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Regulation of oocyte maturation: Role of conserved ERK signaling

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Abstract

During oogenesis, oocytes arrest at meiotic prophase I to acquire competencies for resuming meiosis, fertilization, and early embryonic development. Following this arrested period, oocytes resume meiosis in response to species-specific hormones, a process known as oocyte maturation, that precedes ovulation and fertilization. Involvement of endocrine and autocrine/paracrine factors and signaling events during maintenance of prophase I arrest, and resumption of meiosis is an area of active research. Studies in vertebrate and invertebrate model organisms have delineated the molecular determinants and signaling pathways that regulate oocyte maturation. Cell cycle regulators, such as cyclin-dependent kinase (CDK1), polo-like kinase (PLK1), Wee1/Myt1 kinase and the phosphatase CDC25 play conserved roles during meiotic resumption. Extracellular signal-regulated kinase (ERK), on the other hand, while activated during oocyte maturation in all species, regulates both species-specific, as well as conserved events among different organisms. In this review, we synthesize the general signaling mechanisms and focus on conserved and distinct functions of ERK signaling pathway during oocyte maturation in mammals, non-mammalian vertebrates, and invertebrates such as *Drosophila* and *Caenorhabditis elegans*.

Keywords

oogenesis; meiosis; ERK; cyclin B/CDK1; oocyte maturation

1. Introduction

Oogenesis, the process of oocyte growth and differentiation are crucial for reproductive success. In the final stage of oogenesis, growing oocytes of all metazoan species remain arrested at meiotic prophase I, known as the primary arrest point. While the arrested period varies in different organisms, from minutes (in worm *Caenorhabditis elegans*) to months or years (in mouse and human respectively), this period is essential for differentiation, growth, and development of the oocyte. Oocyte maturation or meiotic resumption is the release of this primary arrest by species-specific hormonal and developmental cues. Upon meiotic resumption, the oocyte progresses through meiotic metaphase leading to ovulation

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Conflict of Interest

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and fertilization in the presence of sperm (Li & Albertini, 2013; Von Stetina & Orr-Weaver, 2011).

Hormonal action at the somatic follicular cells surrounding the oocytes or on the oocyte membrane triggers rapid changes in the intra-oocyte signaling cascades (Hammes, 2004; Jaffe & Egbert, 2017; Zhu et al., 2003). Multiple signaling pathways activate the cytosolic maturation (or M-phase) promoting factor (MPF), a heterodimer of catalytic cyclin-dependent kinase (CDK1) and regulatory subunit, cyclin B (Nurse, 1990). MPF is the universal cell cycle regulator that drives mitosis and meiosis in all eukaryotic cells (Masui & Markert, 1971). Active MPF triggers meiotic resumption by phosphorylating its downstream targets that leads to chromosome condensation, spindle formation, nuclear envelope (germinal vesicle) breakdown (NEBD or GVBD, a hallmark of initiation of oocyte maturation), homologous chromosome segregation and release of the first polar body (Schmitt & Nebreda, 2002). While activation of MPF and its function during oocyte maturation is ubiquitous, species-specific differences exist in the signaling pathways that trigger MPF activation.

Extracellular signal-regulated kinases (ERK) are ubiquitously expressed serine/threonine kinases that are activated by phosphorylation on the TEY motif by upstream MAPK kinase (see Section 2). Once activated, ERK regulates several cellular functions like proliferation, differentiation, migration, and apoptosis (Pearson et al., 2001; Roskoski Jr, 2012; Roux & Blenis, 2004). During oocyte maturation, ERK remains activated in all vertebrate and invertebrate species with different time kinetics. For example, active ERK is detected before GVBD in *Xenopus* (Roy et al., 1996), Zebrafish (Das et al., 2018), *Drosophila* (Sackton et al., 2007) and *C. elegans* (Miller et al., 2001) oocytes, while in mouse (Verlhac et al., 1994) and rat (Lu et al., 2001), ERK is activated after MPF activation and GVBD. Similarly, ERK-mediated function during oocyte maturation varies among species, while some functions are species-specific, others are conserved during oocyte maturation (Fan et al., 2009; Kajiura-Kobayashi et al., 2000; Miller et al., 2001; Sackton et al., 2007; Sagata et al., 1989; Su et al., 2001). Gonadotropin (LH or FSH)-mediated activation of ERK in follicular cells, but not in the oocyte, is essential for the resumption of meiosis in mammals (Fan et al., 2009; Su et al., 2003; Su et al., 2002). In the oocyte, activation of ERK primarily depends on *de novo* synthesis of a germ cell-specific serine/threonine kinase Mos (translated from the proto-oncogene *c-mos*) in almost every species studied, except *C. elegans* [where *c-mos* gene is absent and LET-60/RAS signaling triggers ERK activation (Amiel et al., 2009; Dupré et al., 2011; M.-H. Lee et al., 2007)]. While synthesis of Mos functions as an ‘initiator’ molecule during *Xenopus* oocyte maturation (Posada et al., 1993; Sagata et al., 1989; Yew et al., 1992), Mos/ERK signaling is neither necessary nor sufficient for oocyte maturation in majority of the animal groups (Hashimoto et al., 1994; Ivanovska et al., 2004; Kajiura-Kobayashi et al., 2000). Conversely, Mos/ERK signaling-mediated regulation of microtubules and chromatin organization at metaphase I and maintenance of metaphase II arrest is conserved in all vertebrate oocytes (Kajiura-Kobayashi et al., 2000; Tunquist & Maller, 2003; Verlhac et al., 1996; Verlhac et al., 1994).

The regulation, activation, and function of ERK signaling during oocyte maturation has been extensively studied using several animal models and remains an area of active research. Here

we synthesize the role of ERK signaling from distantly related animals and present parallel's as well as differences in these processes. We shed light on the evolutionary conservation of the ERK-signaling pathway in general, while illustrating its unique role(s) in specific events associated with oocyte maturation.

2. An evolutionarily conserved signaling cascade regulates ERK activation

ERKs are members of the mitogen-activated protein kinase (MAPKs) family and terminal executors of the signaling cascade that transmits extracellular signals to intracellular targets (Pearson et al., 2001; Roskoski Jr, 2012). MAPK group is divided into three major families: the ERK family (ERK1–8), the p38 kinase family (p38α/β/γ/δ), and the c-Jun N-terminal kinase family (JNK1–3) (Pearson et al., 2001; Roskoski Jr, 2012; Roux & Blenis, 2004). All MAPK members have two conserved threonine and tyrosine residues, separated by one amino acid forming the TXY motif, in the activation loop. The middle amino acid (X) of the TXY motif defines the different groups of MAPKs. For instance, 'X' is glutamic acid forming the 'TEY' motif in ERKs, whereas it is proline in JNKs, and glycine in p38 MAPKs (Pearson et al., 2001; Widmann et al., 1999).

Each MAPK is activated by at least a three-tiered conserved kinase cascade. In eukaryotes, the signal transmission steps follow the sequential activation of MAPK kinase kinase (MAP3K), MAPK kinase (MAP2K) and MAPK (Figure 1). As mentioned, ERK activation requires dual phosphorylation on the TEY motif, which is solely mediated by the upstream kinase MEK (Pearson et al., 2001; Shaul & Seger, 2007). Once activated, ERK is dephosphorylated and inactivated; a regulatory event that is conserved across evolution. Dual-specificity phosphatases (DUSPs, also called MAPK phosphatases or MKPs) dephosphorylate and inactivate ERK (Yao & Seger, 2004). Additionally, tyrosine-specific protein phosphatases (PTP), or protein serine/threonine phosphatases also dephosphorylate and inactivate ERK, at least under *in vitro* conditions (Alessi et al., 1995; Anderson et al., 1990). Thus, together with MEK, MKPs shape the magnitude, and spatiotemporal profile of ERK activity.

3. Oocyte maturation and involvement of ERK signaling pathway in mammals

In mammalian females, oocytes enter meiosis I during fetal development and progress through meiotic prophase I to arrest at the diplotene stage of prophase I. As the female reaches puberty, a limited number of primary follicles grow cyclically within follicular microenvironment under the influence of the gonadotrophin, FSH, and other local paracrine factors (Edson et al., 2009). During this growth period, oocytes acquire the competencies that are required for oocyte maturation, fertilization, and embryogenesis (Edson et al., 2009). Fully-grown oocytes under the influence of a second gonadotrophin, LH, resume meiosis [Figure 2A; (Jaffe & Egbert, 2017; Li & Albertini, 2013; Sánchez & Smitz, 2012; Strączyńska et al., 2022)].

3.1. Maintenance of prophase I arrest

High intra-oocyte cyclic adenosine monophosphate (cAMP) maintains meiotic arrest in mammals (Cho et al., 1974; Marco Conti et al., 2002). A bi-directional signaling between the oocyte and the surrounding granulosa cells functions cooperatively to maintain high intra-oocyte cAMP. Oocytes express a constitutively active G protein–coupled orphan receptor, GPR3, that triggers the stimulatory G protein ($G\alpha_s$), which in turn stimulates adenylyl cyclase (AC) to convert ATP into cAMP (Horner et al., 2003; Kalinowski et al., 2004; Mehlmann et al., 2002; Mehlmann et al., 2004). Additionally, during meiotic arrest, phosphodiesterase (PDE)3A enzyme that degrades cAMP to AMP remains inactivated in the oocyte (M. Conti et al., 2002; Shitsukawa et al., 2001). Oocytes from *Pde3a*$^{-/-}$ female mice contain increased cAMP levels and remain arrested at the immature GV stage (Masciarelli et al., 2004). Further studies show that granulosa cells provide another cyclic nucleotide, guanosine monophosphate (cGMP) that blocks PDE3A activity (Norris et al., 2009; Törnell et al., 1990). Guanylyl cyclase natriuretic peptide receptor 2 (NPR2) produces cGMP in the granulosa cells that then diffuses into the oocytes (Tsuji et al., 2012; Zhang et al., 2010). C-type natriuretic peptide (NPPC), a 22-amino acid peptide produced in the granulosa cells, activates NPR2 (Zhang et al., 2010). Expression of *Nppc* is regulated by FSH/FSHR, in collaboration with estradiol (E2)/estrogen receptor, as well as transforming growth factor β (TGFβ)-mediated activation of SMAD3 signaling pathway (Lee et al., 2013; Liu et al., 2017; Yang et al., 2019). Loss of *Npr2* or *Nppc* results in spontaneous oocyte maturation in preovulatory follicle-enclosed oocytes, while addition of NPPC to the culture medium inhibits oocyte maturation *in vitro* (Geister et al., 2013; Tsuji et al., 2012; Zhang et al., 2010). Additionally, oocyte-secreted factors, particularly the growth differentiation factor 9 (GDF9), bone morphogenetic protein 15 (BMP15), and their heterodimer promotes expression of *Npr2* and *Impdh* (inosine monophosphate dehydrogenase), the rate-limiting enzyme required to produce cGMP, *via* The BMP type-II receptor (BMPR-II) and activin receptor-like kinase (ALK) 4/5/7 in cumulus cells (Gilchrist et al., 2008; Richani & Gilchrist, 2018; Wigglesworth et al., 2013). Thus, while an oocyte produces its own cAMP, degradation of the cAMP is prevented by factors from both the oocyte and the granulosa cells (Figure 2B).

