW. 1995. Molecular analysis and developmental expression of the focal adhesion kinase pp125FAK in *Xenopus laevis*. *Dev Biol* 170(2):274-288.
- Hertweck M, Gobel C, Baumeister R. 2004. *C. elegans* SGK-1 is the critical component in the Akt/PKB kinase complex to control stress response and life span. *Dev Cell* 6(4):577-588.
- Hiraoka D, Hori-Oshima S, Fukuhara T, Tachibana K, Okumura E, Kishimoto T. 2004. PDK1 is required for the hormonal signaling pathway leading to meiotic resumption in starfish oocytes. *Dev Biol* 276(2):330-336.
- Hodgman R, Tay J, Mendez R, Richter JD. 2001. CPEB phosphorylation and cytoplasmic polyadenylation are catalyzed by the kinase IAK1/Eg2 in maturing mouse oocytes. *Development* 128(14):2815-2822.

- Homer H. 2011. New insights into the genetic regulation of homologue disjunction in mammalian oocytes. *Cytogenet Genome Res* 133(2-4):209-222.
- Horie K, Takakura K, Taii S, Narimoto K, Noda Y, Nishikawa S, Nakayama H, Fujita J, Mori T. 1991. The expression of c-kit protein during oogenesis and early embryonic development. *Biol Reprod* 45(4):547-552.
- Horner VL, Wolfner MF. 2008. Transitioning from egg to embryo: triggers and mechanisms of egg activation. *Dev Dyn* 237(3):527-544.
- Hoshino Y, Sato E. 2008. Protein kinase B (PKB/Akt) is required for the completion of meiosis in mouse oocytes. *Dev Biol* 314(1):215-223.
- Hoshino Y, Yokoo M, Yoshida N, Sasada H, Matsumoto H, Sato E. 2004. Phosphatidylinositol 3-kinase and Akt participate in the FSH-induced meiotic maturation of mouse oocytes. *Mol Reprod Dev* 69(1):77-86.
- Huang X, Tong JS, Wang ZB, Yang CR, Qi ST, Guo L, Ouyang YC, Quan S, Sun QY, Qi ZQ, Huang RX, Wang HL. 2011. JNK2 participates in spindle assembly during mouse oocyte meiotic maturation. *Microsc Microanal* 17(2):197-205.
- Hudmon A, Schulman H, Kim J, Maltez JM, Tsien RW, Pitt GS. 2005. CaMKII tethers to L-type Ca^{2+} channels, establishing a local and dedicated integrator of Ca^{2+} signals for facilitation. *J Cell Biol* 171(3):537-547.
- Huo LJ, Fan HY, Zhong ZS, Chen DY, Schatten H, Sun QY. 2004. Ubiquitin-proteasome pathway modulates mouse oocyte meiotic maturation and fertilization via regulation of MAPK cascade and cyclin B1 degradation. *Mech Dev* 121(10):1275-1287.
- Hupalowska A, Kalaszczynska I, Hoffmann S, Tsurumi C, Kubiak JZ, Polanski Z, Ciemerych MA. 2008. Metaphase I arrest in LT/Sv mouse oocytes involves the spindle assembly checkpoint. *Biol Reprod* 79(6):1102-1110.
- Hyodo-Miura J, Urushiyama S, Nagai S, Nishita M, Ueno N, Shibuya H. 2002. Involvement of NLK and Sox11 in neural induction in *Xenopus* development. *Genes Cells* 7(5):487-496.
- Inoue D, Sagata N. 2005. The Polo-like kinase Plx1 interacts with and inhibits Myt1 after fertilization of *Xenopus* eggs. *EMBO J* 24(5):1057-1067.
- Ishida A, Fujisawa H. 1995. Stabilization of calmodulin-dependent protein kinase II through the autoinhibitory domain. *J Biol Chem* 270(5):2163-2170.
- Ishimura A, Lee HS, Bong YS, Saucier C, Mood K, Park EK, Daar IO. 2006. Oncogenic Met receptor induces ectopic structures in *Xenopus* embryos. *Oncogene* 25(31):4286-4299.
- Ishitani T, Ishitani S, Matsumoto K, Itoh M. 2009. Nemo-like kinase is involved in NGF-induced neurite outgrowth via phosphorylating MAP1B and paxillin. *J Neurochem* 111(5):1104-1118.
- Ito J, Yoon SY, Lee B, Vanderheyden V, Vermassen E, Wojcikiewicz R, Alfandari D, De Smedt H, Parys JB, Fissore RA. 2008. Inositol 1,4,5-trisphosphate receptor 1, a widespread Ca^{2+} channel, is a novel substrate of polo-like kinase 1 in eggs. *Dev Biol* 320(2):402-413.
- Ito J, Yoshida T, Kasai Y, Wakai T, Parys JB, Fissore RA, Kashiwazaki N. 2010. Phosphorylation of inositol 1,4,5-trisphosphate receptor 1 during in vitro maturation of porcine oocytes. *Anim Sci J* 81(1):34-41.
- Itoh T, Hasegawa J, Tsujita K, Kanaho Y, Takenawa T. 2009. The tyrosine kinase Fer is a downstream target of the PLD-PA pathway that regulates cell migration. *Sci Signal* 2(87):ra52.

- Iwasaki T, Koretomo Y, Fukuda T, Paronetto MP, Sette C, Fukami Y, Sato K. 2008. Expression, phosphorylation, and mRNA-binding of heterogeneous nuclear ribonucleoprotein K in *Xenopus* oocytes, eggs, and early embryos. *Dev Growth Differ* 50(1):23-40.
- Iwasaki T, Sato K, Yoshino K, Itakura S, Kosuge K, Tokmakov AA, Owada K, Yonezawa K, Fukami Y. 2006. Phylogeny of vertebrate Src tyrosine kinases revealed by the epitope region of mAb327. *J Biochem* 139(3):347-354.
- Janicot M, Flores-Riveros JR, Lane MD. 1991. The insulin-like growth factor 1 (IGF-1) receptor is responsible for mediating the effects of insulin, IGF-1, and IGF-2 in *Xenopus laevis* oocytes. *J Biol Chem* 266(15):9382-9391.
- Jeanmart J, Uytendhoef P, De Sutter G, Legros F. 1976. Insulin receptor sites as membrane markers during embryonic development. I. Data obtained with unfertilized and fertilized sea urchin eggs. *Differentiation* 7(1):23-30.
- Jelinkova L, Kubelka M. 2006. Neither Aurora B activity nor histone H3 phosphorylation is essential for chromosome condensation during meiotic maturation of porcine oocytes. *Biol Reprod* 74(5):905-912.
- Jelinkova L, Kubelka M, Motlik J, Guerrier P. 1994. Chromatin condensation and histone H1 kinase activity during growth and maturation of rabbit oocytes. *Mol Reprod Dev* 37(2):210-215.
- Jessmon P, Leach RE, Armant DR. 2009. Diverse functions of HBEGF during pregnancy. *Mol Reprod Dev* 76(12):1116-1127.
- Jiang Y, Chan JL, Zong CS, Wang LH. 1996. Effect of tyrosine mutations on the kinase activity and transforming potential of an oncogenic human insulin-like growth factor I receptor. *J Biol Chem* 271(1):160-167.
- Jove R, Hanafusa H. 1987. Cell transformation by the viral src oncogene. *Annu Rev Cell Biol* 3:31-56.
- Kakita M, Murase K, Iwano M, Matsumoto T, Watanabe M, Shiba H, Isogai A, Takayama S. 2007. Two distinct forms of M-locus protein kinase localize to the plasma membrane and interact directly with S-locus receptor kinase to transduce self-incompatibility signaling in *Brassica rapa*. *Plant Cell* 19(12):3961-3973.
- Kaliva M, Faust JJ, Koeneman BA, Capco DG. 2010. Involvement of the PKC family in regulation of early development. *Mol Reprod Dev* 77(2):95-104.
- Kalous J, Kubelka M, Solc P, Susor A, Motlik J. 2009. AKT (protein kinase B) is implicated in meiotic maturation of porcine oocytes. *Reproduction* 138(4):645-654.
- Kalous J, Solc P, Baran V, Kubelka M, Schultz RM, Motlik J. 2006. PKB/AKT is involved in resumption of meiosis in mouse oocytes. *Biol Cell* 98(2):111-123.
- Kamel C, Veno PA, Kinsey WH. 1986. Quantitation of a src-like tyrosine protein kinase during fertilization of the sea urchin egg. *Biochem Biophys Res Commun* 138(1):349-355.
- Kang MK, Han SJ. 2011. Post-transcriptional and post-translational regulation during mouse oocyte maturation. *BMB Rep* 44(3):147-157.
- Kang MG, Kulisz A, Wasserman WJ. 1998. Raf-1 kinase, a potential regulator of intracellular pH in *Xenopus* oocytes. *Biol Cell* 90(6-7):477-485.
- Karaiskou A, Cayla X, Haccard O, Jesus C, Ozon R. 1998. MPF amplification in *Xenopus* oocyte extracts depends on a two-step activation of cdc25 phosphatase. *Exp Cell Res* 244(2):491-500.