cAMP exerts its function by activating cAMP-dependent protein kinase A (PKA), which maintains meiotic arrest by lowering the activity of CDK1, the catalytic component of MPF. CDK1 activity is regulated by phosphorylation at two sites, threonine 14 and tyrosine 15 (Morgan, 1995). The dual-specificity kinase family enzymes Wee1/Myt1 phosphorylate the specific tyrosine/threonine residues and inactivate CDK1, while CDC25 family phosphatases cleave the inhibitory phosphorylation and activate CDK1 (Morgan, 1995; Mueller et al., 1995). In fully-grown immature oocytes, PKA phosphorylates the kinase Wee1B at serine 15 and promotes its kinase activity which in turn inhibits CDK1 (Han et al., 2005). Additionally, PKA phosphorylates the phosphatase CDC25B on serine 321 promoting its binding with 14–3-3 protein and effectively restricting the localization of CDC25B to the cytoplasm (Pirino et al., 2009). However, CDC25B needs to be translocated to the nucleus to promote GVBD and oocyte maturation. Thus, phosphorylation of CDC25B by PKA helps regulate CDC25B function during meiotic resumption through regulation of CDC25B cellular compartmentalization (Oh et al., 2010; Pirino et al., 2009). Further, active PKA

blocks polyadenylation and synthesis of Mos, the activator of ERK signaling (Lazar et al., 2002). Thus, high cAMP/PKA level inactivates both CDK1 and ERK.

MPF activity can also be decreased by increasing the degradation of cyclin B, the regulatory subunit of MPF. Indeed, rates of cyclin B synthesis and degradation determine the timing of meiotic maturation (Ledan et al., 2001). In immature oocytes, Anaphase promoting complex/cyclosome (APC/C), an E3 ubiquitin ligase, along with its co-activator FZR1 (also known as Cdh1) degrades cyclin B1 (Reis et al., 2006). Mouse oocytes lacking *Fzr1* contain ~5-fold higher cyclin B (Holt et al., 2011). Further, loss of *Fzr1* accelerates meiosis I, leading to premature chromosome segregation that results in a non-disjunction phenotype (Holt et al., 2012; Reis et al., 2007). Conversely, activation of FZR1 (APC/C^{FZR1}) by CDC14B, a highly conserved DUSP, prevents meiotic resumption by degrading cyclin B (Schindler & Schultz, 2009). Thus, low CDK1 activity and lower levels of cyclin B maintain meiotic arrest (Figure 2B). Activation of APC/C regulates distinct events during oocyte maturation based on the binding of specific co-activator to the complex. The co-activator bound to APC regulates the specificity of the complex and guides substrate recognition via motifs or degrons borne on the substrate (Homer, 2013; Pines, 2011). CDC20 functions as a co-activator, in addition to FZR1, and functions during prometaphase I to regulate metaphase I-anaphase I transition and completion of meiosis I (Homer, 2013). Microinjection of mouse oocytes with CDC20 antibody shows that more than 50% of oocytes arrest at metaphase I (Yin et al., 2007) and oocytes harvested from mice expressing hypomorphic *Cdc20* display chromosome lagging and chromosome misalignment during meiosis I (Jin et al., 2010). Thus, regulation of APC/C is tightly monitored during oocyte maturation; while downregulation of APC/C^{FZR1} is essential for initiating oocyte maturation, activation of APC/C^{CDC20} is essential for completion of meiosis I.

3. 2. Resumption of meiosis: Releasing the arrest

In mammals, LH triggers oocyte maturation (Edson et al., 2009). LH functions through its receptor LHCGR (luteinizing hormone/choriogonadotropin receptor) in theca cells and 13–48% of the outer mural granulosa cells (Ascoli et al., 2002; Baena et al., 2020). Thus, LH functions remotely to initiate meiotic resumption. The observation that cGMP from the granulosa cells inhibits cAMP hydrolysis in the oocyte prompted the hypothesis that LH signaling functions by lowering cGMP in the granulosa cells and consequently cAMP levels in the oocyte. Indeed, LH treatment dramatically decreases both the cGMP and cAMP concentration in follicle-enclosed oocytes within 20 minutes (Norris et al., 2009; Shuhaibar et al., 2015; Vaccari et al., 2009).

LH-induced decrease in cGMP results from at least three different complementary processes in the follicular cells (Figure 2C). First, LH decreases the guanylyl cyclase activity of NPR2 (Robinson et al., 2012). Phosphorylation of NPR2 on juxtamembrane regulatory domain correlates with its guanylyl cyclase activity and production of cGMP (Egbert et al., 2014). LH stimulation leads to rapid dephosphorylation of NPR2 possibly by a phospho-protein phosphatase (PPP)-family member and downregulates NPR2-mediated cGMP production (Egbert et al., 2021; Egbert et al., 2014). Second, LH activates cGMP phosphodiesterases, like PDE5 and PDE1 in the granulosa cells. These enzymes hydrolyze cGMP in the

granulosa cells (Egbert et al., 2019; Egbert et al., 2016). And third, a long-term and slower, yet important way to prevent NPR2 activity is to lower the abundance of its ligand, NPPC; which is documented in several mammalian models (Jaffe & Egbert, 2017). Although the identity of the kinase that phosphorylates NPR2 and the mechanisms of NPPC downregulation by LH are currently unknown, these data indicate that LH downregulates cGMP *via* multiple parallel and compensatory mechanisms.

Additionally, LH induces expression of epidermal growth factor (EGF)-like peptides in the granulosa cells, such as amphiregulin, epiregulin, and beta-cellulin (Park et al., 2004; Reizel et al., 2010). These peptides are also capable of inhibiting cGMP production. For example, LH-mediated EGF/EGF receptor (EGFR) signaling elevates intracellular calcium concentration in cumulus cells and reduces NPPC/NPR2 interaction, leading to lowering of NPR2 activity and cGMP production (Hao et al., 2016; Wang et al., 2013). Further, treatment of cultured follicles with amphiregulin suppresses *Nppc* mRNA level to the same extent as in LH (Liu et al., 2014). However, EGFR kinase inhibitor blocks the effect of amphiregulin, but not LH-mediated suppression of *Nppc* mRNA (Liu et al., 2014). Similarly, *Nppc* expression is suppressed by LH in follicles from *Egfr or Areg* (amphiregulin) null mice (Hsieh et al., 2011; Liu et al., 2014), suggesting that EGF-like peptides function independently of LH signaling. Together these data demonstrate the redundancy in signaling pathways that regulate cGMP in follicular cells. As the cGMP level decreases in the granulosa cells PDE3A becomes active in the oocyte and the intra-oocyte cAMP/PKA levels reduce.

Along with PKA inactivation, other kinases that regulate oocyte maturation become active in parallel pathways. For example, serum-glucocorticoid kinase (SGK1) has been shown to phosphorylate and activate CDC25B phosphatase, which in turn removes the inhibitory phosphorylation of CDK1 and activates MPF (del Llano et al., 2022). However, mice lacking either *sgk1* alone or both *sgk1* and *sgk3* do not display any functional abnormalities in the ovary or infertility (Grahammer et al., 2006; Wulff et al., 2002), questioning the involvement of SGK1 during physiological oocyte maturation. The other conserved cell-cycle regulator that promotes meiotic resumption is polo-like kinase (PLK1) (Solc et al., 2015). Active PLK1 is detected at microtubule organizing centers (MTOCs) during oocyte maturation (Solc et al., 2015; Wianny et al., 1998). While mouse oocytes lacking PLK1 do not show any defects in GVBD timing, *Plk1* mutant oocytes fail to extrude the first polar body. These oocytes display abnormal chromosome compaction, fail to form normal bipolar metaphase I spindles, and display defects in forming MTOC (Little & Jordan, 2020). These data suggest that PLK1 is essential for completion of oocyte maturation rather than initiation. PLK1 has also been shown to activate APC/C by degrading the APC/C inhibitor EMI1 and thereby regulating the entry into anaphase I (Solc et al., 2015). As mentioned in the previous section (3.1), activation of APC/C^{CDC20} regulates the entry into anaphase I, it is plausible that PLK1 activates APC/C^{CDC20} for the completion of meiosis I.

The possible upstream kinase that regulates PLK1 functions in mouse oocyte is Aurora kinase A (AURKA), a member of conserved serine/threonine kinase family, that regulates chromosome segregation and progression of meiosis I (Blengini et al., 2021; Carmena & Earnshaw, 2003). Depletion or inhibition of AURKA in mouse oocytes leads to a failure

in completion of meiosis and arrest in metaphase I, a phenotype similar to *plk1* null oocytes (Blengini et al., 2021; Little & Jordan, 2020; Saskova et al., 2008). Studies show that PLK1 remains unphosphorylated (on Thr 210) and thus inactive in oocytes lacking AURKA (Blengini et al., 2021). These data suggest that AURKA is essential for meiosis I in mouse oocytes and may regulate PLK1 activity. Additionally, depletion of AURKA from oocytes blocks phosphorylation and activation of CDC25B (Ser 351) (Zhao et al., 2015). Intriguingly, spindle defects in AURKA-depleted oocytes is rescued by phospho-mimetic CDC25B (S351D) mRNA co-injection, suggesting that AURKA regulates spindle assembly in meiosis I by controlling CDC25B phosphorylation on serine 351. Thus, inactivation of PKA along with activation of conserved cell cycle regulators like AURK and PLK1 is essential for completion of oocyte maturation in mammals.

Apart from these signaling molecules, recent studies show that different isoforms of cyclin B (B1–3) interacts with CDK1 and regulates unique as well as overlapping functions during different stages of oocyte maturation (Daldello et al., 2019; Karasu et al., 2019; Li et al., 2018). For example, cyclin B2 can compensate for cyclin B1 to regulate MPF activation during meiosis I. Oocyte-specific deletion of *Ccnb1* promotes cyclin B2 synthesis and resumption of meiosis (Li et al., 2018). *Ccnb2*-null oocytes show delayed GVBD and defects in metaphase I-anaphase I transition (Daldello et al., 2019). The double knockout oocytes permanently fail to initiate maturation, which can be restored by synthesis of only cyclin B2 (Li et al., 2018). Notably, *Ccnb1*-null oocytes fail to arrest at the metaphase II and display a premature interphase-like stage, possibly due to overcompensation by cyclin B2 which leads to overactivation of MPF (Li et al., 2018), suggesting that a tight temporal regulation of these isoforms is essential for precise meiotic progression. *Ccnb3*-null oocytes, on the other hand, initiate oocyte maturation and undergo GVBD but fail to progress through metaphase I-anaphase I transition (Karasu et al., 2019; Zhang et al., 2015). Conversely, overexpression of cyclin B3 leads to a release of metaphase II arrest and oocytes enter interphase (Meng et al., 2020), further highlighting the temporal regulation of cyclin B3 in controlling meiotic progression. In future, studies are warranted to identify the mechanisms that regulate the precise level of different cyclin B isoforms as well as potential distinct and/or overlapping substrates for these isoforms.

3.3. ERK signaling associated with oocyte maturation in mammals

In mammalian oocytes, ERK activation requires synthesis of Mos that functions as an upstream kinase to MEK (Figure 2A). Mos is synthesized after initiation of oocyte maturation and thus active ERK is primarily detected after GVBD in the oocyte (Choi et al., 1996; Verlhac et al., 2000; Verlhac et al., 1994). In accordance with this, mouse oocytes lacking Mos protein or oocytes treated with MEK inhibitor, resume meiosis normally (Choi et al., 1996; Hashimoto et al., 1994; Su et al., 2001; Verlhac et al., 1996; Verlhac et al., 1994). However, these oocytes are defective of meiotic spindle morphology, polar body size and extrusion, as well as metaphase II arrest (Hashimoto et al., 1994; Tong et al., 2003). These data suggest that while Mos/ERK activation in the oocytes is dispensable for initiation of oocyte maturation, post-GVBD Mos/ERK signaling is essential for successful completion of meiosis I and metaphase arrest at meiosis II. A more recent study, however, showed that a low level of active ERK may be present prior to GVBD in mouse oocytes (Cao et al., 2020).

In this context, the basal level of ERK, in cooperation with CDK1, triggers post-GVBD synthesis of cyclin B1 and Mos prior to metaphase I, further boosting the MPF and ERK activity through a positive feedback loop (Cao et al., 2020). Additionally, active ERK and CDK1 restrain APC/C activity thereby block cyclin B degradation, resulting in completion of meiosis I (Nabti et al., 2014).

ERK-activation in somatic follicular cells is essential for gonadotrophin-induced oocyte maturation in mammals (Fan et al., 2009). LH activates ERK through paracrine circuits and intracellular pathways in follicular cells. LH-mediated production of EGF-like peptides triggers ERK activation through EGFR/Ras/Raf/MEK cascade in cumulus cells, which is essential for cumulus expansion and meiotic maturation of follicle-enclosed murine oocytes (Park et al., 2004; Reizel et al., 2010). Further, follicular ERK triggers rapid phosphorylation and closure of gap junction proteins like connexin 43 (Cx43) and Cx37, thereby interrupting follicular cell communications with oocyte, which terminates the supply of cGMP from the somatic cells to the oocytes leading to meiotic resumption (Norris et al., 2008; Norris et al., 2009; Sela-Abramovich et al., 2005; Su et al., 2003; Su et al., 2001; Su et al., 2002). Moreover, EGFR-mediated ERK activation uncouples the oocyte from the somatic follicular compartment during ovulation (Abbassi et al., 2021).

Another intriguing role of ERK signaling in granulosa cells is to regulate steroidogenesis, which is essential for every aspects of ovarian function, including maintenance of reproductive tissues to establishment of pregnancy. While steroidal hormones, like androgens, are shown to stimulate in vitro oocyte maturation in mice and pig (Gill et al., 2004; Li et al., 2008), several studies argue against the involvement of androgen or any other steroid signaling in regulating physiological meiotic resumption in mammals (Motola et al., 2007; Tsafriri & Motola, 2007). Nonetheless, steroids are a major player triggering oocyte maturation in non-mammalian vertebrates including frogs and fishes (discussed later). Thus, ERK-mediated steroidogenesis in mammals and non-mammalian vertebrates could be a conserved mechanism. In mammals, activation of ERK in the granulosa cells determine, at least in part, whether the granulosa cells produce either progesterone (P4) or E2 in response to FSH (Dewi et al., 2002; Moore et al., 2001). Inhibition of MEK/ERK pathway seems to favor synthesis of E2 over P4 (Moore et al., 2001). In contrast, available data also suggests that inhibition of MEK triggers LH-induced P4 production in human and rat preovulatory granulosa cells indicating that ERK may function as a modulator of steroidogenesis (Tajima et al., 2003). However, compared to wild-type mice, in granulosa cell-specific ERK1/2 knockout mice, LH-mimic human chorionic gonadotrophin (hCG) fails to turn off the expression of *Cyp19a1*, an FSH-target gene, essential for E2 synthesis (Fan et al., 2009). Thus, ERK activation in the granulosa cells likely inhibits the expression of E2 leading to (indirectly) an increase in progesterone, a hormone essential for pregnancy maintenance.

In addition to its function in the granulosa cells, ERK activation controls several post-GVBD events in an oocyte autonomous manner. In mice, the Mos/ERK pathway regulates spindle and chromosome morphology (Verlhac et al., 1996). MEK inhibited or *Mos* knockout oocytes thus fail to arrest in metaphase II and instead undergo spontaneous parthenogenetic activation (Hashimoto et al., 1994; Tong et al., 2003). Further, active ERK regulates

the translational machinery during oocyte meiosis. ERK regulates mammalian target of rapamycin (mTOR), eukaryotic translation initiation factor 4E (eIF4E) and cytoplasmic polyadenylation element binding protein 1 (CPEB1) activity either alone or in cooperation with CDK1 to control synthesis of new proteins in the oocytes (Kalous et al., 2018; Sha et al., 2017). Finally, once the oocyte resumes meiosis, active CDK1 and ERK cooperatively phosphorylate poly(A) polymerase α (PAPα). Phosphorylation of PAPα increases its enzymatic activity, leading to global mRNA polyadenylation and meiotic cell cycle progression (Jiang et al., 2021). Phosphorylation of PAP by active CDK1 has been reported in *Xenopus* oocytes undergoing maturation (Colgan et al., 1998; Colgan et al., 1996). Intriguingly, however, in these studies CDK1-mediated hyperphosphorylation reduces the enzymatic activity of PAP. Thus, while involvement of polyadenylation in regulating oocyte maturation in both mice and *Xenopus* is evident (Barkoff et al., 1998; Paynton & Bachvarova, 1994), future studies are required to solve these apparently contradictory results.

4. Oocyte maturation and ERK signaling pathway in non-mammalian vertebrates

In oviparous vertebrates, including frogs and fishes, oocytes enter meiosis and remain arrested at diplotene stage during primary follicular stage (Lubzens et al., 2010; Rasar & Hammes, 2006). Oocytes then enter follicular growth phase, when yolk proteins are incorporated into the oocyte, a process called vitellogenesis (Hara et al., 2016). Finally, fully-grown oocytes resume meiosis under the influence of maturation inducing steroid (MIS), a progesterone or androgen derivative, from the follicular cells (Das et al., 2017; Ferrell Jr, 1999; Lutz et al., 2001; Nagahama & Yamashita, 2008).

4.1. Prophase I arrest in non-mammalian vertebrates

As in mammals, high intra-oocyte cAMP concentration and PKA activity maintains prophase I arrest in non-mammalian vertebrates (Das et al., 2017; Ferrell Jr, 1999; Nagahama & Yamashita, 2008). In both *Xenopus* and zebrafish, an elevation of intra-oocyte cAMP blocks MIS-induced oocyte maturation; conversely, inhibition of PKA triggers meiotic resumption independent of MIS (Maitra et al., 2014; Matten et al., 1994; Schmitt & Nebreda, 2002). *Xenopus* oocytes express the mammalian isoform of constitutively active GPR3, XGPR3, that activates AC possibly *via* Gβγ signaling to produce high intra-oocyte cAMP (Deng et al., 2008). Conversely, depletion of XGPR3 reduces cAMP levels and enhances steroid- and gonadotropin-induced oocyte maturation (Deng et al., 2008), suggesting that XGPR3 participates in maintaining meiotic arrest in *Xenopus* oocytes (Figure 3). In zebrafish, membrane-bound G-protein coupled estrogen receptor (Gper) maintains meiotic arrest *in vitro*. Binding of E2 to Gper triggers $G\alpha_s$/AC-mediated cAMP production (Pang & Thomas, 2010). Further, E2 activation of Gper promotes Npr2/cGMP pathway and inhibits PDE activity in the oocyte (Pang & Thomas, 2018), resulting in meiotic arrest in zebrafish (Figure 4). However, *gper* knockout female zebrafish do not present with any defects in maintaining prophase I arrest (Crowder et al., 2018), thus bringing into question the involvement of E2/Gper system in physiological meiotic arrest. However, other local factors, such as pituitary adenylate cyclase-activating polypeptide

(PACAP), TGFβ, BMP15, as well as gaseous hormone nitric oxide (NO) have been shown to function in an autocrine/paracrine manner to inhibit oocyte maturation in zebrafish (Clelland & Peng, 2009; Deng et al., 2022; Nath et al., 2018; Tan et al., 2009; Zhou et al., 2011). Thus, in fish oocytes, maintenance of meiotic arrest involves both endocrine and autocrine/paracrine factors.

Active PKA regulates diverse substrates to maintain the oocyte arrest. In *Xenopus*, PKA phosphorylates ARPP19 (cAMP-regulated phosphoprotein-19), which is necessary and sufficient for maintaining prophase I arrest (Dupré et al., 2014). Further, PKA-mediated inhibitory phosphorylation of Cdc25 is another mechanism to inhibit oocyte maturation (Duckworth et al., 2002). Additionally, microinjection of PKA catalytic subunit prevents progesterone-induced synthesis of Mos protein in the oocyte (Matten et al., 1994). Unlike *Xenopus*, targets of PKA are not well studied in fish oocytes. While synthesis of cyclin B is essential for oocyte maturation in zebrafish (Kondo et al., 1997), currently there is no documented link between PKA activity and translational regulation.

4.2. Oocyte maturation in non-mammalian vertebrates

In *Xenopus*, different steroids, including P4, androgens, cortisone, and hydrocortisone trigger oocyte maturation *in vitro* (Smith & Ecker, 1971). However, frogs injected with hCG display robust production of androgens rather than P4; suggesting the possibility that androgens are the physiological MIS in Xenopus (Hammes, 2004; Lutz et al., 2001). P4 triggers oocyte maturation either by nuclear progesterone receptor (XPR) bound to the membrane (Bayaa et al., 2000) or by novel G-protein coupled progestin receptors (mPR) (Josefsberg Ben-Yehoshua et al., 2007; Nader et al., 2020), while androgens function through the classical androgen receptors that are localized throughout oocytes, including within the plasma membrane (Lutz et al., 2003). Both P4 and androgens lower cAMP levels, downregulate PKA activity and promote new protein synthesis, such as cyclins (B1, B2, B4 and B5), Ringo/Speedy – the non-canonical activators of CDK1, and Mos – activator of MEK/ERK pathway (Eyers et al., 2005; Ferby et al., 1999; Ferrell Jr, 1999; Haccard & Jessus, 2006b; Hammes, 2004; Meneau et al., 2020; Sadler & Maller, 1981; Wang & Liu, 2004). In immature oocytes, cyclin B2 and B5 remain bound to Cdk1 and form inactive pre-MPF (Haccard & Jessus, 2006a; Hochegger et al., 2001). Once intra-oocyte cAMP/PKA signaling is reduced, Cdc25 phosphatase is activated by polo-like kinase (Plx1); active Cdc25 then cleaves the inhibitory phosphorylation of Cdk1, converting the pre-MPF to active MPF (Duckworth et al., 2002; Qian et al., 1998). Mos, on the other hand, triggers ERK activation which in turn inactivates Myt1, the kinase that blocks Cdk1 activity (Palmer et al., 1998; Peter et al., 2002). Additionally, cAMP/PKA-independent progesterone-induced nongenomic signaling is also documented (Nader et al., 2016), where a signaling endosome of mPRβ interacts with adaptor proteins and Akt2 to promote maturation (Nader et al., 2020). Thus, activation of MPF possibly proceeds through a parallel cAMP/PKA-dependent and independent pathway and may converge to promote *Xenopus* oocyte maturation (Figure 3).