- Karaiskou A, Lepretre AC, Pahlavan G, Du Pasquier D, Ozon R, Jessus C. 2004. Polo-like kinase confers MPF autoamplification competence to growing *Xenopus* oocytes. *Development* 131(7):1543-1552.
- Katsu Y, Minshall N, Nagahama Y, Standart N. 1999. Ca^{2+} is required for phosphorylation of clam p82/CPEB in vitro: implications for dual and independent roles of MAP and Cdc2 kinases. *Dev Biol* 209(1):186-199.
- Kawamura K, Ye Y, Kawamura N, Jing L, Groenen P, Gelpke MS, Rauch R, Hsueh AJ, Tanaka T. 2008. Completion of Meiosis I of preovulatory oocytes and facilitation of preimplantation embryo development by glial cell line-derived neurotrophic factor. *Dev Biol* 315(1):189-202.
- Keady BT, Kuo P, Martinez SE, Yuan L, Hake LE. 2007. MAPK interacts with XGef and is required for CPEB activation during meiosis in *Xenopus* oocytes. *J Cell Sci* 120(Pt 6):1093-1103.
- Kierszenbaum AL, Rivkin E, Talmor-Cohen A, Shalgi R, Tres LL. 2009. Expression of full-length and truncated Fyn tyrosine kinase transcripts and encoded proteins during spermatogenesis and localization during acrosome biogenesis and fertilization. *Mol Reprod Dev* 76(9):832-843.
- Kikuchi K, Naito K, Daen FP, Izaike Y, Toyoda Y. 1995. Histone H1 kinase activity during in vitro fertilization of pig follicular oocytes matured in vitro. *Theriogenology* 43(2):523-532.
- Kinoshita K, Noetzel TL, Pelletier L, Mechtler K, Drechsel DN, Schwager A, Lee M, Raff JW, Hyman AA. 2005. Aurora A phosphorylation of TACC3/maskin is required for centrosome-dependent microtubule assembly in mitosis. *J Cell Biol* 170(7):1047-1055.
- Kinsey WH. 1995. Differential phosphorylation of a 57-KDa protein tyrosine kinase during egg activation. *Biochem Biophys Res Commun* 208(1):204-209.
- Kinsey WH. 1996. Biphasic activation of Fyn kinase upon fertilization of the sea urchin egg. *Dev Biol* 174(2):281-287.
- Kinsey WH, Shen SS. 2000. Role of the Fyn kinase in calcium release during fertilization of the sea urchin egg. *Dev Biol* 225(1):253-264.
- Kinsey WH, Wu W, Macgregor E. 2003. Activation of Src-family PTK activity at fertilization: role of the SH2 domain. *Dev Biol* 264(1):255-262.
- Klerkx EP, Lazo PA, Askjaer P. 2009. Emerging biological functions of the vaccinia-related kinase (VRK) family. *Histol Histopathol* 24(6):749-759.
- Kokai Y, Wada T, Myers JN, Brown VI, Dobashi K, Cohen J, Hamuro J, Weiner DB, Greene MI. 1988. The role of the neu oncogene product in cell transformation and normal development. *Princess Takamatsu Symp* 19:45-57.
- Kosako H, Gotoh Y, Matsuda S, Ishikawa M, Nishida E. 1992. *Xenopus* MAP kinase activator is a serine/threonine/tyrosine kinase activated by threonine phosphorylation. *EMBO J* 11(8):2903-2908.
- Kostellow AB, Ma GY, Morrill GA. 1996. Progesterone triggers the rapid activation of phospholipase D in the amphibian oocyte plasma membrane when initiating the G2/M transition. *Biochim Biophys Acta* 1304(3):263-271.
- Kubiak JZ, Weber M, Geraud G, Maro B. 1992. Cell cycle modification during the transitions between meiotic M-phases in mouse oocytes. *J Cell Sci* 102 (Pt 3):457-467.
- Kume S, Endo T, Nishimura Y, Kano K, Naito K. 2007. Porcine SPDYA2 (RINGO A2) stimulates CDC2 activity and accelerates meiotic maturation of porcine oocytes. *Biol Reprod* 76(3):440-447.

- Kuo P, Runge E, Lu X, Hake LE. 2011. XGef influences XRINGO/CDK1 signaling and CPEB activation during *Xenopus* oocyte maturation. *Differentiation* 81(2):133-140.
- Kurokawa M, Sato K, Smyth J, Wu H, Fukami K, Takenawa T, Fissore RA. 2004. Evidence that activation of Src family kinase is not required for fertilization-associated $[Ca^{2+}]_i$ oscillations in mouse eggs. *Reproduction* 127(4):441-454.
- Kurvari V, Snell WJ. 1996. SksC, a fertilization-related protein kinase in *Chlamydomonas*, is expressed throughout the cell cycle and gametogenesis, and a phosphorylated form is present in both flagella and cell bodies. *Biochem Biophys Res Commun* 228(1):45-54.
- Kurvari V, Zhang Y, Luo Y, Snell WJ. 1996. Molecular cloning of a protein kinase whose phosphorylation is regulated by genetic adhesion during *Chlamydomonas* fertilization. *Proc Natl Acad Sci U S A* 93(1):39-43.
- Kushima S, Mammadova G, Mahbub Hasan AK, Fukami Y, Sato K. 2011. Characterization of Lipovitellin 2 as a tyrosine-phosphorylated protein in oocytes, eggs and early embryos of *Xenopus laevis*. *Zoolog Sci* 28(8):550-559.
- Lancaster OM, Cullen CF, Ohkura H. 2007. NHK-1 phosphorylates BAF to allow karyosome formation in the *Drosophila* oocyte nucleus. *J Cell Biol* 179(5):817-824.
- LaRosa C, Downs SM. 2006. Stress stimulates AMP-activated protein kinase and meiotic resumption in mouse oocytes. *Biol Reprod* 74(3):585-592.
- Ledan E, Polanski Z, Terret ME, Maro B. 2001. Meiotic maturation of the mouse oocyte requires an equilibrium between cyclin B synthesis and degradation. *Dev Biol* 232(2):400-413.
- Lee B, Vermassen E, Yoon SY, Vanderheyden V, Ito J, Alfandari D, De Smedt H, Parys JB, Fissore RA. 2006. Phosphorylation of IP3R1 and the regulation of $[Ca^{2+}]_i$ responses at fertilization: a role for the MAP kinase pathway. *Development* 133(21):4355-4365.
- Lee HC, Tsai JN, Liao PY, Tsai WY, Lin KY, Chuang CC, Sun CK, Chang WC, Tsai HJ. 2007. Glycogen synthase kinase 3 alpha and 3 beta have distinct functions during cardiogenesis of zebrafish embryo. *BMC Dev Biol* 7:93.
- Lefebvre DL, Charest DL, Yee A, Crawford BJ, Pelech SL. 1999. Characterization of fertilization-modulated myelin basic protein kinases from sea star: regulation of Mapk. *J Cell Biochem* 75(2):272-287.
- Leiva L, Carrasco D, Taylor A, Veliz M, Gonzalez C, Allende CC, Allende JE. 1987. Casein kinase II is a major protein phosphorylating activity in the nuclei of *Xenopus laevis* oocytes. *Biochem Int* 14(4):707-717.
- Lev S, Moreno H, Martinez R, Canoll P, Peles E, Musacchio JM, Plowman GD, Rudy B, Schlessinger J. 1995. Protein tyrosine kinase PYK2 involved in Ca^{2+} -induced regulation of ion channel and MAP kinase functions. *Nature* 376(6543):737-745.
- Levi M, Maro B, Shalgi R. 2010. Fyn kinase is involved in cleavage furrow ingression during meiosis and mitosis. *Reproduction* 140(6):827-834.
- Li M, Li S, Yuan J, Wang ZB, Sun SC, Schatten H, Sun QY. 2009. Bub3 is a spindle assembly checkpoint protein regulating chromosome segregation during mouse oocyte meiosis. *PLoS One* 4(11):e7701.
- Li C, Sun Y, Yi K, Ma Y, Zhang W, Zhou X. 2010. Detection of nerve growth factor (NGF) and its specific receptor (TrkA) in ejaculated bovine sperm, and the effects of NGF on sperm function. *Theriogenology* 74(9):1615-1622.
- Li X, Earp HS. 1997. Paxillin is tyrosine-phosphorylated by and preferentially associates with the calcium-dependent tyrosine kinase in rat liver epithelial cells. *J Biol Chem* 272(22):14341-14348.

- Liang CG, Su YQ, Fan HY, Schatten H, Sun QY. 2007. Mechanisms regulating oocyte meiotic resumption: roles of mitogen-activated protein kinase. *Mol Endocrinol* 21(9):2037-2055.
- Linher K, Wu D, Li J. 2007. Glial cell line-derived neurotrophic factor: an intraovarian factor that enhances oocyte developmental competence in vitro. *Endocrinology* 148(9):4292-4301.
- Littlepage LE, Ruderman JV. 2002. Identification of a new APC/C recognition domain, the A box, which is required for the Cdh1-dependent destruction of the kinase Aurora-A during mitotic exit. *Genes Dev* 16(17):2274-2285.
- Littlepage LE, Wu H, Andresson T, Deanehan JK, Amundadottir LT, Ruderman JV. 2002. Identification of phosphorylated residues that affect the activity of the mitotic kinase Aurora-A. *Proc Natl Acad Sci U S A* 99(24):15440-15445.
- Liu J, Grimison B, Lewellyn AL, Maller JL. 2006. The anaphase-promoting complex/cyclosome inhibitor Emi2 is essential for meiotic but not mitotic cell cycles. *J Biol Chem* 281(46):34736-34741.
- Liu J, Maller JL. 2005. Calcium elevation at fertilization coordinates phosphorylation of XErp1/Emi2 by Plx1 and CaMK II to release metaphase arrest by cytosstatic factor. *Curr Biol* 15(16):1458-1468.
- Liu L, Rajareddy S, Reddy P, Jagarlamudi K, Du C, Shen Y, Guo Y, Boman K, Lundin E, Ottander U, Selstam G, Liu K. 2007. Phosphorylation and inactivation of glycogen synthase kinase-3 by soluble kit ligand in mouse oocytes during early follicular development. *J Mol Endocrinol* 38(1-2):137-146.
- Liu Y, Misamore MJ, Snell WJ. 2010. Membrane fusion triggers rapid degradation of two gamete-specific, fusion-essential proteins in a membrane block to polygamy in *Chlamydomonas*. *Development* 137(9):1473-1481.
- Lohka MJ, Hayes MK, Maller JL. 1988. Purification of maturation-promoting factor, an intracellular regulator of early mitotic events. *Proc Natl Acad Sci U S A* 85(9):3009-3013.
- Long T, Cailliau K, Beckmann S, Browaeys E, Trolet J, Grevelding CG, Dissous C. 2010. *Schistosoma mansoni* Polo-like kinase 1: A mitotic kinase with key functions in parasite reproduction. *Int J Parasitol* 40(9):1075-1086.
- Lu N, Guarnieri DJ, Simon MA. 2004. Localization of Tec29 to ring canals is mediated by Src64 and PtdIns(3,4,5)P₃-dependent mechanisms. *EMBO J* 23(5):1089-1100.
- Lu Q, Smith GD, Chen DY, Han ZM, Sun QY. 2002. Activation of protein kinase C induces mitogen-activated protein kinase dephosphorylation and pronucleus formation in rat oocytes. *Biol Reprod* 67(1):64-69.
- Luo J, McGinnis LK, Kinsey WH. 2009. Fyn kinase activity is required for normal organization and functional polarity of the mouse oocyte cortex. *Mol Reprod Dev* 76(9):819-831.
- Luria A, Tennenbaum T, Sun QY, Rubinstein S, Breitbart H. 2000. Differential localization of conventional protein kinase C isoforms during mouse oocyte development. *Biol Reprod* 62(6):1564-1570.
- Ma C, Cummings C, Liu XJ. 2003. Biphasic activation of Aurora-A kinase during the meiosis I- meiosis II transition in *Xenopus* oocytes. *Mol Cell Biol* 23(5):1703-1716.
- Machaca K. 2007. Ca²⁺ signaling differentiation during oocyte maturation. *J Cell Physiol* 213(2):331-340.