In majority of fishes, progesterone-derivative 17α,20β-dihyroxy-4-pregnen-3-one (DHP) is the MIS, that works primarily through mPR (Das et al., 2017; Nagahama & Yamashita,

2008; Zhu et al., 2003). Seven paralogs of *mpr* gene function redundantly during physiological oocyte maturation in zebrafish (Wu et al., 2020). Further, progestin receptor membrane component 1 and 2 (Pgmrc1/2), the mPR interacting proteins, play essential roles during zebrafish oocyte maturation (Aizen et al., 2018; Wu et al., 2018). MIS binding to mPRs activates $G\alpha_i$ resulting in cAMP downregulation and PKA inactivation (Hanna et al., 2006; Pace & Thomas, 2005; Zhu et al., 2003). Additionally, MIS triggers rapid activation of PI3K/Akt and ERK signaling during in vitro and in vivo oocyte maturation (Das, Pal, et al., 2016; Hanna et al., 2006; Pace & Thomas, 2005). Thus, down regulation of PKA, along with activation of PI3K/Akt and ERK presumably regulates synthesis of cyclin to form MPF (Figure 4).

4.3. ERK signaling during oocyte maturation in non-mammalian vertebrates

The kinetics of intra-oocyte ERK activation and its essentiality in oocyte maturation is species-specific in non-mammalian vertebrates (Figure 5). In *Xenopus*, Mos is synthesized prior to GVBD. Accordingly, microinjection of Mos or its constitutively active downstream target (MEK, ERK2 or p90rsk) triggers oocyte maturation, even in the absence of progesterone (Liang et al., 2007; Sagata et al., 1989; Yew et al., 1992). However, inhibition of ERK signaling fails to block steroid-induced oocyte maturation, suggesting that Mos/ERK activation is sufficient but not necessary for oocyte maturation in this species (Gross et al., 2000). Later work demonstrated that steroid induced MPF activation requires the synthesis of either cyclin B or Mos protein (Haccard & Jessus, 2006b), suggesting that cyclin B and Mos function redundantly to promote oocyte maturation. Importantly, activation of ERK in *Xenopus* oocytes is under powerful feedback loop of MPF. Degradation of Mos directly depends on the degradation of cyclin B, rather than APC/C^{cdc20}, and accumulation of Mos requires a Cdk1-mediated stabilizing phosphorylation on Ser 3 (Castro et al., 2001; Frank-Vaillant et al., 1999). Further, microinjection of oocytes with a kinase-dead Cdk1 blocks accumulation, but not synthesis of Mos protein (Nebreda et al., 1995). These data suggest that while Mos synthesis and accumulation starts earlier than GVBD, maintenance of Mos protein and prolonged ERK activation requires MPF activation.

Mos-independent ERK activation in *Xenopus* oocytes, injected with V12 H-Ras, triggers MPF activation and GVBD (Daar et al., 1991). Similarly, Raf-1 kinase is phosphorylated and activated in progesterone-stimulated oocytes (Fabian et al., 1993). However, expression of a kinase-defective mutant of the human Raf-1 protein (KD-RAF) fails to inhibit progesterone-induced oocyte maturation and the progression to Meiosis II (Fabian et al., 1993), suggesting that redundant signaling pathways exist between Mos/ERK and Ras/Raf-1 in *Xenopus* oocytes.

In fishes, a clear role for ERK signaling in promoting oocyte maturation under physiological condition is currently missing. While synthesis of Mos is well documented in different fish species, activation of Mos/ERK signaling is neither required for MIS-induced oocyte maturation, nor sufficient to promote oocyte maturation in goldfish and Atlantic croaker (Kajiura-Kobayashi et al., 2000; Pace & Thomas, 2005). Although in zebrafish, active Erk is detected as early as 15 mins of MIS stimulation, inhibition of Mek has no impact on MIS-induced oocyte maturation (Das et al., 2018).

However, in both frogs and fishes, insulin and IGF-mediated oocyte maturation, through receptor tyrosine kinase (RTKs), involves the activation of both phosphatidylinositol 3-kinase (PI3K)/Akt and the Ras-ERK pathway (Andersen et al., 2003; Das & Arur, 2017; Das et al., 2013, 2017; Das, Nath, et al., 2016; Das, Pal, et al., 2016). Unlike steroid-induced oocyte maturation, inhibition of Raf-1 or MEK significantly delays insulin/IGF-mediated oocyte maturation in both *Xenopus* and zebrafish (Baert et al., 2003; Fabian et al., 1993; Maitra et al., 2014). These results demonstrate that insulin/IGF and MIS participate in overlapping yet distinct signaling pathways to activate MPF and promote oocyte maturation in non-mammalian vertebrates (Figure 4).

Further, as in mammals, Lh stimulates Erk phosphorylation in follicular cells and the activation of Erk is essential for ovarian steroidogenesis in fishes (Benninghoff & Thomas, 2006; Chung & Ge, 2013). However, unlike mammals, Lh-mediated Erk activation does not involve any Egf-like factors, rather Lhcgr-mediated cAMP/Pka pathway promotes Erk activation (Chung & Ge, 2013). Thus, while the signaling pathway leading to ERK activation is different in mammals and fish, Erk-mediated steroidogenesis is likely conserved throughout vertebrates.

5. Oocyte maturation and ERK signaling pathway in invertebrates

Drosophila egg chamber contains one oocyte and 15 nurse cells, covered by epithelial follicular monolayer (Figure 6A). The oocyte enters meiosis by stage 2A and by stage 5 arrests at diplotene until initiating meiotic maturation at stage 13 of oogenesis (Spradling et al., 1997; Von Stetina et al., 2008). Compared to mammals and non-mammalian vertebrates, much less is known about the role of follicular cells during oocyte maturation in flies. Gap junction channel protein innexin maintains direct connections between follicular cells and the oocytes during *Drosophila* oogenesis (Stebbings et al., 2002). Inhibition of gap junction significantly affects the development of the oocyte, cell fate determination and patterning of the embryo (Bohrmann & Zimmermann, 2008; González-Reyes et al., 1997; Ray & Schüpbach, 1996). However, whether it affects oocyte maturation has not been examined. Further, PKA and its interacting partner A-kinase anchoring proteins (AKAPs) are essential for the stabilization of egg chamber membrane (Jackson & Berg, 2002; Lane & Kalderon, 1995); however, any role of intra-oocyte cAMP/PKA has yet to be documented for meiotic arrest or maturation.

While no extrinsic hormone or receptor for oocyte maturation is identified, intra-oocyte signaling pathway for MPF activation is well documented in *Drosophila* (Figure 6B). The Polo-like kinase (Polo) regulates MPF activity. Inhibition of Polo maintains meiotic arrest. Premature activity of Polo is blocked by direct binding with Matrimony (a sterile alpha motif-containing protein) (Bonner et al., 2013; Xiang et al., 2007). Additionally, Greatwall kinase antagonizes Polo activity during meiosis (Archambault et al., 2007). Activation of Polo, on the other hand, results in activation of Twine, the meiotic homolog of Cdc25 phosphatase that promotes Cdk1 activation. Additionally, a conserved phosphoprotein, α-endosulfine homolog, Endos regulates multiple aspects of *Drosophila* oocyte maturation (Von Stetina et al., 2008). Endos increases the stability and thus protein levels of both Twine and Polo (Von Stetina et al., 2008), leading to oocyte maturation. Independently, Endos also

physically interacts with and inhibits a predicted E3 ubiquitin ligase encoded by Early Girl, which in turn inhibits oocyte maturation in a mechanism yet to be identified (Von Stetina et al., 2008). Further, active MPF is formed by Cdk1 and one of the three cyclins—Cyclin A, B, or B3. While CycA/Cdk1 complex initiates GVBD, CycB/Cdk1 complex completes oocyte maturation and meiotic spindle formation (Bourouh et al., 2016; Kawaguchi et al., 2020; Vardy et al., 2009).

In the hermaphroditic nematode *Caenorhabditis elegans,* development of the oocyte occurs in two gonad arms within the somatic female (Hubbard & Greenstein, 2000). During the 4th Larval stage, *C. elegans* hermaphroditic germline produces 160 sperm and switches the gametic sex to oogenesis for the remaining life of the adult. Each gonad arm has proximal to distal polarity with respect to a common uterus; the oocytes are arranged proximally in a linear row based on their birth order [Figure 7A, (Hubbard & Greenstein, 2000; Hubbard, 2007)]. The proximal-most oocyte (also called −1 oocyte) that remains adjacent to spermatheca undergoes meiotic maturation, prior to and independent of fertilization, in response to major sperm protein (MSP), a sperm-derived secreted short-range hormonal signal (Arur, 2017; Greenstein, 2005; Huelgas-Morales & Greenstein, 2018; Kim et al., 2013; McCarter et al., 1999; Miller et al., 2001).

Gonadal sheath cells, like mammalian follicular cells, communicate with the oocyte in *C. elegans*. Sheath cells are the primary sensors for MSP and control the timing of meiotic maturation (Govindan et al., 2006; Govindan et al., 2009). Oocyte maturation is inhibited by signals from $G\alpha_{o/i}$ that possibly remain active in the absence of sperm (Govindan et al., 2006; Kim et al., 2013). Further, the connection between oocyte and sheath cells are maintained by the gap junction proteins innexins, INX-14 and INX-22 that blocks oocyte maturation (Whitten & Miller, 2007). In the presence of sperm signal, MSP binds to a currently unidentified GPCR on sheath cells and activates stimulatory G-protein $G\alpha_s$ (*gsa-1*), that in turn activates ACY-4 (AC) to elevate cAMP levels. Genetic mosaic analysis shows that in the gonadal sheath cells GSA-1 ($G\alpha_s$), ACY-4 (AC), and KIN-1 (PKAc) are required to trigger oocyte maturation, while these proteins are dispensable in the oocyte (Govindan et al., 2009). Further, mutation of *inx-22* suppresses the maturation failure of a *gsa-1* mutant (Govindan et al., 2009), suggesting that there is an inhibitory function for gap junctions in regulating meiotic arrest which is blocked by GSA-1.

In addition to gonadal sheath cells, oocyte specific MSP receptor, the ephrin receptor VAB-1, is expressed on the oocyte surface (Miller et al., 2003). In the oocyte, MSP triggers PTP-2/Ras activation and reactive oxygen species (ROS) production to stimulate MPK-1 (mammalian homolog of ERK) activity (Yang et al., 2010). However, the function of MSP signaling within oocyte in inducing meiotic maturation remains to be determined.

As in mammalian and non-mammalian vertebrates, cell cycle regulators Polo-like kinase (PLK-1), CDC25 ortholog CDC-25.2 and CDK-1 function as positive regulators and Myt1 ortholog WEE-1.3 functions as a negative regulator of meiotic maturation in *C. elegans* (Boxem et al., 1999; Burrows et al., 2006; Chase et al., 2000; Kim et al., 2010). While RNAi of either *plk-1* or *cdk-1* delays GVBD, depletion of *wee-1.3* causes precocious oocyte maturation (Boxem et al., 1999; Burrows et al., 2006; Chase et al., 2000). Further, *cdc-25.2*

mutants counteract the precocious oocyte maturation defects due to *wee-1.3* depletion (Kim et al., 2010). Additionally, a conserved DEAD-box helicase SACY-1/DDX41 functions within the oocyte to negatively regulate meiotic maturation (Kim et al., 2012). SACY-1/DDX41 inhibits OMA-1 and OMA-2, two worm-specific CCCH zinc finger domain-containing proteins that function redundantly to promote oocyte maturation (Detwiler et al., 2001; Shimada et al., 2002). OMA-1/2 regulate maternal mRNAs by binding to and inhibiting their translation during oocyte maturation, upstream of the WEE-1.3 and CDK-1 during oocyte maturation in *C. elegans* (Detwiler et al., 2001; Kaymak & Ryder, 2013; Spike et al., 2014). Further research into this process will provide insights into the mechanical underpinnings and connections between signaling pathways as shown in (Figure 7B).

5.1. Involvement of ERK signaling in regulating oocyte maturation in invertebrates

In *Drosophila*, active ERK is detected in early-stage germ cells (1–10) at levels comparable to late-stage (11–14) oocytes, and drop strikingly during the oocyte-to-embryo transition (Sackton et al., 2007). In fully-grown oocytes, Mos homolog (DMOS) primarily regulates ERK activation (Ivanovska et al., 2004). While *dmos* deletion results in a reduction in female fertility and apoptosis of a few oocytes, most oocytes mature, fertilize, and develop into healthy embryos (Ivanovska et al., 2004). These data suggest that Mos/ERK signaling is not essential for oocyte maturation or metaphase II arrest in flies (Ivanovska et al., 2004).

In *C. elegans*, MPK-1/ERK regulates almost every aspect of oogenesis (Arur, 2017). In the germline, active MPK-1/ERK is detected in two distinct regions of the germline (Figure 7A). First, in the mid-to-late pachytene region and second, in the proximal few oocytes (M. H. Lee et al., 2007; Miller et al., 2001). In the pachytene region, an insulin-like signaling system triggers MPK-1/ERK activation that regulates several aspects of germline development, including pachytene-to-diplotene progression, chromosomal synapsis of the germ cells, oocyte number and size, germ cell death as well as germ cell membrane organization (Arur et al., 2011; Arur et al., 2009; Das et al., 2020; M. H. Lee et al., 2007; Lopez III et al., 2013). In the proximal oocytes, MPK-1/ERK is activated by the MSP signal *via* Ephrin receptor that results in successful transition of the diakinesis-arrested oocyte to MI, which is immediately coupled with fertilization (M. H. Lee et al., 2007; Miller et al., 2001).

MSP-mediated MPK-1/ERK activity is essential for the initiation of oocyte maturation, such as nuclear translocation from the center of the cell to the future anterior of the zygote and rearrangement of cortical granules (Harris et al., 2006; Kim et al., 2013; M. H. Lee et al., 2007). While active MPK-1/ERK is detected in ~5 oocytes adjacent to spermatheca, only −1 oocyte undergoes maturation (Govindan et al., 2009; Harris et al., 2006; Kim et al., 2013; M. H. Lee et al., 2007; McCarter et al., 1999), suggesting that MPK-1/ERK activation alone is not sufficient for triggering oocyte maturation. These data also suggest that additional regulatory mechanisms likely block oocyte maturation of the −2 through −5 oocytes (McCarter et al., 1999). These mechanisms could be translational control of proteins (e.g., cyclin) which is spatially restricted to −1 oocyte, and/or secretion of inhibitory factors from sheath cells. Interestingly, regulators of oocyte meiotic maturation such as CEH-18 (A POU domain transcription factor) and EGRH-1 (an early growth response factor

family member) have been documented to function in the soma and repress MPK-1/ERK activation in the oocyte and mediate meiotic arrest (Clary & Okkema, 2010; Rose et al., 1997). However, the exact molecular mechanism remains to be identified.

6. Concluding remarks

Synthesizing currently available data it is evident that while meiotic arrest and maturation is a universal phenomenon, regulation of these processes are largely species-specific. Despite the specific regulation of this event in a species-specific manner, common themes across animal kingdom exist such as activation of CDK1, through a balance between the activity of Wee1/Myt1 kinase and the CDC25 phosphatase to control meiotic maturation and PLK1's function as a positive regulator of oocyte maturation in each of the species. ERK signaling is unique in that the pathway regulates diverse species-specific and conserved events in different organisms (Table 1), either alone or in cooperation with other signaling molecules that have likely evolved based on the reproductive needs of the species. For instance, Mos/ERK signaling-mediated initiation of meiotic maturation is specific to *Xenopus* oocyte and is not detected in any other animal group. Conversely, ERK activation in follicular cells regulates steroidogenesis throughout vertebrates, where an intricate endocrine system functions to modulate ovarian function. However, whether a similar function is present in flies or worms is currently not known. Further, in vertebrates, Mos/ERK pathway is essential for metaphase II arrest and thus active ERK is detected until metaphase II stage. However, in *C. elegans*, levels of active ERK drop dramatically before the completion of meiotic maturation. This difference likely reflects the reproductive needs of the species. In vertebrates, oocytes need to maintain metaphase II arrest before the entry of sperm. In *C. elegans*, however, metaphase II arrest is absent, and presence of sperm ensures that oocyte maturation is coupled with ovulation and fertilization. Thus, an inability to downregulate ERK activity in the oocyte, just before fertilization, may result in a metaphase II arrest-like state and developmental defects. This idea is further supported by the fact that *mos* gene is absent in *C. elegans* genome (Amiel et al., 2009). In *Drosophila*, ERK remains activated in fully-grown oocytes and becomes inactivated during oocyte-to-embryo transition, independent of fertilization. Moreover, although deletion of *dmos* has no impact on development of healthy embryos, DMOS/ERK possesses cytostatic activity. It will be interesting to test whether keeping high ERK activity experimentally in fertilized *Drosophila* oocyte hampers embryonic development.

Conversely, a universal function of ERK signaling during oocyte maturation seems to be to control the levels of cyclins. While MPF activity declines with the first polar body extrusion, it rises again in metaphase II. ERK, on the other hand, remains active throughout these phases. High MPF activity is necessary to prevent DNA replication between the first and the second meiotic divisions. Presumably, APC/C-mediated degradation of cyclins contribute to this modulation of MPF activity. Although these two events occur concurrently in *C. elegans*, in mammals and *Xenopus* oocytes, active ERK either stimulates cyclin B translation, or inhibits APC/C-mediated cyclin B degradation, or both, either alone or in cooperation with CDK1. Thus, active ERK ensures high MPF activity, by regulating cyclin B levels.

Finally, one remarkable feature of ERK signaling in meiotic cell cycle is the distinct role of ERK activity at different phases of the cell cycle in the same organism. For example, in vertebrate oocytes, high ERK activity is required for metaphase II arrest. However, active ERK is also detected in metaphase I oocytes. The interesting puzzle that remains to be solved is to determine the mechanism that is responsible for this differential function of ERK that regulates the exit of meiosis I into meiosis II. One possibility is the differential regulation of ERK activity. A recent study using a time-course proteomics approach tested the mechanisms regulating meiosis I-meiosis II transition in synchronized sea star oocytes (Swartz et al., 2021). The authors found that there is a differential regulation between serine and threonine dephosphorylation during the meiosis I-meiosis II transition. Protein phosphatase PP2A-B55 preferentially dephosphorylates threonine residues and thus temporally regulates the activity of its substrates, including CDK and ERK (Swartz et al., 2021). Another possibility is the involvement of other signaling regulators, such as CDK1 or PLK1, which along with ERK, control specific subsets of substrates during the meiosis I-meiosis II transition. While we still do not know the identity of majority of ERK substrates that individually regulate each intricate biological process, the dynamics of ERK activation and its related functions reveals the flexibility afforded by the signaling pathway in integrating diverse signals from multiple pathways that fine-tune different events to mediate precise meiotic cell cycle.

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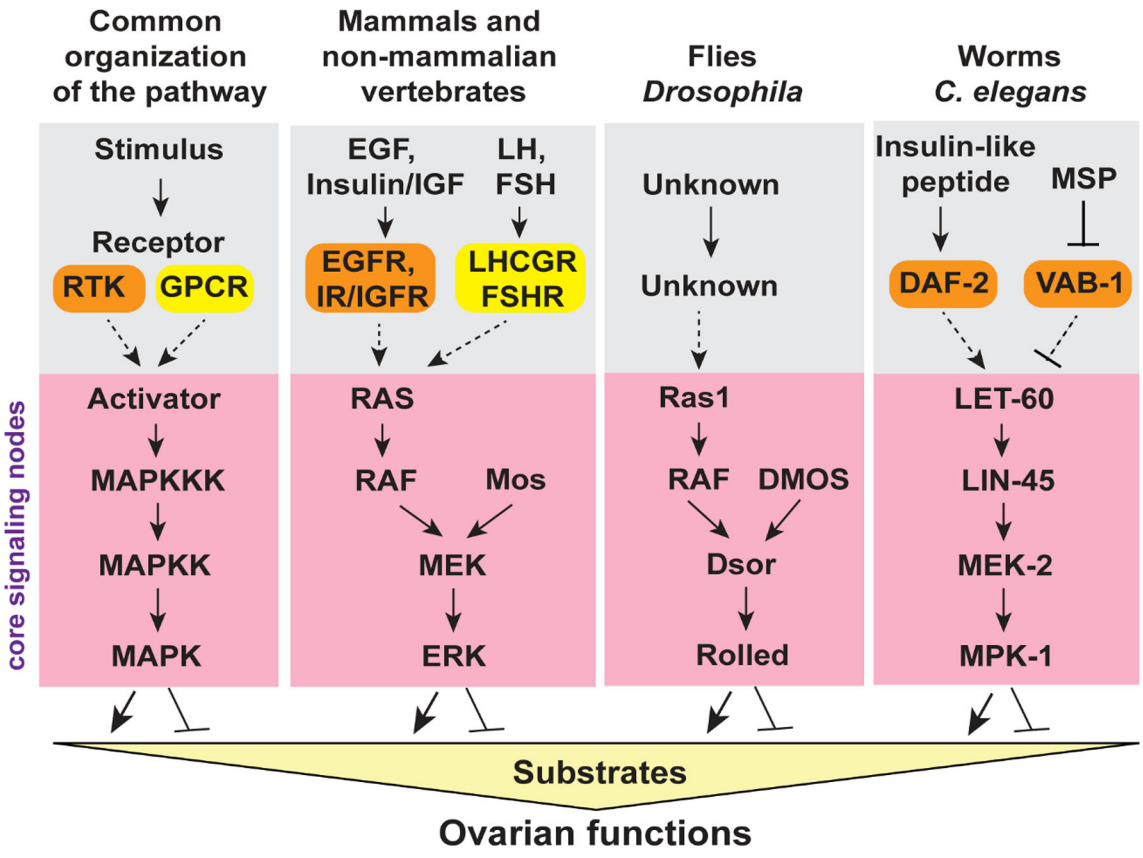

Figure 1:

A conserved MAPK-signaling pathway in the ovary. Activation of the receptors leads to cellular signaling through pathways whose members have orthologs among all metazoans. The ligand and the receptor that regulates the RAS/ERK signaling cascade in the *Drosophila* ovary are currently unknown. Synthesis of the serine/threonine kinase Mos, during oocyte maturation is conserved throughout animal kingdom, except *C. elegans* where *mos* gene is absent. See text for details.