- MacNicol AM, Muslin AJ, Howard EL, Kikuchi A, MacNicol MC, Williams LT. 1995. Regulation of Raf-1-dependent signaling during early *Xenopus* development. *Mol Cell Biol* 15(12):6686-6693.
- Madgwick S, Hansen DV, Levasseur M, Jackson PK, Jones KT. 2006. Mouse Emi2 is required to enter meiosis II by reestablishing cyclin B1 during interkinesis. *J Cell Biol* 174(6):791-801.
- Madgwick S, Jones KT. 2007. How eggs arrest at metaphase II: MPF stabilisation plus APC/C inhibition equals Cytostatic Factor. *Cell Div* 2:4.
- Madgwick S, Nixon VL, Chang HY, Herbert M, Levasseur M, Jones KT. 2004. Maintenance of sister chromatid attachment in mouse eggs through maturation-promoting factor activity. *Dev Biol* 275(1):68-81.
- Madgwick S, Levasseur M, Jones KT. 2005. Calmodulin-dependent protein kinase II, and not protein kinase C, is sufficient for triggering cell-cycle resumption in mammalian eggs. *J Cell Sci* 118(Pt 17):3849-3859.
- Mahbub Hasan AK, Fukami Y, Sato KI. 2011. Gamete membrane microdomains and their associated molecules in fertilization signaling. *Mol Reprod Dev*. 78(10-11):814-830.
- Mahbub Hasan AK, Ou Z, Sakakibara K, Hirahara S, Iwasaki T, Sato K, Fukami Y. 2007. Characterization of *Xenopus* egg membrane microdomains containing uroplakin Ib/III complex: roles of their molecular interactions for subcellular localization and signal transduction. *Genes Cells* 12(2):251-267.
- Mahbub Hasan AK, Sato K, Sakakibara K, Ou Z, Iwasaki T, Ueda Y, Fukami Y. 2005. Uroplakin III, a novel Src substrate in *Xenopus* egg rafts, is a target for sperm protease essential for fertilization. *Dev Biol* 286(2):483-492.
- Malcuit C, Knott JG, He C, Wainwright T, Parys JB, Robl JM, Fissore RA. 2005. Fertilization and inositol 1,4,5-trisphosphate (IP3)-induced calcium release in type-1 inositol 1,4,5-trisphosphate receptor down-regulated bovine eggs. *Biol Reprod* 73(1):2-13.
- Maller JL. 1990. *Xenopus* oocytes and the biochemistry of cell division. *Biochemistry* 29(13):3157-3166.
- Maller JL, Schwab MS, Roberts BT, Gross SD, Taieb FE, Tunquist BJ. 2001. The pathway of MAP kinase mediation of CSF arrest in *Xenopus* oocytes. *Biol Cell* 93(1-2):27-33.
- Mammadova G, Iwasaki T, Tokmakov AA, Fukami Y, Sato K. 2009. Evidence that phosphatidylinositol 3-kinase is involved in sperm-induced tyrosine kinase signaling in *Xenopus* egg fertilization. *BMC Dev Biol* 9:68.
- Marangos P, Verschuren EW, Chen R, Jackson PK, Carroll J. 2007. Prophase I arrest and progression to metaphase I in mouse oocytes are controlled by Emi1-dependent regulation of APC(Cdh1). *J Cell Biol* 176(1):65-75.
- Marotta V, Guerra A, Sapio MR, Vitale M. 2011. RET/PTC rearrangement in benign and malignant thyroid diseases: a clinical standpoint. *Eur J Endocrinol* 165(4):499-507.
- Masui Y, Markert CL. 1971. Cytoplasmic control of nuclear behavior during meiotic maturation of frog oocytes. *J Exp Zool* 177(2):129-145.
- Masui Y. 1992. Towards understanding the control of the division cycle in animal cells. *Biochem Cell Biol* 70(10-11):920-945.
- Masui Y. 2000. The elusive cytostatic factor in the animal egg. *Nat Rev Mol Cell Biol* 1(3):228-232.
- Maton G, Lorca T, Girault JA, Ozon R, Jessus C. 2005. Differential regulation of Cdc2 and Aurora-A in *Xenopus* oocytes: a crucial role of phosphatase 2A. *J Cell Sci* 118(Pt 11):2485-2494.

- Maton G, Thibier C, Castro A, Lorca T, Prigent C, Jessus C. 2003. Cdc2-cyclin B triggers H3 kinase activation of Aurora-A in *Xenopus* oocytes. *J Biol Chem* 278(24):21439-21449.
- Matsumoto S, Abe Y, Fujibuchi T, Takeuchi T, Kito K, Ueda N, Shigemoto K, Gyo K. 2004. Characterization of a MAPKK-like protein kinase TOPK. *Biochem Biophys Res Commun* 325(3):997-1004.
- Matten W, Daar I, Vande Woude GF. 1994. Protein kinase A acts at multiple points to inhibit *Xenopus* oocyte maturation. *Mol Cell Biol* 14(7):4419-4426.
- Mayes MA, Sirard MA. 2002. Effect of type 3 and type 4 phosphodiesterase inhibitors on the maintenance of bovine oocytes in meiotic arrest. *Biol Reprod* 66(1):180-184.
- Mazia D. 1937. The release of calcium in *Arbacia* eggs upon fertilization. *J Cell and Comp Phys* 10(3):291-304.
- McGinnis LK, Albertini DF, Kinsey WH. 2007. Localized activation of Src-family protein kinases in the mouse egg. *Dev Biol* 306(1):241-254.
- McGinnis LK, Carroll DJ, Kinsey WH. 2011a. Protein tyrosine kinase signaling during oocyte maturation and fertilization. *Mol Reprod Dev*. 78(10-11):831-845.
- McGinnis LK, Hong X, Christenson LK, Kinsey WH. 2011b. Fer tyrosine kinase is required for germinal vesicle breakdown and meiosis-I in mouse oocytes. *Mol Reprod Dev* 78(1):33-47.
- McGinnis LK, Kinsey WH, Albertini DF. 2009. Functions of Fyn kinase in the completion of meiosis in mouse oocytes. *Dev Biol* 327(2):280-287.
- Mehlmann LM. 2005. Stops and starts in mammalian oocytes: recent advances in understanding the regulation of meiotic arrest and oocyte maturation. *Reproduction* 130(6):791-799.
- Mehlmann LM, Jaffe LA. 2005. SH2 domain-mediated activation of an SRC family kinase is not required to initiate Ca²⁺ release at fertilization in mouse eggs. *Reproduction* 129(5):557-564.
- Mehlmann LM, Jones TL, Jaffe LA. 2002. Meiotic arrest in the mouse follicle maintained by a Gs protein in the oocyte. *Science* 297(5585):1343-1345.
- Meijer L, Arion D, Golsteyn R, Pines J, Brizuela L, Hunt T, Beach D. 1989a. Cyclin is a component of the sea urchin egg M-phase specific histone H1 kinase. *EMBO J* 8(8):2275-2282.
- Meijer L, Azzi L, Wang JY. 1991. Cyclin B targets p34cdc2 for tyrosine phosphorylation. *EMBO J* 10(6):1545-1554.
- Meijer L, Dostmann W, Genieser HG, Butt E, Jastorff B. 1989b. Starfish oocyte maturation: evidence for a cyclic AMP-dependent inhibitory pathway. *Dev Biol* 133(1):58-66.
- Meijer L, Pondaven P. 1988. Cyclic activation of histone H1 kinase during sea urchin egg mitotic divisions. *Exp Cell Res* 174(1):116-129.
- Mendez R, Hake LE, Andresson T, Littlepage LE, Ruderman JV, Richter JD. 2000. Phosphorylation of CPE binding factor by Eg2 regulates translation of c-mos mRNA. *Nature* 404(6775):302-307.
- Meng XQ, Zheng KG, Yang Y, Jiang MX, Zhang YL, Sun QY, Li YL. 2006. Proline-rich tyrosine kinase2 is involved in F-actin organization during in vitro maturation of rat oocyte. *Reproduction* 132(6):859-867.
- Minshull J, Pines J, Golsteyn R, Standart N, Mackie S, Colman A, Blow J, Ruderman JV, Wu M, Hunt T. 1989. The role of cyclin synthesis, modification and destruction in the control of cell division. *J Cell Sci Suppl* 12:77-97.
- Mitra J, Schultz RM. 1996. Regulation of the acquisition of meiotic competence in the mouse: changes in the subcellular localization of cdc2, cyclin B1, cdc25C and wee1, and in

- the concentration of these proteins and their transcripts. *J Cell Sci* 109 (Pt 9):2407-2415.
- Miyata Y, Nishida E. 1999. Distantly related cousins of MAP kinase: biochemical properties and possible physiological functions. *Biochem Biophys Res Commun* 266(2):291-295.
- Miyazaki S, Ito M. 2006. Calcium signals for egg activation in mammals. *J Pharmacol Sci* 100(5):545-552.
- Mochida S, Maslen SL, Skehel M, Hunt T. 2010. Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. *Science* 330(6011):1670-1673.
- Mood K, Friesel R, Daar IO. 2002. SNT1/FRS2 mediates germinal vesicle breakdown induced by an activated FGF receptor1 in *Xenopus* oocytes. *J Biol Chem* 277(36):33196-33204.
- Mood K, Saucier C, Bong YS, Lee HS, Park M, Daar IO. 2006. Gab1 is required for cell cycle transition, cell proliferation, and transformation induced by an oncogenic met receptor. *Mol Biol Cell* 17(9):3717-3728.
- Moore KL, Kinsey WH. 1994. Identification of an abl-related protein tyrosine kinase in the cortex of the sea urchin egg: possible role at fertilization. *Dev Biol* 164(2):444-455.
- Mori M, Hara M, Tachibana K, Kishimoto T. 2006. p90Rsk is required for G1 phase arrest in unfertilized starfish eggs. *Development* 133(9):1823-1830.
- Mori T, Guo MW, Sato E, Baba T, Takasaki S, Mori E. 2000. Molecular and immunological approaches to mammalian fertilization. *J Reprod Immunol* 47(2):139-158.
- Mori T, Wu GM, Mori E. 1991. Expression of CD4-like structure on murine egg vitelline membrane and its signal transductive roles through p56lck in fertilization. *Am J Reprod Immunol* 26(3):97-103.
- Morrison DL, Yee A, Paddon HB, Vilimek D, Aebersold R, Pelech SL. 2000. Regulation of the meiosis-inhibited protein kinase, a p38(MAPK) isoform, during meiosis and following fertilization of seastar oocytes. *J Biol Chem* 275(44):34236-34244.
- Murakami MS, Vande Woude GF. 1998. Analysis of the early embryonic cell cycles of *Xenopus*; regulation of cell cycle length by *Xe-wee1* and *Mos*. *Development* 125(2):237-248.
- Murase K, Shiba H, Iwano M, Che FS, Watanabe M, Isogai A, Takayama S. 2004. A membrane-anchored protein kinase involved in *Brassica* self-incompatibility signaling. *Science* 303(5663):1516-1519.
- Muslin AJ, MacNicol AM, Williams LT. 1993. Raf-1 protein kinase is important for progesterone-induced *Xenopus* oocyte maturation and acts downstream of *mos*. *Mol Cell Biol* 13(7):4197-4202.
- Nakaya M, Fukui A, Izumi Y, Akimoto K, Asashima M, Ohno S. 2000. Meiotic maturation induces animal-vegetal asymmetric distribution of aPKC and ASIP/PAR-3 in *Xenopus* oocytes. *Development* 127(23):5021-5031.
- Narasimhan V, Hamill O, Cerione RA. 1992. The effects of the normal and oncogenic forms of the neu tyrosine kinase, and the corresponding forms of an immunoglobulin E receptor/neu tyrosine kinase fusion protein, on *Xenopus* oocyte maturation. *FEBS Lett* 303(2-3):164-168.
- Nebreda AR, Martin-Zanca D, Kaplan DR, Parada LF, Santos E. 1991. Induction by NGF of meiotic maturation of *Xenopus* oocytes expressing the *trk* proto-oncogene product. *Science* 252(5005):558-561.

- Newhall KJ, Criniti AR, Cheah CS, Smith KC, Kafer KE, Burkart AD, McKnight GS. 2006. Dynamic anchoring of PKA is essential during oocyte maturation. *Curr Biol* 16(3):321-327.
- Niault T, Hached K, Sotillo R, Sorger PK, Maro B, Benezra R, Wassmann K. 2007. Changing Mad2 levels affects chromosome segregation and spindle assembly checkpoint control in female mouse meiosis I. *PLoS One* 2(11):e1165.
- Nishi Y, Lin R. 2005. DYRK2 and GSK-3 phosphorylate and promote the timely degradation of OMA-1, a key regulator of the oocyte-to-embryo transition in *C. elegans*. *Dev Biol* 288(1):139-149.
- Nishiyama T, Ohsumi K, Kishimoto T. 2007a. Phosphorylation of Erp1 by p90rsk is required for cytotostatic factor arrest in *Xenopus laevis* eggs. *Nature* 446(7139):1096-1099.
- Nishiyama T, Yoshizaki N, Kishimoto T, Ohsumi K. 2007b. Transient activation of calcineurin is essential to initiate embryonic development in *Xenopus laevis*. *Nature* 449(7160):341-345.
- Nishizuka Y. 1984. The role of protein kinase C in cell surface signal transduction and tumour promotion. *Nature* 308(5961):693-698.
- Nishizuka Y. 1986. Studies and perspectives of protein kinase C. *Science* 233(4761):305-312.
- Nishizuka Y. 1988. The molecular heterogeneity of protein kinase C and its implications for cellular regulation. *Nature* 334(6184):661-665.
- Nissley SP, Haskell JF, Sasaki N, De Vroede MA, Rechler MM. 1985. Insulin-like growth factor receptors. *J Cell Sci Suppl* 3:39-51.
- Norris RP, Ratzan WJ, Freudzon M, Mehlmann LM, Krall J, Movsesian MA, Wang H, Ke H, Nikolaev VO, Jaffe LA. 2009. Cyclic GMP from the surrounding somatic cells regulates cyclic AMP and meiosis in the mouse oocyte. *Development* 136(11):1869-1878.
- Nurse P. 1990. Universal control mechanism regulating onset of M-phase. *Nature* 344(6266):503-508.
- Nutt LK, Margolis SS, Jensen M, Herman CE, Dunphy WG, Rathmell JC, Kornbluth S. 2005. Metabolic regulation of oocyte cell death through the CaMKII-mediated phosphorylation of caspase-2. *Cell* 123(1):89-103.
- Nuttinck F, Charpigny G, Mermillod P, Loosfelt H, Meduri G, Freret S, Grimard B, Heyman Y. 2004. Expression of components of the insulin-like growth factor system and gonadotropin receptors in bovine cumulus-oocyte complexes during oocyte maturation. *Domest Anim Endocrinol* 27(2):179-195.
- O'Neill FJ, Gillett J, Foltz KR. 2004. Distinct roles for multiple Src family kinases at fertilization. *J Cell Sci* 117(Pt 25):6227-6238.
- O'Reilly AM, Ballew AC, Miyazawa B, Stocker H, Hafen E, Simon MA. 2006. Csk differentially regulates Src64 during distinct morphological events in *Drosophila* germ cells. *Development* 133(14):2627-2638.
- Oh JS, Han SJ, Conti M. 2010. Wee1B, Myt1, and Cdc25 function in distinct compartments of the mouse oocyte to control meiotic resumption. *J Cell Biol* 188(2):199-207.
- Okamoto K, Nakajo N, Sagata N. 2002. The existence of two distinct Wee1 isoforms in *Xenopus*: implications for the developmental regulation of the cell cycle. *EMBO J* 21(10):2472-2484.
- Okamura Y, Myoumoto A, Manabe N, Tanaka N, Okamura H, Fukumoto M. 2001. Protein tyrosine kinase expression in the porcine ovary. *Mol Hum Reprod* 7(8):723-729.

- Okumura E, Fukuhara T, Yoshida H, Hanada Si S, Kozutsumi R, Mori M, Tachibana K, Kishimoto T. 2002. Akt inhibits Myt1 in the signalling pathway that leads to meiotic G2/M-phase transition. *Nat Cell Biol* 4(2):111-116.
- Olds JL, Favit A, Nelson T, Ascoli G, Gerstein A, Cameron M, Cameron L, Lester DS, Rakow T, De Barry J, et al. 1995. Imaging protein kinase C activation in living sea urchin eggs after fertilization. *Dev Biol* 172(2):675-682.
- Ota R, Kotani T, Yamashita M. 2011a. Biochemical characterization of Pumilio1 and Pumilio2 in *Xenopus* oocytes. *J Biol Chem* 286(4):2853-2863.
- Ota R, Kotani T, Yamashita M. 2011b. Possible involvement of Nemo-like kinase 1 in *Xenopus* oocyte maturation as a kinase responsible for Pumilio1, Pumilio2, and CPEB phosphorylation. *Biochemistry* 50(25):5648-5659.
- Ou XH, Li S, Xu BZ, Wang ZB, Quan S, Li M, Zhang QH, Ouyang YC, Schatten H, Xing FQ, Sun QY. 2010. p38alpha MAPK is a MTOC-associated protein regulating spindle assembly, spindle length and accurate chromosome segregation during mouse oocyte meiotic maturation. *Cell Cycle* 9(20):4130-4143.
- Pahlavan G, Polanski Z, Kalab P, Golsteyn R, Nigg EA, Maro B. 2000. Characterization of polo-like kinase 1 during meiotic maturation of the mouse oocyte. *Dev Biol* 220(2):392-400.
- Palacios EH, Weiss A. 2004. Function of the Src-family kinases, Lck and Fyn, in T-cell development and activation. *Oncogene* 23(48):7990-8000.
- Palmer A, Gavin AC, Nebreda AR. 1998. A link between MAP kinase and p34(cdc2)/cyclin B during oocyte maturation: p90(rsk) phosphorylates and inactivates the p34(cdc2) inhibitory kinase Myt1. *EMBO J* 17(17):5037-5047.
- Pan J, Snell WJ. 2000. Signal transduction during fertilization in the unicellular green alga, *Chlamydomonas*. *Curr Opin Microbiol* 3(6):596-602.
- Park M, Dean M, Cooper CS, Schmidt M, O'Brien SJ, Blair DG, Vande Woude GF. 1986. Mechanism of met oncogene activation. *Cell* 45(6):895-904.
- Pascreau G, Delcros JG, Cremet JY, Prigent C, Arlot-Bonnemains Y. 2005. Phosphorylation of maskin by Aurora-A participates in the control of sequential protein synthesis during *Xenopus laevis* oocyte maturation. *J Biol Chem* 280(14):13415-13423.
- Pascreau G, Delcros JG, Morin N, Prigent C, Arlot-Bonnemains Y. 2008. Aurora-A kinase Ser349 phosphorylation is required during *Xenopus laevis* oocyte maturation. *Dev Biol* 317(2):523-530.
- Pascreau G, Eckerdt F, Lewellyn AL, Prigent C, Maller JL. 2009. Phosphorylation of p53 is regulated by TPX2-Aurora A in *xenopus* oocytes. *J Biol Chem* 284(9):5497-5505.
- Pati D, Lohka MJ, Habibi HR. 2000. Time-related effect of GnRH on histone H1 kinase activity in the goldfish follicle-enclosed oocyte. *Can J Physiol Pharmacol* 78(12):1067-1071.
- Pauken CM, Capco DG. 2000. The expression and stage-specific localization of protein kinase C isotypes during mouse preimplantation development. *Dev Biol* 223(2):411-421.
- Pavlok A, Kalab P, Bobak P. 1997. Fertilisation competence of bovine normally matured or aged oocytes derived from different antral follicles: morphology, protein synthesis, H1 and MBP kinase activity. *Zygote* 5(3):235-246.
- Pelech SL, Meijer L, Krebs EG. 1987. Characterization of maturation-activated histone H1 and ribosomal S6 kinases in sea star oocytes. *Biochemistry* 26(24):7960-7968.
- Pelech SL, Tombes RM, Meijer L, Krebs EG. 1988. Activation of myelin basic protein kinases during echinoderm oocyte maturation and egg fertilization. *Dev Biol* 130(1):28-36.