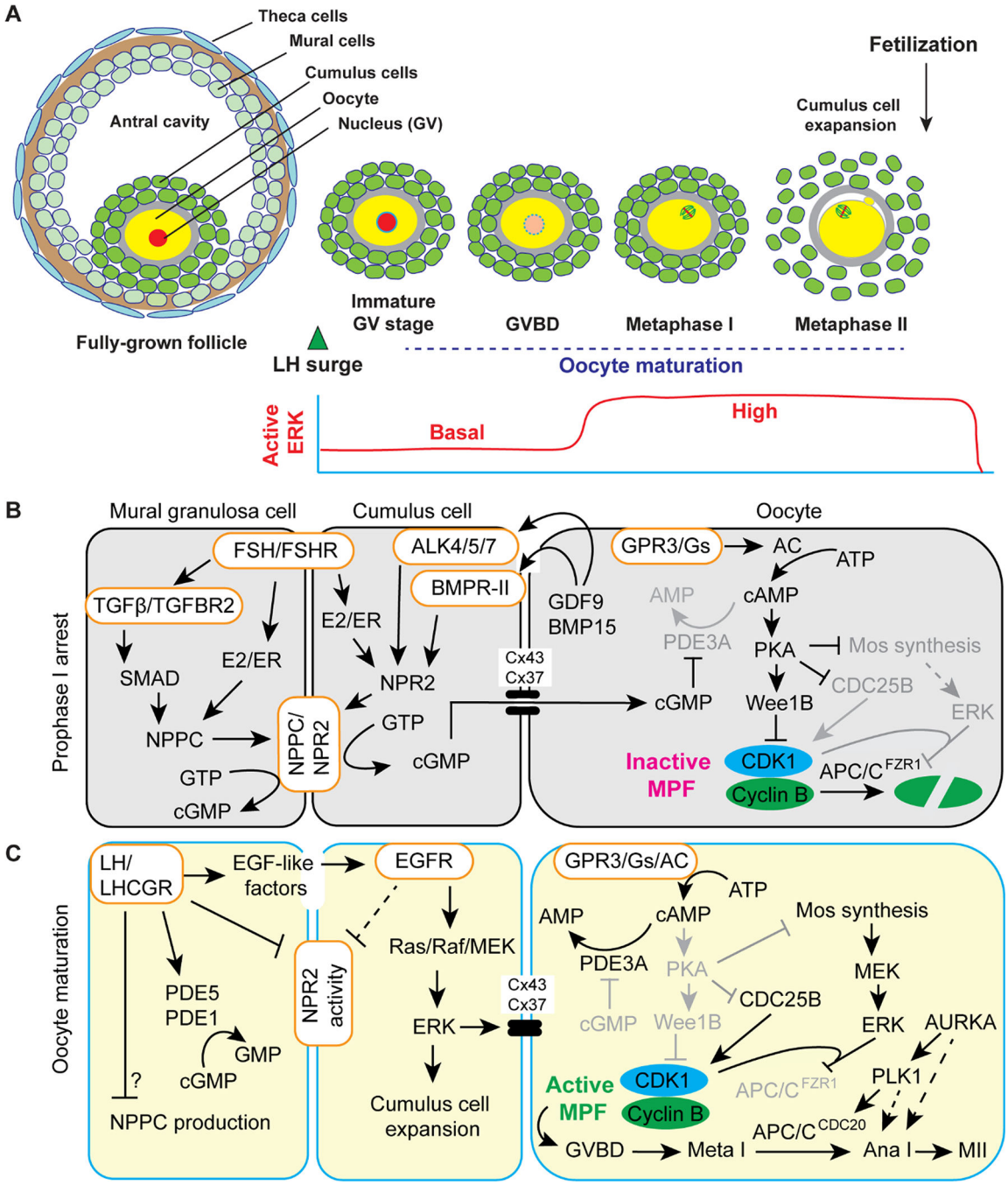

Figure 2:

Regulation of meiotic arrest and oocyte maturation in mammals. (A) A fully-grown follicle with different stages of oocyte maturation with a focus on the nuclear events is shown. The oocyte is surrounded by proximal cumulus cells and distal mural granulosa cells in preovulatory follicles. In response to LH oocytes undergo meiotic maturation. Pattern of ERK activation during different stages of oocyte maturation is depicted below the oocyte stages. Active ERK is detected at basal level in immature GV stage oocyte, the levels of active ERK rapidly increase upon GVBD and remain high until fertilization.

Green triangle indicates the stimulus that triggers meiotic resumption. (B) Schematic view depicting the mechanisms of meiotic arrest. Meiotic arrest is maintained by high intra-oocyte cAMP/PKA level. Oocyte produces its own cAMP by the constitutively active G-protein coupled receptor, GPR3, while cGMP produced in the surrounding follicular cells enters in the oocyte *via* gap junctions and blocks the phosphodiesterase (PDE3) and prevents the breakdown of cAMP. Active PKA downstream of cAMP regulates multiple substrates to keep the MPF inactive. (C) Schematic view for oocyte maturation. LH signal triggers oocyte maturation. In the mural granulosa cells where LH functions, it causes the downregulation of cGMP level. Additionally, EGFR-mediated activation of ERK closes the gap junctions and blocks the entry of cGMP to the oocytes. PDE3 in the oocytes cleaves cAMP to AMP, which in turn down regulates PKA activity and promotes oocyte maturation. See text for details. Active signaling molecule(s) or pathway(s) are shown in black, while inactive signaling molecule(s) or pathway(s) are shown in grey. The yellow bordered elliptical shapes are the receptor on the cell membrane either with or without ligands, → indicates activation or positive influence and ⊣ indicates inhibition or negative influence of the pathway, broken line indicates multiple steps, question mark (?) in the pathway suggest either the mechanism is unknown, or the pathway is only predicted at this time.

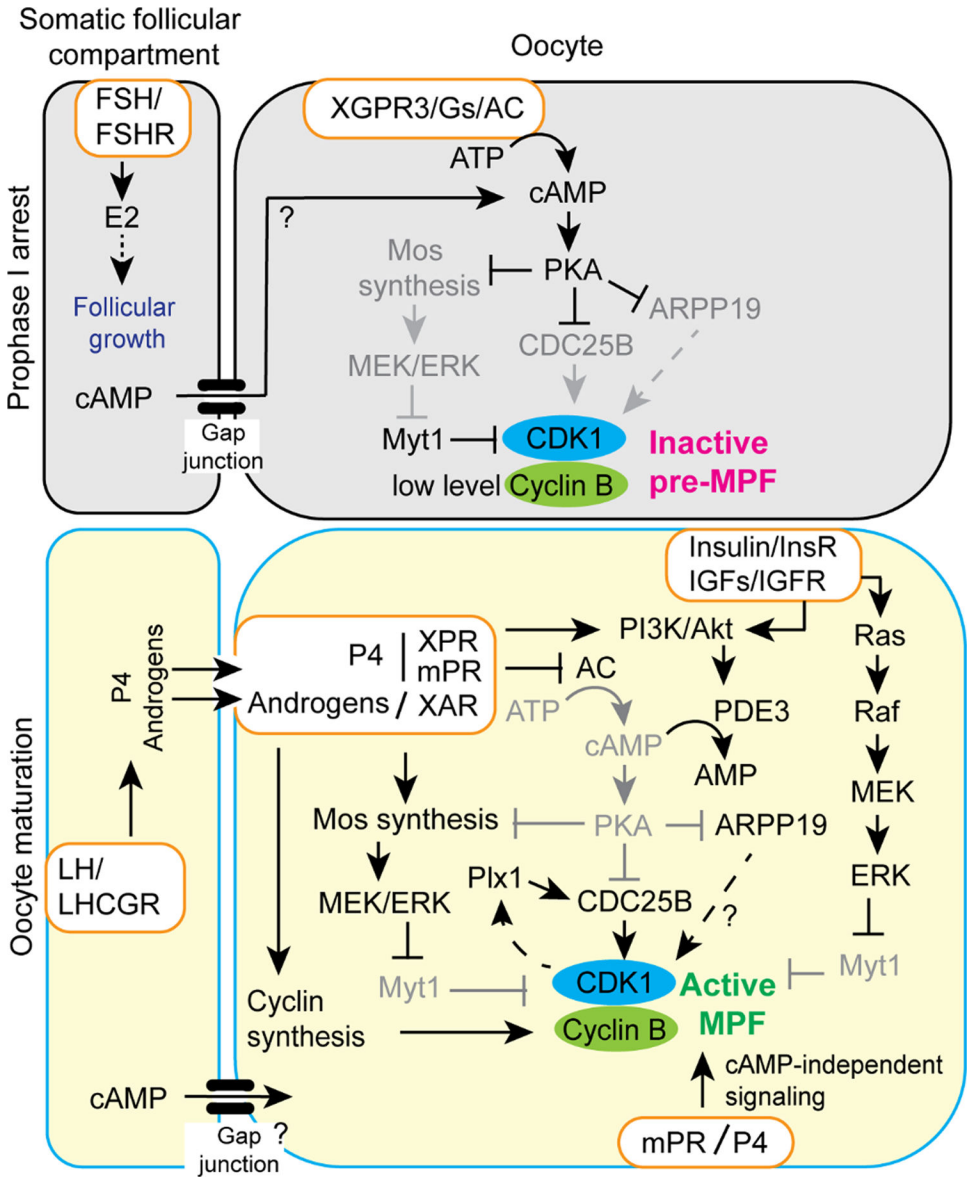

Figure 3:

Schematic model showing the regulation of prophase I arrest and oocyte maturation in *Xenopus*. High cAMP and its downstream kinase PKA in the oocytes keep the oocyte in an arrested state. PKA inhibits multiple substrates essential for activation of MPF. Conversely, during oocyte maturation androgens or progesterone (P4) through their cell surface receptors blocks cAMP production by either inhibiting adenylyl cyclase (AC) or activating oocyte-specific phosphodiesterase PDE3, that in turn inhibits PKA activity and triggers MPF activation. Apart from steroids, insulin and insulin-like growth factors (IGFs) are potent stimulator of oocyte maturation in *Xenopus* and regulates overlapping signaling molecules. Recent studies also indicate the involvement of cAMP-independent signaling in *Xenopus* oocyte maturation. See text for details. Active signaling molecule(s) or pathway(s) are shown in black, while inactive signaling molecule(s) or pathway(s) are shown in grey. The yellow bordered elliptical shapes are receptors on the cell membrane either with or

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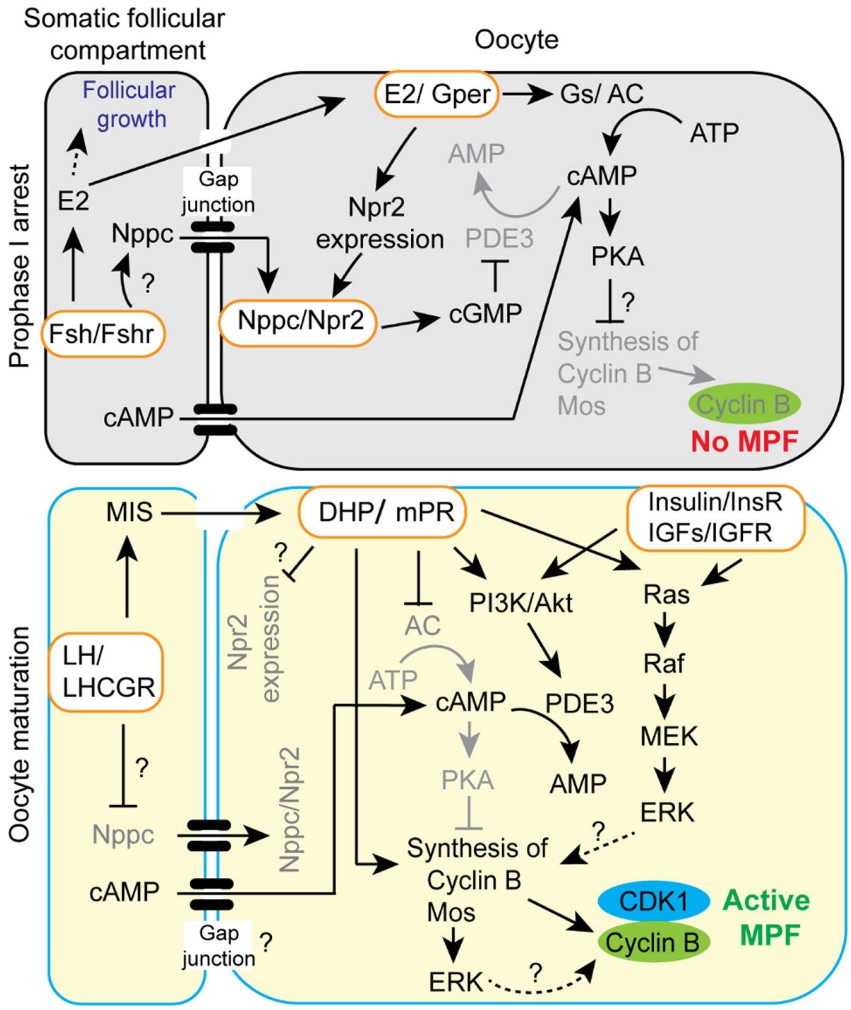

Figure 4:

Schematic model showing the regulation of prophase I arrest and oocyte maturation in zebrafish. As in mammals and *Xenopus*, high cAMP/PKA prevents oocyte maturation in zebrafish. High cAMP is maintained by both oocyte and surrounding somatic follicular cells. Estradiol (E2) and C-type natriuretic peptide (Nppc) produced by the follicular cells play a critical role during the arrest phase in maintaining high cAMP level. While E2 promotes cAMP synthesis in the oocytes via membrane associated G-protein coupled estrogen receptor (Gper), Nppc binds to the Npr2 receptor in the oocyte surface triggers the production of cGMP and blocks the oocyte-specific phosphodiesterase PDE3 activity. The targets of PKA are not well documented in zebrafish. PKA-mediated inhibition of cyclin synthesis is one possible mechanism of action. During oocyte maturation, 17α,20β-dihyroxy-4-pregnen-3-one (DHP) binds to the cell surface membrane progestin receptor (mPR) and activates multiple signaling cascades that ultimately triggers MPF activation. See text for details. Active signaling molecule(s) or pathway(s) are shown in black, while inactive signaling molecule(s) or pathway(s) are shown in grey. The yellow bordered elliptical shapes are receptors on the cell membrane either with or without ligands, → indicates activation or positive influence and ⊣ indicates inhibition or negative influence of

the pathway, broken line indicates multiple steps, question mark (?) in the pathway suggest either the mechanism is unknown, or the pathway is predicted.

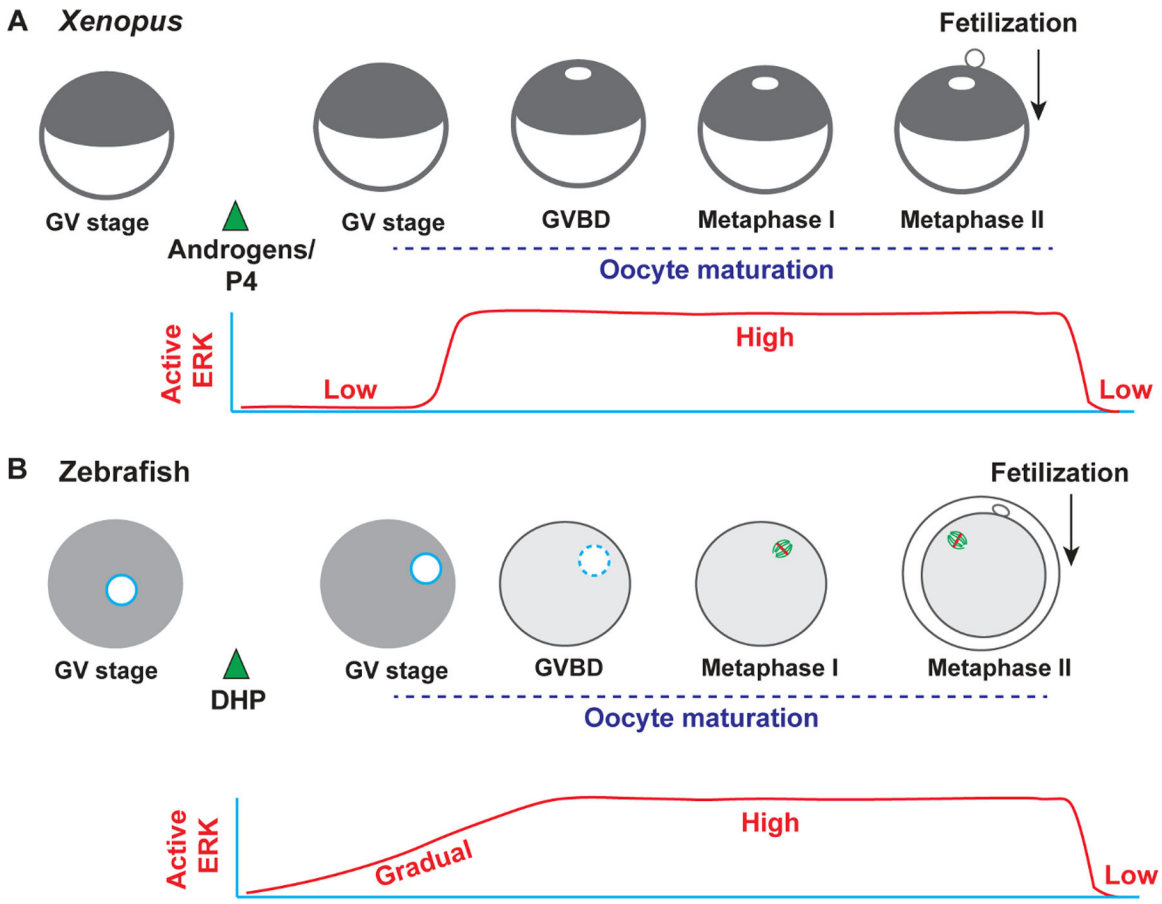

Figure 5:

Comparison of stages of oocyte maturation and ERK activation pattern during these stages in amphibia (*Xenopus*) and fish (zebrafish). (A) Fully-grown immature (GV stage) *Xenopus* oocytes resume meiosis upon induction of androgens or progesterone (P4). Active ERK is detected prior to initiation of GVBD and requires translation of maternally stored *c-mos* mRNA. Once activated, ERK remains high through metaphase I and II and is inactivated after fertilization. (B) In zebrafish, 17α,20β-dihyroxy-4-pregnen-3-one (DHP) triggers oocyte maturation. Active ERK is detected within 15 min of DHP stimulation during GVBD and remains high thereafter possibly until metaphase II. Down regulation of active ERK after fertilization (predicted) in mammals and *Xenopus*. The green triangle indicates the stimulus that triggers meiotic resumption.

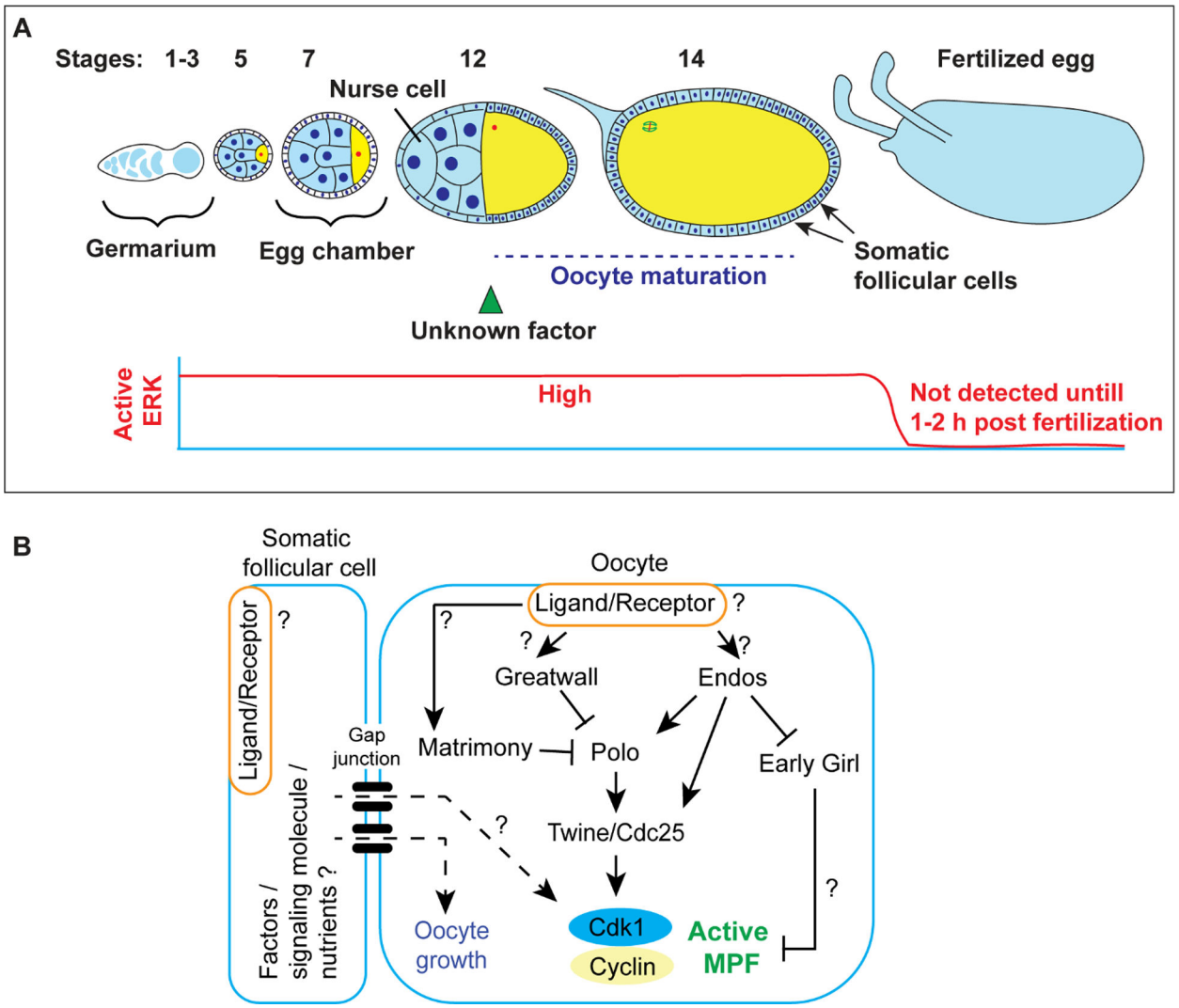

Figure 6:

Development of *Drosophila* egg chamber and regulation of oocyte maturation. (A) The ovariole is composed of the germarium in the anterior-most part followed by the progressively older egg chambers. Meiosis begins at stage 2A of the germarium, and the oocyte arrests at diplotene of prophase-I at stage 5. Oocyte develops within a 16-cell germline cyst surrounded by a single layer of somatic follicle cells. The posterior-most germ cell develops into the oocyte, whereas the remaining 15 cells develop into nurse cells. At Stage 13, an unknown cue, triggers meiotic resumption and progression to MI. Pattern of ERK activation during different stages of oocyte development and maturation are labeled below the oocyte stages. Active ERK is detected in each of the stages evenly until fertilization. The green triangle indicates the unknown stimulus that triggers meiotic resumption. (B) Signaling network regulating meiotic maturation in *Drosophila*. While the role of somatic cells and gap junctions in regulating oocyte maturation is not documented, inhibition of gap junction affects oocyte development. Conserved cell cycle regulators such as Cdk1/Cyclin B, Polo kinase and the phosphatase Twine/Cdc25 are linked with signaling pathway that coordinate events during meiotic resumption. See text for details. The yellow

bordered elliptical shapes are the ligand/receptor complex on the somatic follicular cells or on oocyte membrane which is currently unknown in *Drosophila*, → indicates activation or positive influence and ⊣ indicates inhibition or negative influence of the pathway, broken line indicates multiple steps, question mark (?) in the pathway suggest either the mechanism is unknown, or the pathway is only predicted at this time.

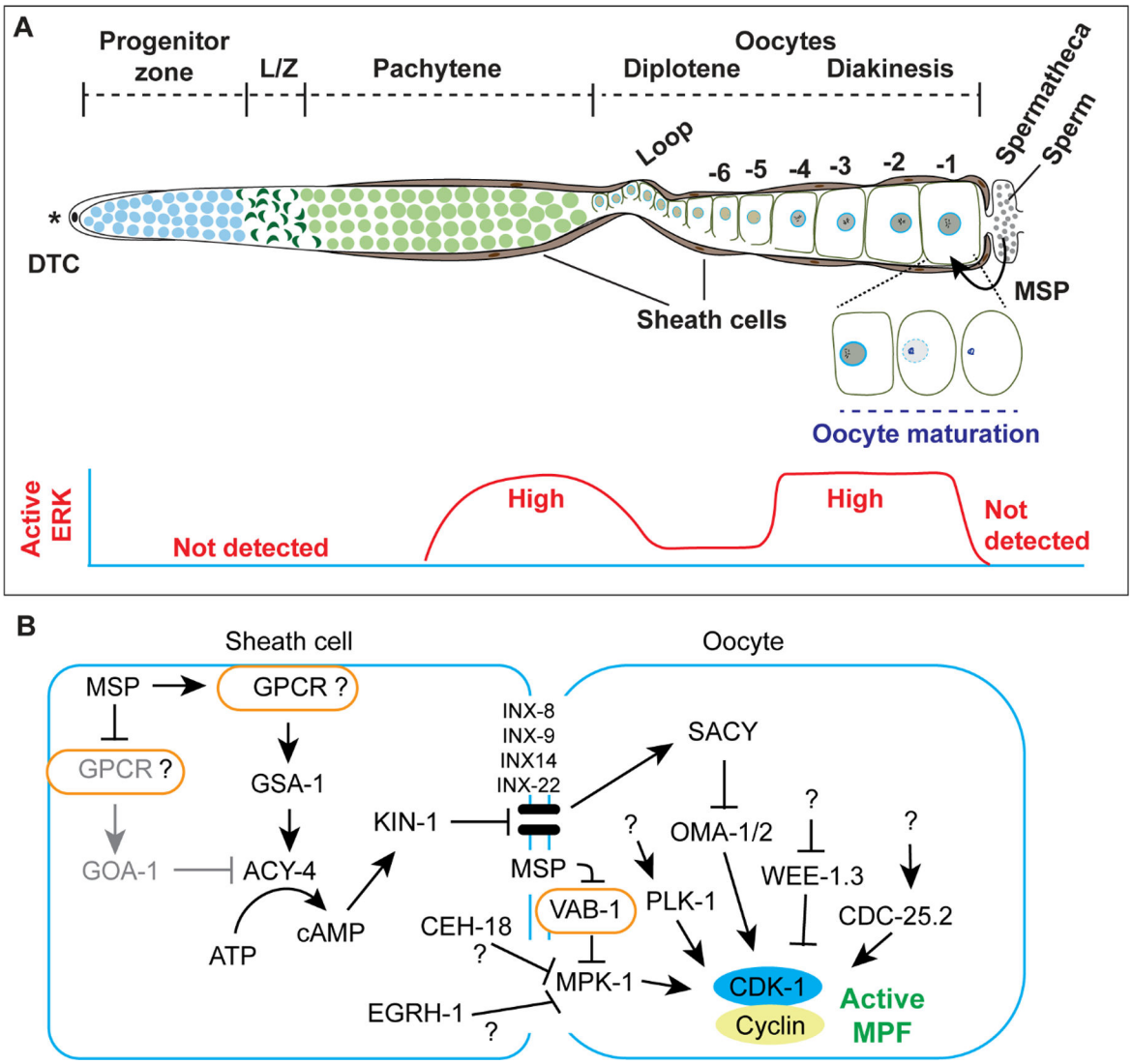

Figure 7:

Regulation of oocyte maturation in *C. elegans*. (A) Surface view of a hermaphroditic *C. elegans* germline displaying the spatiotemporal nature of germ cell organization with a distal (*) to proximal orientation from left to right. Progenitor cells are in the distal region, capped by the distal tip cell (DTC). Germ cells enter meiosis in the leptotene/zygotene (L/Z) stage, followed by progression through different stages of meiosis I. The loop region forms the anatomic bend in the gonad. At the loop region, diplotene stage germ cells start to form oocytes and remain arrested at diakinesis. In response to sperm and its secreted factor, MSP, the proximal most −1 oocyte undergoes meiotic maturation. Active ERK is detected *via* immunostaining using anti–di-phosphorylated ERK in the germline, where it shows a bimodal pattern of activation– first in the mid-to-late pachytene region and then in the proximal ~4–6 oocytes in response to MSP. ERK becomes inactivated once the oocyte undergoes GVBD. (B) A model for signaling network regulating meiotic maturation in *C. elegans*. MSP-mediated signaling in the somatic sheath cells promotes oocyte maturation by activating adenylyl cyclase (ACY-4)/ protein kinase A (KIN-1), which in turn blocks gap

junctions between the sheath cells and oocyte. In the oocytes, conserved cell cycle regulators such as CDK-1, Polo-like kinase (PLK-1) and Wee1/Myt1 family kinase WEE-1.3 and the phosphatase CDC-25.2 coordinate events during meiotic resumption. Mechanism through which these regulators are connected are currently unknown. See text for details. The yellow bordered elliptical shapes are the receptor on the sheath cells and oocyte membrane, → indicates activation or positive influence and ⊣ indicates inhibition or negative influence of the pathway, broken line indicates multiple steps, question mark (?) in the pathway suggest either the mechanism is unknown, or the pathway is only predicted at this time.

Table 1:

A summary of ERK activation and functions during oocyte maturation in different animal groups.

		Mammals	*Xenopus*	Zebrafish	*Drosophila*	*C. elegans*
Activators of ERK	**Full grown Oocytes:**	- Early stage unknown - Post-GVBD Mos	- Primarily Mos	- Early stage MIS/mPR-mediated Ras/ERK - Post-GVBD Mos	- Primarily Mos	- MSP/VAB-1
	Follicular cells:	- EGF-like ligands/EGFR-mediated Ras/ERK (LH promotes EGF-like ligand synthesis)	- Unknown	- Lh/Lhcgr	- Unknown	- Unknown
Maturation stages where active ERK is detected		- Basal level (*) prior to MPF activation, fully activated after GVBD until fertilization (Figure 2A) * needs further testing	- Fully activated before GVBD until fertilization (Figure 3A)	- Gradual increase until GVBD remains fully active thereafter possibly till fertilization (Figure 3B)	- In all stages of follicular development until fetilization (Figure 6A)	- In the diakinesis arrested oocyte until GVBD (Figure 7A)
Functions during oocyte maturation		- Cumulus expansion - Gap junction closure - Uncoupling oocyte from the follicular compartment - Restrain APC/C activity - Global mRNA polyadenylation - Translational activation - Meiotic spindle assembly - Maintains MII arrest and normal spindle configuration	- Involve in MIS and insulin/lgf-mediated MPF activation - Restrain APC/C activity - Meiotic spindle assembly - Maintains MII arrest and normal spindle configuration	- Essential for insulin/Igf-mediated oocyte maturation - Maintains MII arrest	- DMOS blocks apoptosis of the germ cells - DMOS has cytostatic activity but not essential for MII arrest	- Initiation of oocyte maturation such as nuclear translocation and rearrangement of cortical granules