- Perdiguero E, Pillaire MJ, Bodart JF, Hennersdorf F, Frodin M, Duesbery NS, Alonso G, Nebreda AR. 2003. Xp38gamma/SAPK3 promotes meiotic G(2)/M transition in *Xenopus* oocytes and activates Cdc25C. *EMBO J* 22(21):5746-5756.
- Perry AC, Verlhac MH. 2008. Second meiotic arrest and exit in frogs and mice. *EMBO Rep* 9(3):246-251.
- Pesando D, Pesci-Bardon C, Huitorel P, Girard JP. 1999. Caulerpenyne blocks MBP kinase activation controlling mitosis in sea urchin eggs. *Eur J Cell Biol* 78(12):903-910.
- Peter M, Labbe JC, Doree M, Mandart E. 2002. A new role for Mos in *Xenopus* oocyte maturation: targeting Myt1 independently of MAPK. *Development* 129(9):2129-2139.
- Philipova R, Whitaker M. 1998. MAP kinase activity increases during mitosis in early sea urchin embryos. *J Cell Sci* 111 (Pt 17):2497-2505.
- Pirino G, Wescott MP, Donovan PJ. 2009. Protein kinase A regulates resumption of meiosis by phosphorylation of Cdc25B in mammalian oocytes. *Cell Cycle* 8(4):665-670.
- Pitetti JL, Torre D, Conne B, Papaioannou MD, Cederroth CR, Xuan S, Kahn R, Parada LF, Vassalli JD, Efstratiadis A, Nef S. 2009. Insulin receptor and IGF1R are not required for oocyte growth, differentiation, and maturation in mice. *Sex Dev* 3(5):264-272.
- Potapova TA, Daum JR, Byrd KS, Gorbsky GJ. 2009. Fine tuning the cell cycle: activation of the Cdk1 inhibitory phosphorylation pathway during mitotic exit. *Mol Biol Cell* 20(6):1737-1748.
- Qian YW, Erikson E, Taieb FE, Maller JL. 2001. The polo-like kinase Plx1 is required for activation of the phosphatase Cdc25C and cyclin B-Cdc2 in *Xenopus* oocytes. *Mol Biol Cell* 12(6):1791-1799.
- Qu Y, Adler V, Chu T, Platica O, Michl J, Pestka S, Izotova L, Boutjdir M, Pincus MR. 2006. Two dual specificity kinases are preferentially induced by wild-type rather than by oncogenic RAS-P21 in *Xenopus* oocytes. *Front Biosci* 11:2420-2427.
- Qu Y, Adler V, Izotova L, Pestka S, Bowne W, Michl J, Boutjdir M, Friedman FK, Pincus MR. 2007. The dual-specificity kinases, TOPK and DYRK1A, are critical for oocyte maturation induced by wild-type--but not by oncogenic--ras-p21 protein. *Front Biosci* 12:5089-5097.
- Quadri SK. 2011. Cross talk between focal adhesion kinase and cadherins: Role in regulating endothelial barrier function. *Microvasc Res*.
- Quan HM, Fan HY, Meng XQ, Huo LJ, Chen DY, Schatten H, Yang PM, Sun QY. 2003. Effects of PKC activation on the meiotic maturation, fertilization and early embryonic development of mouse oocytes. *Zygote* 11(4):329-337.
- Rappolee DA, Patel Y, Jacobson K. 1998. Expression of fibroblast growth factor receptors in peri-implantation mouse embryos. *Mol Reprod Dev* 51(3):254-264.
- Rauh NR, Schmidt A, Bormann J, Nigg EA, Mayer TU. 2005. Calcium triggers exit from meiosis II by targeting the APC/C inhibitor XErp1 for degradation. *Nature* 437(7061):1048-1052.
- Reddy P, Shen L, Ren C, Boman K, Lundin E, Ottander U, Lindgren P, Liu YX, Sun QY, Liu K. 2005. Activation of Akt (PKB) and suppression of FKHRL1 in mouse and rat oocytes by stem cell factor during follicular activation and development. *Dev Biol* 281(2):160-170.
- Rentzsch F, Hobmayer B, Holstein TW. 2005. Glycogen synthase kinase 3 has a proapoptotic function in *Hydra* gametogenesis. *Dev Biol* 278(1):1-12.
- Resh MD. 1998. Fyn, a Src family tyrosine kinase. *Int J Biochem Cell Biol* 30(11):1159-1162.

- Reut TM, Mattan L, Dafna T, Ruth KK, Ruth S. 2007. The role of Src family kinases in egg activation. *Dev Biol* 312(1):77-89.
- Rice A, Parrington J, Jones KT, Swann K. 2000. Mammalian sperm contain a Ca^{2+} -sensitive phospholipase C activity that can generate $\text{InsP}(3)$ from $\text{PIP}(2)$ associated with intracellular organelles. *Dev Biol* 228(1):125-135.
- Rime H, Huchon D, De Smedt V, Thibier C, Galaktionov K, Jesus C, Ozon R. 1994. Microinjection of Cdc25 protein phosphatase into *Xenopus* prophase oocyte activates MPF and arrests meiosis at metaphase I. *Biol Cell* 82(1):11-22.
- Rime H, Ozon R. 1990. Protein phosphatases are involved in the in vivo activation of histone H1 kinase in mouse oocyte. *Dev Biol* 141(1):115-122.
- Robbie EP, Peterson M, Amaya E, Musci TJ. 1995. Temporal regulation of the *Xenopus* FGF receptor in development: a translation inhibitory element in the 3' untranslated region. *Development* 121(6):1775-1785.
- Robison GA, Butcher RW, Sutherland EW. 1968. Cyclic AMP. *Annu Rev Biochem* 37:149-174.
- Roelle S, Grosse R, Buech T, Chubanov V, Gudermann T. 2008. Essential role of Pyk2 and Src kinase activation in neuropeptide-induced proliferation of small cell lung cancer cells. *Oncogene* 27(12):1737-1748.
- Rogers E, Bishop JD, Waddle JA, Schumacher JM, Lin R. 2002. The aurora kinase AIR-2 functions in the release of chromosome cohesion in *Caenorhabditis elegans* meiosis. *J Cell Biol* 157(2):219-229.
- Rogers NT, Hobson E, Pickering S, Lai FA, Braude P, Swann K. 2004. Phospholipase C ζ causes Ca^{2+} oscillations and parthenogenetic activation of human oocytes. *Reproduction* 128(6):697-702.
- Roghi C, Giet R, Uzbekov R, Morin N, Chartrain I, Le Guellec R, Couturier A, Doree M, Philippe M, Prigent C. 1998. The *Xenopus* protein kinase pEg2 associates with the centrosome in a cell cycle-dependent manner, binds to the spindle microtubules and is involved in bipolar mitotic spindle assembly. *J Cell Sci* 111 (Pt 5):557-572.
- Rongish BJ, Kinsey WH. 2000. Transient nuclear localization of Fyn kinase during development in zebrafish. *Anat Rec* 260(2):115-123.
- Ruiz EJ, Hunt T, Nebreda AR. 2008. Meiotic inactivation of *Xenopus* Myt1 by CDK/XRINGO, but not CDK/cyclin, via site-specific phosphorylation. *Mol Cell* 32(2):210-220.
- Ruiz EJ, Vilar M, Nebreda AR. 2010. A two-step inactivation mechanism of Myt1 ensures CDK1/cyclin B activation and meiosis I entry. *Curr Biol* 20(8):717-723.
- Runft LL, Carroll DJ, Gillett J, Giusti AF, O'Neill FJ, Foltz KR. 2004. Identification of a starfish egg PLC- γ that regulates Ca^{2+} release at fertilization. *Dev Biol* 269(1):220-236.
- Runft LL, Jaffe LA. 2000. Sperm extract injection into ascidian eggs signals Ca^{2+} release by the same pathway as fertilization. *Development* 127(15):3227-3236.
- Runft LL, Jaffe LA, Mehlmann LM. 2002. Egg activation at fertilization: where it all begins. *Dev Biol* 245(2):237-254.
- Sackton KL, Buehner NA, Wolfner MF. 2007. Modulation of MAPK activities during egg activation in *Drosophila*. *Fly (Austin)* 1(4):222-227.
- Sadler KC, Yuce O, Hamaratoglu F, Verge V, Peaucellier G, Picard A. 2004. MAP kinases regulate unfertilized egg apoptosis and fertilization suppresses death via Ca^{2+} signaling. *Mol Reprod Dev* 67(3):366-383.

- Sadler SE, Angleson JK, Dsouza M. 2010. IGF-1 receptors in *Xenopus laevis* ovarian follicle cells support the oocyte maturation response. *Biol Reprod* 82(3):591-598.
- Sakakibara K, Sato K, Yoshino K, Oshiro N, Hirahara S, Mahbub Hasan AK, Iwasaki T, Ueda Y, Iwao Y, Yonezawa K, Fukami Y. 2005. Molecular identification and characterization of *Xenopus* egg uroplakin III, an egg raft-associated transmembrane protein that is tyrosine-phosphorylated upon fertilization. *J Biol Chem* 280(15):15029-15037.
- Sakamoto I, Takahara K, Yamashita M, Iwao Y. 1998. Changes in cyclin B during oocyte maturation and early embryonic cell cycle in the newt, *Cynops pyrrhogaster*: requirement of germinal vesicle for MPF activation. *Dev Biol* 195(1):60-69.
- Sakuma M, Onodera H, Suyemitsu T, Yamasu K. 1997. The protein tyrosine kinases of the sea urchin *Anthocidaris crassispina*. *Zoolog Sci* 14(6):941-946.
- Salas C, Julio-Pieper M, Valladares M, Pommer R, Vega M, Mastronardi C, Kerr B, Ojeda SR, Lara HE, Romero C. 2006. Nerve growth factor-dependent activation of trkA receptors in the human ovary results in synthesis of follicle-stimulating hormone receptors and estrogen secretion. *J Clin Endocrinol Metab* 91(6):2396-2403.
- Sam MR, Elliott BE, Mueller CR. 2007. A novel activating role of SRC and STAT3 on HGF transcription in human breast cancer cells. *Mol Cancer* 6:69.
- Sanghera JS, Charlton LA, Paddon HB, Pelech SL. 1992. Purification and characterization of echinoderm casein kinase II. Regulation by protein kinase C. *Biochem J* 283 (Pt 3):829-837.
- Sanghera JS, Paddon HB, Bader SA, Pelech SL. 1990. Purification and characterization of a maturation-activated myelin basic protein kinase from sea star oocytes. *J Biol Chem* 265(1):52-57.
- Sardon T, Peset I, Petrova B, Vernos I. 2008. Dissecting the role of Aurora A during spindle assembly. *EMBO J* 27(19):2567-2579.
- Sasaki K, Chiba K. 2004. Induction of apoptosis in starfish eggs requires spontaneous inactivation of MAPK (extracellular signal-regulated kinase) followed by activation of p38MAPK. *Mol Biol Cell* 15(3):1387-1396.
- Sato K, Aoto M, Mori K, Akasofu S, Tokmakov AA, Sahara S, Fukami Y. 1996. Purification and characterization of a Src-related p57 protein-tyrosine kinase from *Xenopus* oocytes. Isolation of an inactive form of the enzyme and its activation and translocation upon fertilization. *J Biol Chem* 271(22):13250-13257.
- Sato K, Fukami Y, Stith BJ. 2006a. Signal transduction pathways leading to Ca²⁺ release in a vertebrate model system: lessons from *Xenopus* eggs. *Semin Cell Dev Biol* 17(2):285-292.
- Sato K, Iwao Y, Fujimura T, Tamaki I, Ogawa K, Iwasaki T, Tokmakov AA, Hatano O, Fukami Y. 1999. Evidence for the involvement of a Src-related tyrosine kinase in *Xenopus* egg activation. *Dev Biol* 209(2):308-320.
- Sato K, Iwasaki T, Hirahara S, Nishihira Y, Fukami Y. 2004. Molecular dissection of egg fertilization signaling with the aid of tyrosine kinase-specific inhibitor and activator strategies. *Biochim Biophys Acta* 1697(1-2):103-121.
- Sato K, Iwasaki T, Ogawa K, Konishi M, Tokmakov AA, Fukami Y. 2002. Low density detergent-insoluble membrane of *Xenopus* eggs: subcellular microdomain for tyrosine kinase signaling in fertilization. *Development* 129(4):885-896.
- Sato K, Ogawa K, Tokmakov AA, Iwasaki T, Fukami Y. 2001. Hydrogen peroxide induces Src family tyrosine kinase-dependent activation of *Xenopus* eggs. *Dev Growth Differ* 43(1):55-72.

- Sato K, Tokmakov AA, He CL, Kurokawa M, Iwasaki T, Shirouzu M, Fissore RA, Yokoyama S, Fukami Y. 2003. Reconstitution of Src-dependent phospholipase Cgamma phosphorylation and transient calcium release by using membrane rafts and cell-free extracts from *Xenopus* eggs. *J Biol Chem* 278(40):38413-38420.
- Sato K, Tokmakov AA, Iwasaki T, Fukami Y. 2000. Tyrosine kinase-dependent activation of phospholipase Cgamma is required for calcium transient in *Xenopus* egg fertilization. *Dev Biol* 224(2):453-469.
- Sato K, Yoshino K, Tokmakov AA, Iwasaki T, Yonezawa K, Fukami Y. 2006b. Studying fertilization in cell-free extracts: focusing on membrane/lipid raft functions and proteomics. *Methods Mol Biol* 322:395-411.
- Saunders CM, Larman MG, Parrington J, Cox LJ, Royse J, Blayney LM, Swann K, Lai FA. 2002. PLC zeta: a sperm-specific trigger of Ca^{2+} oscillations in eggs and embryo development. *Development* 129(15):3533-3544.
- Schindler T, Bornmann W, Pellicena P, Miller WT, Clarkson B, Kuriyan J. 2000. Structural mechanism for STI-571 inhibition of abelson tyrosine kinase. *Science* 289(5486):1938-1942.
- Schmitt A, Nebreda AR. 2002b. Inhibition of *Xenopus* oocyte meiotic maturation by catalytically inactive protein kinase A. *Proc Natl Acad Sci U S A* 99(7):4361-4366.
- Schmidt A, Rauh NR, Nigg EA, Mayer TU. 2006. Cytostatic factor: an activity that puts the cell cycle on hold. *J Cell Sci* 119(Pt 7):1213-1218.
- Schmitt A, Nebreda AR. 2002a. Signalling pathways in oocyte meiotic maturation. *J Cell Sci* 115(Pt 12):2457-2459.
- Schober CS, Aydiner F, Booth CJ, Seli E, Reinke V. 2011. The kinase VRK1 is required for normal meiotic progression in mammalian oogenesis. *Mech Dev* 128(3-4):178-190.
- Schultz RM, Kopf GS. 1995. Molecular basis of mammalian egg activation. *Curr Top Dev Biol* 30:21-62.
- Schwab MS, Kim SH, Terada N, Edfjall C, Kozma SC, Thomas G, Maller JL. 1999. p70(S6K) controls selective mRNA translation during oocyte maturation and early embryogenesis in *Xenopus laevis*. *Mol Cell Biol* 19(4):2485-2494.
- Schwartz Y, Ben-Dor I, Navon A, Motro B, Nir U. 1998. Tyrosine phosphorylation of the TATA element modulatory factor by the FER nuclear tyrosine kinases. *FEBS Lett* 434(3):339-345.
- Segawa Y, Suga H, Iwabe N, Oneyama C, Akagi T, Miyata T, Okada M. 2006. Functional development of Src tyrosine kinases during evolution from a unicellular ancestor to multicellular animals. *Proc Natl Acad Sci U S A* 103(32):12021-12026.
- Sehgal A, Wall DA, Chao MV. 1988. Efficient processing and expression of human nerve growth factor receptors in *Xenopus laevis* oocytes: effects on maturation. *Mol Cell Biol* 8(5):2242-2246.
- Sette C, Dolci S, Geremia R, Rossi P. 2000. The role of stem cell factor and of alternative c-kit gene products in the establishment, maintenance and function of germ cells. *Int J Dev Biol* 44(6):599-608.
- Sette C, Paronetto MP, Barchi M, Bevilacqua A, Geremia R, Rossi P. 2002. Tr-kit-induced resumption of the cell cycle in mouse eggs requires activation of a Src-like kinase. *EMBO J* 21(20):5386-5395.
- Sharma D, Kinsey WH. 2006. Fertilization triggers localized activation of Src-family protein kinases in the zebrafish egg. *Dev Biol* 295(2):604-614.
- Sharma D, Kinsey WH. 2008. Regionalized calcium signaling in zebrafish fertilization. *Int J Dev Biol* 52(5-6):561-570.

- Shen SS, Buck WR. 1990. A synthetic peptide of the pseudosubstrate domain of protein kinase C blocks cytoplasmic alkalinization during activation of the sea urchin egg. *Dev Biol* 140(2):272-280.
- Shen SS, Kinsey WH, Lee SJ. 1999. Protein tyrosine kinase-dependent release of intracellular calcium in the sea urchin egg. *Dev Growth Differ* 41(3):345-355.
- Sherr CJ, Roussel MF, Rettenmier CW. 1988. Colony-stimulating factor-1 receptor (c-fms). *J Cell Biochem* 38(3):179-187.
- Shibuya EK, Boulton TG, Cobb MH, Ruderman JV. 1992. Activation of p42 MAP kinase and the release of oocytes from cell cycle arrest. *EMBO J* 11(11):3963-3975.
- Shibuya EK, Morris J, Rapp UR, Ruderman JV. 1996. Activation of the *Xenopus* oocyte mitogen-activated protein kinase pathway by Mos is independent of Raf. *Cell Growth Differ* 7(2):235-241.
- Shibuya M. 1995. Role of VEGF-flt receptor system in normal and tumor angiogenesis. *Adv Cancer Res* 67:281-316.
- Shilling FM, Carroll DJ, Muslin AJ, Escobedo JA, Williams LT, Jaffe LA. 1994. Evidence for both tyrosine kinase and G-protein-coupled pathways leading to starfish egg activation. *Dev Biol* 162(2):590-599.
- Shirahata S, Rawson C, Loo D, Chang YJ, Barnes D. 1990. ras and neu oncogenes reverse serum inhibition and epidermal growth factor dependence of serum-free mouse embryo cells. *J Cell Physiol* 144(1):69-76.
- Shoji S, Yoshida N, Amanai M, Ohgishi M, Fukui T, Fujimoto S, Nakano Y, Kajikawa E, Perry AC. 2006. Mammalian Emi2 mediates cytostatic arrest and transduces the signal for meiotic exit via Cdc20. *EMBO J* 25(4):834-845.
- Silva AJ, Paylor R, Wehner JM, Tonegawa S. 1992a. Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. *Science* 257(5067):206-211.
- Silva AJ, Stevens CF, Tonegawa S, Wang Y. 1992b. Deficient hippocampal long-term potentiation in alpha-calcium-calmodulin kinase II mutant mice. *Science* 257(5067):201-206.
- Sirard MA. 2001. Resumption of meiosis: mechanism involved in meiotic progression and its relation with developmental competence. *Theriogenology* 55(6):1241-1254.
- Sirard MA, Bilodeau S. 1990a. Effects of granulosa cell co-culture on in-vitro meiotic resumption of bovine oocytes. *J Reprod Fertil* 89(2):459-465.
- Sirard MA, Bilodeau S. 1990b. Granulosa cells inhibit the resumption of meiosis in bovine oocytes in vitro. *Biol Reprod* 43(5):777-783.
- Solc P, Schultz RM, Motlik J. 2010. Prophase I arrest and progression to metaphase I in mouse oocytes: comparison of resumption of meiosis and recovery from G2-arrest in somatic cells. *Mol Hum Reprod* 16(9):654-664.
- Stanford JS, Ruderman JV. 2005. Changes in regulatory phosphorylation of Cdc25C Ser287 and Wee1 Ser549 during normal cell cycle progression and checkpoint arrests. *Mol Biol Cell* 16(12):5749-5760.
- Steele RE. 1985. Two divergent cellular src genes are expressed in *Xenopus laevis*. *Nucleic Acids Res* 13(5):1747-1761.
- Steele RE, Deng JC, Ghosn CR, Fero JB. 1990. Structure and expression of fyn genes in *Xenopus laevis*. *Oncogene* 5(3):369-376.
- Steele RE, Irwin MY, Knudsen CL, Collett JW, Fero JB. 1989a. The yes proto-oncogene is present in amphibians and contributes to the maternal RNA pool in the oocyte. *Oncogene Res* 4(3):223-233.

- Steele RE, Unger TF, Mardis MJ, Fero JB. 1989b. The two *Xenopus laevis* SRC genes are co-expressed and each produces functional pp60src. *J Biol Chem* 264(18):10649-10653.
- Steinhardt RA, Epel D. 1974. Activation of sea-urchin eggs by a calcium ionophore. *Proc Natl Acad Sci U S A* 71(5):1915-1919.
- Stitzel ML, Cheng KC, Seydoux G. 2007. Regulation of MBK-2/Dyrk kinase by dynamic cortical anchoring during the oocyte-to-zygote transition. *Curr Biol* 17(18):1545-1554.
- Stitzel ML, Pellettieri J, Seydoux G. 2006. The *C. elegans* DYRK Kinase MBK-2 Marks Oocyte Proteins for Degradation in Response to Meiotic Maturation. *Curr Biol* 16(1):56-62.
- Stricker SA. 1999. Comparative biology of calcium signaling during fertilization and egg activation in animals. *Dev Biol* 211(2):157-176.
- Stricker SA. 2009. Interactions between mitogen-activated protein kinase and protein kinase C signaling during oocyte maturation and fertilization in a marine worm. *Mol Reprod Dev* 76(8):708-721.
- Stricker SA. 2011. Potential upstream regulators and downstream targets of AMP-activated kinase signaling during oocyte maturation in a marine worm. *Reproduction* 142(1):29-39.
- Stricker SA, Carroll DJ, Tsui WL. 2010a. Roles of Src family kinase signaling during fertilization and the first cell cycle in the marine protostome worm *Cerebratulus*. *Int J Dev Biol* 54(5):787-793.
- Stricker SA, Smythe TL. 2006. Differing mechanisms of cAMP- versus seawater-induced oocyte maturation in marine nemertean worms I. The roles of serine/threonine kinases and phosphatases. *Mol Reprod Dev* 73(12):1578-1590.
- Stricker SA, Swiderek L, Nguyen T. 2010b. Stimulators of AMP-activated kinase (AMPK) inhibit seawater- but not cAMP-induced oocyte maturation in a marine worm: Implications for interactions between cAMP and AMPK signaling. *Mol Reprod Dev* 77(6):497-510.
- Sugiura K, Naito K, Iwamori N, Kagii H, Goto S, Ohashi S, Naruoka H, Yada E, Yamanouchi K, Tojo H. 2002. Activation of ribosomal S6 kinase (RSK) during porcine oocyte maturation. *Zygote* 10(1):31-36.
- Sumara I, Vorlaufer E, Stukenberg PT, Kelm O, Redemann N, Nigg EA, Peters JM. 2002. The dissociation of cohesin from chromosomes in prophase is regulated by Polo-like kinase. *Mol Cell* 9(3):515-525.
- Sun CK, Ng KT, Lim ZX, Cheng Q, Lo CM, Poon RT, Man K, Wong N, Fan ST. 2011. Proline-rich tyrosine kinase 2 (Pyk2) promotes cell motility of hepatocellular carcinoma through induction of epithelial to mesenchymal transition. *PLoS One* 6(4):e18878.
- Sun CK, Ng KT, Sun BS, Ho JW, Lee TK, Ng I, Poon RT, Lo CM, Liu CL, Man K, Fan ST. 2007. The significance of proline-rich tyrosine kinase2 (Pyk2) on hepatocellular carcinoma progression and recurrence. *Br J Cancer* 97(1):50-57.
- Sun QY, Rubinstein S, Breitbart H. 1999. MAP kinase activity is downregulated by phorbol ester during mouse oocyte maturation and egg activation in vitro. *Mol Reprod Dev* 52(3):310-318.
- Sun QY, Miao YL, Schatten H. 2009. Towards a new understanding on the regulation of mammalian oocyte meiosis resumption. *Cell Cycle* 8(17):2741-2747.
- Swann K, Igusa Y, Miyazaki S. 1989. Evidence for an inhibitory effect of protein kinase C on G-protein-mediated repetitive calcium transients in hamster eggs. *EMBO J* 8(12):3711-3718.

- Swann K, Saunders CM, Rogers NT, Lai FA. 2006. PLCzeta(zeta): a sperm protein that triggers Ca^{2+} oscillations and egg activation in mammals. *Semin Cell Dev Biol* 17(2):264-273.
- Taghon MS, Sadler SE. 1994. Insulin-like growth factor 1 receptor-mediated endocytosis in *Xenopus laevis* oocytes. A role for receptor tyrosine kinase activity. *Dev Biol* 163(1):66-74.
- Talmor A, Kinsey WH, Shalgi R. 1998. Expression and immunolocalization of p59c-fyn tyrosine kinase in rat eggs. *Dev Biol* 194(1):38-46.
- Talmor-Cohen A, Tomashov-Matar R, Eliyahu E, Shapiro R, Shalgi R. 2004a. Are Src family kinases involved in cell cycle resumption in rat eggs? *Reproduction* 127(4):455-463.
- Talmor-Cohen A, Tomashov-Matar R, Tsai WB, Kinsey WH, Shalgi R. 2004b. Fyn kinase-tubulin interaction during meiosis of rat eggs. *Reproduction* 128(4):387-393.
- Tang W, Wu JQ, Guo Y, Hansen DV, Perry JA, Freel CD, Nutt L, Jackson PK, Kornbluth S. 2008. Cdc2 and Mos regulate Emi2 stability to promote the meiosis I-meiosis II transition. *Mol Biol Cell* 19(8):3536-3543.
- Tatone C, Delle Monache S, Francione A, Gioia L, Barboni B, Colonna R. 2003. Ca^{2+} -independent protein kinase C signalling in mouse eggs during the early phases of fertilization. *Int J Dev Biol* 47(5):327-333.
- Thomas SM, Brugge JS. 1997. Cellular functions regulated by Src family kinases. *Annu Rev Cell Dev Biol* 13:513-609.
- Thorpe CJ, Moon RT. 2004. nemo-like kinase is an essential co-activator of Wnt signaling during early zebrafish development. *Development* 131(12):2899-2909.
- Toker A, Newton AC. 2000. Cellular signaling: pivoting around PDK-1. *Cell* 103(2):185-188.
- Tokmakov A, Iwasaki T, Itakura S, Sato K, Shirouzu M, Fukami Y, Yokoyama S. 2005. Regulation of Src kinase activity during *Xenopus* oocyte maturation. *Dev Biol* 278(2):289-300.
- Tokmakov AA, Sato KI, Iwasaki T, Fukami Y. 2002. Src kinase induces calcium release in *Xenopus* egg extracts via PLCgamma and IP3-dependent mechanism. *Cell Calcium* 32(1):11-20.
- Tomashov-Matar R, Levi M, Shalgi R. 2008. The involvement of Src family kinases (SFKs) in the events leading to resumption of meiosis. *Mol Cell Endocrinol* 282(1-2):56-62.
- Tomek W, Smiljakovic T. 2005. Activation of Akt (protein kinase B) stimulates metaphase I to metaphase II transition in bovine oocytes. *Reproduction* 130(4):423-430.
- Tong C, Fan HY, Lian L, Li SW, Chen DY, Schatten H, Sun QY. 2002. Polo-like kinase-1 is a pivotal regulator of microtubule assembly during mouse oocyte meiotic maturation, fertilization, and early embryonic mitosis. *Biol Reprod* 67(2):546-554.
- Tonou-Fujimori N, Takahashi M, Onodera H, Kikuta H, Koshida S, Takeda H, Yamasu K. 2002. Expression of the FGF receptor 2 gene (fgfr2) during embryogenesis in the zebrafish *Danio rerio*. *Mech Dev* 119 Suppl 1:S173-178.
- Tornell J, Billig H, Hillensjo T. 1991. Regulation of oocyte maturation by changes in ovarian levels of cyclic nucleotides. *Hum Reprod* 6(3):411-422.
- Tosca L, Uzbekova S, Chabrolle C, Dupont J. 2007. Possible role of 5'AMP-activated protein kinase in the metformin-mediated arrest of bovine oocytes at the germinal vesicle stage during in vitro maturation. *Biol Reprod* 77(3):452-465.
- Tosuji H, Fusetani N, Seki Y. 2003. Calyculin A causes the activation of histone H1 kinase and condensation of chromosomes in unfertilized sea urchin eggs independently of the maturation-promoting factor. *Comp Biochem Physiol C Toxicol Pharmacol* 135(4):415-424.

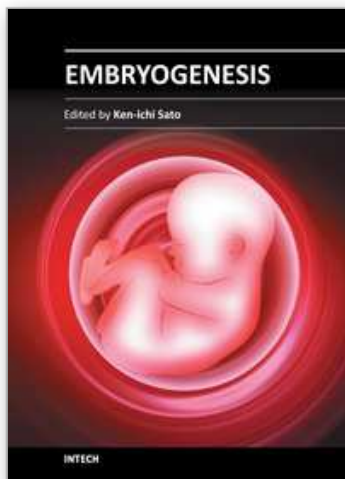
- Townley IK, Roux MM, Foltz KR. 2006. Signal transduction at fertilization: the Ca^{2+} release pathway in echinoderms and other invertebrate deuterostomes. *Semin Cell Dev Biol* 17(2):293-302.
- Townley IK, Schuyler E, Parker-Gur M, Foltz KR. 2009. Expression of multiple Src family kinases in sea urchin eggs and their function in Ca^{2+} release at fertilization. *Dev Biol* 327(2):465-477.
- Trepanier CH, Jackson MF, Macdonald JF. 2011. Regulation of NMDA receptors by the tyrosine kinase Fyn. *FEBS J*.
- Tripathi A, Kumar KV, Chaube SK. 2010. Meiotic cell cycle arrest in mammalian oocytes. *J Cell Physiol* 223(3):592-600.
- Trounson A, Anderiesz C, Jones G. 2001. Maturation of human oocytes in vitro and their developmental competence. *Reproduction* 121(1):51-75.
- Truong LD, Shen SS. 2011. Immunohistochemical diagnosis of renal neoplasms. *Arch Pathol Lab Med* 135(1):92-109.
- Tsafriri A, Chun SY, Zhang R, Hsueh AJ, Conti M. 1996. Oocyte maturation involves compartmentalization and opposing changes of cAMP levels in follicular somatic and germ cells: studies using selective phosphodiesterase inhibitors. *Dev Biol* 178(2):393-402.
- Tsai WB, Zhang X, Sharma D, Wu W, Kinsey WH. 2005. Role of Yes kinase during early zebrafish development. *Dev Biol* 277(1):129-141.
- Uzbekova S, Salhab M, Perreau C, Mermillod P, Dupont J. 2009. Glycogen synthase kinase 3B in bovine oocytes and granulosa cells: possible involvement in meiosis during in vitro maturation. *Reproduction* 138(2):235-246.
- Vaccari S, Horner K, Mehlmann LM, Conti M. 2008. Generation of mouse oocytes defective in cAMP synthesis and degradation: endogenous cyclic AMP is essential for meiotic arrest. *Dev Biol* 316(1):124-134.
- Valbuena A, Sanz-Garcia M, Lopez-Sanchez I, Vega FM, Lazo PA. 2011. Roles of VRK1 as a new player in the control of biological processes required for cell division. *Cell Signal* 23(8):1267-1272.
- Vigneron S, Brioudes E, Burgess A, Labbe JC, Lorca T, Castro A. 2009. Greatwall maintains mitosis through regulation of PP2A. *EMBO J* 28(18):2786-2793.
- Villa-Diaz LG, Miyano T. 2004. Activation of p38 MAPK during porcine oocyte maturation. *Biol Reprod* 71(2):691-696.
- Vincent C, Cheek TR, Johnson MH. 1992. Cell cycle progression of parthenogenetically activated mouse oocytes to interphase is dependent on the level of internal calcium. *J Cell Sci* 103 (Pt 2):389-396.
- Viveiros MM, O'Brien M, Eppig JJ. 2004. Protein kinase C activity regulates the onset of anaphase I in mouse oocytes. *Biol Reprod* 71(5):1525-1532.
- Viveiros MM, O'Brien M, Wigglesworth K, Eppig JJ. 2003. Characterization of protein kinase C-delta in mouse oocytes throughout meiotic maturation and following egg activation. *Biol Reprod* 69(5):1494-1499.
- Walker G, Burgess D, Kinsey WH. 1996. Fertilization promotes selective association of the Abl [correction of Abl] kinase with the egg cytoskeleton. *Eur J Cell Biol* 70(2):165-171.
- Walter SA, Guadagno SN, Ferrell JE, Jr. 2000. Activation of Wee1 by p42 MAPK in vitro and in cycling xenopus egg extracts. *Mol Biol Cell* 11(3):887-896.
- Wang JY, Prywes R, Baltimore D. 1983. Structure and function of the Abelson murine leukemia virus transforming gene. *Prog Clin Biol Res* 119:57-63.

- Wang Q, Snell WJ. 2003. Flagellar adhesion between mating type plus and mating type minus gametes activates a flagellar protein-tyrosine kinase during fertilization in *Chlamydomonas*. *J Biol Chem* 278(35):32936-32942.
- Wassmann K, Niault T, Maro B. 2003. Metaphase I arrest upon activation of the Mad2-dependent spindle checkpoint in mouse oocytes. *Curr Biol* 13(18):1596-1608.
- Westmark CJ, Ghose R, Huber PW. 2002. Phosphorylation of *Xenopus* transcription factor IIIA by an oocyte protein kinase CK2. *Biochem J* 362(Pt 2):375-382.
- Wessel GM, Brooks JM, Green E, Haley S, Voronina E, Wong J, Zaydfudim V, Conner S. 2001. The biology of cortical granules. *Int Rev Cytol* 209:117-206.
- Wessel GM, Wong JL. 2009. Cell surface changes in the egg at fertilization. *Mol Reprod Dev* 76(10):942-953.
- Whitaker M. 2006. Calcium at fertilization and in early development. *Physiol Rev* 86(1):25-88.
- Wianny F, Tavares A, Evans MJ, Glover DM, Zernicka-Goetz M. 1998. Mouse polo-like kinase 1 associates with the acentriolar spindle poles, meiotic chromosomes and spindle midzone during oocyte maturation. *Chromosoma* 107(6-7):430-439.
- Wojcik EJ, Sharifpoor S, Miller NA, Wright TG, Watering R, Tremblay EA, Swan K, Mueller CR, Elliott BE. 2006. A novel activating function of c-Src and Stat3 on HGF transcription in mammary carcinoma cells. *Oncogene* 25(19):2773-2784.
- Wu JQ, Hansen DV, Guo Y, Wang MZ, Tang W, Freel CD, Tung JJ, Jackson PK, Kornbluth S. 2007a. Control of Emi2 activity and stability through Mos-mediated recruitment of PP2A. *Proc Natl Acad Sci U S A* 104(42):16564-16569.
- Wu JQ, Kornbluth S. 2008. Across the meiotic divide - CSF activity in the post-Emi2/XErp1 era. *J Cell Sci* 121(Pt 21):3509-3514.
- Wu Q, Guo Y, Yamada A, Perry JA, Wang MZ, Araki M, Freel CD, Tung JJ, Tang W, Margolis SS, Jackson PK, Yamano H, Asano M, Kornbluth S. 2007b. A role for Cdc2- and PP2A-mediated regulation of Emi2 in the maintenance of CSF arrest. *Curr Biol* 17(3):213-224.
- Wu W, Kinsey WH. 2000. Fertilization triggers activation of Fyn kinase in the zebrafish egg. *Int J Dev Biol* 44(8):837-841.
- Wu W, Kinsey WH. 2002. Role of PTPase(s) in regulating Fyn kinase at fertilization of the zebrafish egg. *Dev Biol* 247(2):286-294.
- Wu W, Kinsey WH. 2004. Detection and measurement of membrane-bound protein tyrosine kinases in the zebrafish egg. *Methods Mol Biol* 253:273-283.
- Wu XR, Kong XP, Pellicer A, Kreibich G, Sun TT. 2009. Uroplakins in urothelial biology, function, and disease. *Kidney Int* 75(11):1153-1165.
- Wu XR, Lin JH, Walz T, Haner M, Yu J, Aebi U, Sun TT. 1994. Mammalian uroplakins. A group of highly conserved urothelial differentiation-related membrane proteins. *J Biol Chem* 269(18):13716-13724.
- Wu XR, Manabe M, Yu J, Sun TT. 1990. Large scale purification and immunolocalization of bovine uroplakins I, II, and III. Molecular markers of urothelial differentiation. *J Biol Chem* 265(31):19170-19179.
- Xie Z, Sanada K, Samuels BA, Shih H, Tsai LH. 2003. Serine 732 phosphorylation of FAK by Cdk5 is important for microtubule organization, nuclear movement, and neuronal migration. *Cell* 114(4):469-482.
- Xiong B, Sun SC, Lin SL, Li M, Xu BZ, OuYang YC, Hou Y, Chen DY, Sun QY. 2008. Involvement of Polo-like kinase 1 in MEK1/2-regulated spindle formation during mouse oocyte meiosis. *Cell Cycle* 7(12):1804-1809.

- Xu X, Sun TT, Gupta PK, Zhang P, Nasuti JF. 2001. Uroplakin as a marker for typing metastatic transitional cell carcinoma on fine-needle aspiration specimens. *Cancer* 93(3):216-221.
- Yamamoto TM, Blake-Hodek K, Williams BC, Lewellyn AL, Goldberg ML, Maller JL. 2011. Regulation of Greatwall kinase during *Xenopus* oocyte maturation. *Mol Biol Cell* 22(13):2157-2164.
- Yamashita M, Fukada S, Yoshikuni M, Bulet P, Hirai T, Yamaguchi A, Yasuda H, Ohba Y, Nagahama Y. 1992. M-phase-specific histone H1 kinase in fish oocytes. Purification, components and biochemical properties. *Eur J Biochem* 205(2):537-543.
- Yang D, Hinton SD, Eckberg WR. 2004. Regulation of cleavage by protein kinase C in *Chaetopterus*. *Mol Reprod Dev* 69(3):308-315.
- Yang KT, Li SK, Chang CC, Tang CJ, Lin YN, Lee SC, Tang TK. 2010b. Aurora-C kinase deficiency causes cytokinesis failure in meiosis I and production of large polyploid oocytes in mice. *Mol Biol Cell* 21(14):2371-2383.
- Yao LJ, Fan HY, Tong C, Chen DY, Schatten H, Sun QY. 2003. Polo-like kinase-1 in porcine oocyte meiotic maturation, fertilization and early embryonic mitosis. *Cell Mol Biol (Noisy-le-grand)* 49(3):399-405.
- Yim DL, Opresko LK, Wiley HS, Nuccitelli R. 1994. Highly polarized EGF receptor tyrosine kinase activity initiates egg activation in *Xenopus*. *Dev Biol* 162(1):41-55.
- Yu B, Wang Y, Liu Y, Li X, Wu D, Zong Z, Zhang J, Yu D. 2005. Protein kinase A regulates cell cycle progression of mouse fertilized eggs by means of MPF. *Dev Dyn* 232(1):98-105.
- Yu BZ, Zheng J, Yu AM, Shi XY, Liu Y, Wu DD, Fu W, Yang J. 2004. Effects of protein kinase C on M-phase promoting factor in early development of fertilized mouse eggs. *Cell Biochem Funct* 22(5):291-298.
- Yu Y, Halet G, Lai FA, Swann K. 2008. Regulation of diacylglycerol production and protein kinase C stimulation during sperm- and PLC ζ -mediated mouse egg activation. *Biol Cell* 100(11):633-643.
- Zernicka-Goetz M. 1991. Spontaneous and induced activation of rat oocytes. *Mol Reprod Dev* 28(2):169-176.
- Zhang K, Hansen PJ, Ealy AD. 2010a. Fibroblast growth factor 10 enhances bovine oocyte maturation and developmental competence in vitro. *Reproduction* 140(6):815-826.
- Zhang L, Liang Y, Liu Y, Xiong CL. 2010b. The role of brain-derived neurotrophic factor in mouse oocyte maturation in vitro involves activation of protein kinase B. *Theriogenology* 73(8):1096-1103.
- Zhang WL, Huitorel P, Genevriere AM, Chiri S, Ciapa B. 2006. Inactivation of MAPK in mature oocytes triggers progression into mitosis via a Ca²⁺-dependent pathway but without completion of S phase. *J Cell Sci* 119(Pt 17):3491-3501.
- Zhang M, Ouyang H, Xia G. 2009. The signal pathway of gonadotrophins-induced mammalian oocyte meiotic resumption. *Mol Hum Reprod* 15(7):399-409.
- Zhang X, Wright CV, Hanks SK. 1995. Cloning of a *Xenopus laevis* cDNA encoding focal adhesion kinase (FAK) and expression during early development. *Gene* 160(2):219-222.
- Zhang Y, Luo Y, Emmett K, Snell WJ. 1996. Cell adhesion-dependent inactivation of a soluble protein kinase during fertilization in *Chlamydomonas*. *Mol Biol Cell* 7(4):515-527.

- Zhang Y, Zhang Z, Xu XY, Li XS, Yu M, Yu AM, Zong ZH, Yu BZ. 2008. Protein kinase A modulates Cdc25B activity during meiotic resumption of mouse oocytes. *Dev Dyn* 237(12):3777-3786.
- Zhao J, Taverne MA, Van Der Weijden GC, Bevers MM, Van Den Hurk R. 2001. Insulin-like growth factor-I (IGF-I) stimulates the development of cultured rat pre-antral follicles. *Mol Reprod Dev* 58(3):287-296.
- Zhao Y, Haccard O, Wang R, Yu J, Kuang J, Jesus C, Goldberg ML. 2008. Roles of Greatwall kinase in the regulation of cdc25 phosphatase. *Mol Biol Cell* 19(4):1317-1327.
- Zhong W, Sun T, Wang QT, Wang Y, Xie Y, Johnson A, Leach R, Puscheck EE, Rappolee DA. 2004. SAPKgamma/JNK1 and SAPKalpha/JNK2 mRNA transcripts are expressed in early gestation human placenta and mouse eggs, preimplantation embryos, and trophoblast stem cells. *Fertil Steril* 82 Suppl 3:1140-1148.
- Zhou RP, Oskarsson M, Paules RS, Schulz N, Cleveland D, Vande Woude GF. 1991. Ability of the c-mos product to associate with and phosphorylate tubulin. *Science* 251(4994):671-675.

IntechOpen



Embryogenesis

Edited by Dr. Ken-Ichi Sato

ISBN 978-953-51-0466-7

Hard cover, 652 pages

Publisher InTech

Published online 20, April, 2012

Published in print edition April, 2012

The book "Embryogenesis" is a compilation of cutting edge views of current trends in modern developmental biology, focusing on gametogenesis, fertilization, early and/or late embryogenesis in animals, plants, and some other small organisms. Each of 27 chapters contributed from the authorships of world-wide 20 countries provides an introduction as well as an in-depth review to classical as well as contemporary problems that challenge to understand how living organisms are born, grow, and reproduce at the levels from molecule and cell to individual.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

A.K.M. Mahbub Hasan, Takashi Matsumoto, Shigeru Kihira, Junpei Yoshida and Ken-ichi Sato (2012). Phospho-Signaling at Oocyte Maturation and Fertilization: Set Up for Embryogenesis and Beyond Part I. Protein Kinases, Embryogenesis, Dr. Ken-Ichi Sato (Ed.), ISBN: 978-953-51-0466-7, InTech, Available from: <http://www.intechopen.com/books/embryogenesis/phospho-signaling-at-oocyte-maturation-and-fertilization-set-up-for-embryogenesis-and-beyond-part-i>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen