Chapter 4
Signaling-Mediated Regulation of Meiotic Prophase I and Transition During Oogenesis

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Abstract Generation of healthy oocytes requires coordinated regulation of multiple cellular events and signaling pathways. Oocytes undergo a unique developmental growth and differentiation pattern interspersed with long periods of arrest. Oocytes from almost all species arrest in prophase I of oogenesis that allows for long period of growth and differentiation essential for normal oocyte development. Depending on species, oocytes that transit from prophase I to meiosis I also arrest at meiosis I for fairly long periods of time and then undergo a second arrest at meiosis II that is completed upon fertilization. While there are species-specific differences in *C. elegans*, *D. melanogaster*, and mammalian oocytes in stages of prophase I, meiosis I, or meiosis II arrest, in all cases cell signaling pathways coordinate the developmental events controlling oocyte growth and differentiation to regulate these crucial phases of transition. In particular, the ERK MAP kinase signaling pathway, cyclic AMP second messengers, and the cell cycle regulators CDK1/cyclin B are key signaling pathways that seem evolutionarily conserved in their control of oocyte growth and meiotic maturation across species. Here, I identify the common themes and differences in the regulation of key meiotic events during oocyte growth and maturation.

4.1 Introduction

In mammals, females are born with oocytes arrested at meiosis I. Meiosis I is composed of multiple interconnected differentiation programs, the key events being pairing and recombination of chromosomes and arrest of growing oocytes at the end of meiosis I. Due to the lack of germ line stem cells in vertebrate females, model systems like *C. elegans* and *Drosophila* have pioneered the studies on female meiotic I progression and the key signaling and molecular pathways that govern this progression. In this chapter, I highlight our current understanding on the

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environmental, hormonal, and signaling events that regulate the progression of meiosis I during female gametogenesis and compare and contrast the similarities and differences between worms, flies, and mammalian oocyte growth and meiotic maturation.

4.2 *C. elegans* Germ Line Development

C. elegans germ cells are specified in the embryo as Primordial Germ Cells (PGCs), but unlike in flies and mammals these cells do not undergo migration, but instead form the focal points that divide symmetrically along with the somatic gonad progenitors to populate the U-shaped gonad arms in a somatically female animal (Hubbard and Greenstein 2000; Strome and Updike 2015). During early stages of larval development, the germ line progenitors continue to divide symmetrically, until the end of Larval molt 3, at which point the progenitor stem cells in the hermaphroditic germ line differentiate into spermatocytes that progress through meiosis I and II eventually to form haploid mature sperm (reviewed in Hubbard and Greenstein 2000). The process of germ line stem cell proliferation and the balance and switch of a mitotic stem cell cycle to a meiotic cell cycle are discussed in Chap. 2. The end of the last larval molt-Larval Stage 4 completes the events of spermatogenesis that eventually results in mature sperm in a hermaphroditic germ line stored in a spermatheca. Upon the completion of spermatogenesis, coupled with the last molt into adulthood, a switch in sex determination of the germ cells results in onset of the female meiotic program in the hermaphroditic germ line. Through the remaining life of a hermaphroditic adult, the germ line produces oocytes (Hubbard and Greenstein 2000). A feminized germ line on the other hand only produces the female oogenic precursors and mature oocytes starting from larval stage 3. This chapter will focus on the oogenic events in the hermaphroditic germ line and highlight key differences (where relevant) from a feminized germ line.

4.2.1 Oogenic Meiotic Prophase Progression

The *C. elegans* germ line grows as a syncytial mass of nuclei that are attached to a common cytoplasm and appear very much like a growing stalk of brussel sprouts (Hall et al. 1999). In the syncytial germ line, plasma membranes do not fully surround each germ nucleus, and cytoplasmic bridge connects each germ nucleus to a common cytoplasm (Maddox et al. 2007). By convention, each nucleus surrounding cytoplasm and membranes are referred to as a germ cell. From the mitotic region that harbors the progenitor cells through the end of pachytene, germ cells are arranged on the surface of the gonadal tube with an interior cell/nucleus-free cytoplasmic region called the “rachis” or “core.” In oogenesis, the majority of

pachytene cells appear to function as nurse cells, undergoing apoptosis after providing RNAs and proteins to the rachis (Gibert et al. 1984; Gumienny et al. 1999; Wolke et al. 2007).

The oogenic germ cells are in a very long meiotic prophase I, with the pachytene region being the longest, wherein each germ cell is thought to reside in pachytene for ~54–60 h (Jaramillo-Lambert et al. 2007). Events specific to meiotic pairing, recombination, and resolution of homologous sisters are covered in Chap. 4. This long stretch of pachytene can be divided into three major regions, early pachytene, mid-pachytene, and late pachytene, based on the distinct chromosomal behaviors (Phillips et al. 2009). Besides chromosomal events, the germ cells in this stage execute multiple cell biological events such as onset of meiosis (reviewed in Chap. 8, after the mitotic populations), apoptosis [wherein over 50–80 % of the female germ cells die and are either cleared from the germ line, by the nonprofessional phagocytic cells of the somatic gonad (Gumienny et al. 1999)], and plasma membrane synthesis. All of these chromosomal and cell biological behaviors are exquisitely coordinated in a normal growing germ line and occur in stereotypic spatial regions, within the context of the pachytene, suggesting that there must either be autonomous cues that the germ cells are executing as they progress through the long meiotic prophase I or that these nuclei are responding to spatially restricted molecular or environmental cues during the different stages of pachytene. At this time, not much is known regarding whether cues autonomous to the germ cells dictate normal meiotic progression in different regions of the germ line, but a clear understanding is beginning to emerge of the spatial cues at each of the stages of the germ cells that coordinate and drive these events.

Only a handful of signaling pathways have been identified in *C. elegans* that regulate progression through meiotic prophase, with the extracellular RAS/ERK MAPK pathway being one such key pathway. Activation of MPK-1 (*C. elegans* ERK) occurs in two distinct regions of the germ line: zone 1, or mid-pachytene, and zone 2 of growing mature oocytes (Lopez et al. 2013; Miller et al. 2001). In between these two zones active MPK-1 is downregulated at a stage where the germ cells are transiting from pachytene to diplotene (Lee et al. 2007; Lopez et al. 2013). Total MPK-1 is continuously expressed throughout the germ line. The two distinct zones of active MPK-1 signaling are triggered by (a) insulin receptor DAF-2 based activation in zone 1 (Lopez et al. 2013) in response to nutritional cues and (b) sperm-derived MSP signaling through the VAB-1 Ephrin (Eph) receptor in oocytes (Miller et al. 2001). In zone 1 or the pachytene region, MPK-1 is active for a sustained amount of time, with current estimates averaging at ~18 h/germ cell; in the proximal individual oocytes, MPK-1 is active for about 20 min each (Lee et al. 2007; Mattingly et al. 2015). During these stages of meiotic prophase, the germ line is transcriptionally silent and the meiotic events are controlled via translational or posttranslational events.

4.2.2 *The LET-60 RAS/MPK-1 ERK Signaling Pathway as a Major Regulator of Meiotic Progression During Oogenesis*

Abrogation of either DAF-2 (the Insulin receptor), LET-60 (ras), MEK-2 (mek), LIN-45 (raf), or MPK-1(erk) all result in female germ cells arrested in pachytene resulting in sterile adults that do not generate any gametes (Church et al. 1995; Lee et al. 2007; Lopez et al. 2013; Ohmachi et al. 2002). This leads to the model that the RAS/ERK pathway governs exit of oogenic germ cells from pachytene to the diplotene stage of meiotic prophase (Church et al. 1995). However, this observation is inconsistent with normal MPK-1 signaling in the germ line; MPK-1 is active from mid- to late pachytene and drops below detectable levels at the end of pachytene (Fig. 4.1a). This spatial activation pattern would suggest that active MPK-1 has to be downregulated to exit pachytene, rather than linger in pachytene, as the case seemed to be when *mpk-1* was genetically abrogated. Given that pachytene is the longest phase of meiotic prophase, a key question that arises is, does the rise of active MPK-1 in the mid-pachytene regulate any meiotic event, or is that rise important to exit pachytene, which given that the cells did not exit until the end of pachytene, and in fact remained in pachytene upon the rise of active MPK-1 was a flawed logic. Thus, the question that was posed was, is the rise in active MPK-1 correlative with progression of pachytene from early to mid-stage? And would the loss of *mpk-1* signaling cause an inability of these cells to exit, resulting in their arrest. To answer this question, Lee et al. (2007) used the RNA-binding proteins DAZ-1 and GLD-1 as molecular markers to distinguish between early, mid-, and late pachytene and assayed the stage of the arrested pachytene stage germ cells in the mpk-1 null mutant. DAZ-1 is high in the mitotic and transition zone and falls mid-way through pachytene in wild-type germ lines (Maruyama et al. 2005), with a reciprocal staining pattern with active MPK-1. Interestingly, in *mpk-1* null germ lines, DAZ-1 levels remain elevated throughout the arrested pachytene germ cells, indicating that these cells retain distal/mid-pachytene character (Lee et al. 2007). Additionally, GLD-1 (RNA-binding protein) and CEP-1 (the p53 homolog) levels were analyzed; GLD-1 falls at the end of pachytene where CEP-1 starts to rise in normal pachytene stage germ cells. In *mpk-1* null mutants, however, GLD-1 is continuously high in the arrested pachytene stage germ cells, while CEP-1 never accumulates (Lee et al. 2007). All of these data lead to a new model on the role of RAS/ERK pathway in controlling meiotic progression. The model proposes that active MPK-1 controls two distinct aspects of meiotic progression: first, the pathway enables progression from early to mid-pachytene, presumably, this is coupled by chromosomal behaviors some of which are now coming to light [(Nadarajan et al. 2016), also covered in Chap. 4] and second that it regulates pachytene progression, such that reduction of MPK-1 signaling (analyzed through the use of single point mutations in the MPK-1 gene, which reduces binding to MEK at nonpermissive temperatures and causes a reduction in MPK-1 signaling).

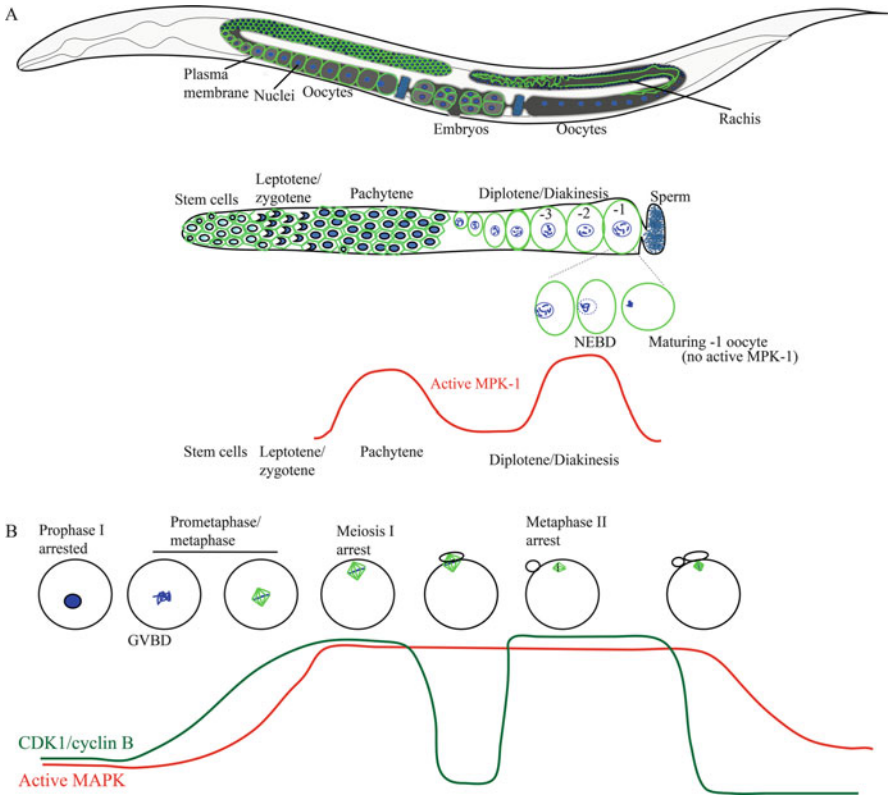

Fig. 4.1 MAP kinase signaling pathway regulates varied aspects of oocyte growth and maturation in worms and mammals. (**a**) (*Top*) An adult *C. elegans* hermaphroditic animal carries two U-shaped gonad arms. In the figure, the arm on the *left* represents the surface view of the gonad with plasma membranes in *green* and nuclei in *blue*. The *right* arm represents an internal view of the gonad, with plasma membranes that open into a common cytoplasm, rachis, and each growing oocyte is connected to the rachis via an opening. (*Middle*) Oogenic germ cells in one gonad arm of *C. elegans*, from stem cell pool on the *left* to growing oocytes on the *right*. In *C. elegans*, oocytes arrest in prophase I. (*Bottom*) MPK-1 ERK MAP kinase is active in two regions of the meiotic prophase in *C. elegans*: pachytene and growing oocytes. MPK-1 signal in pachytene is maintained by insulin like receptor DAF-2 and in growing oocytes by MSP signal from sperm. (Figure Adapted from Lee et al., Genetics, 2007. Express permission to reproduce the figure obtained from Tim Schedl and Genetics.) (**b**) Various stages of mammalian oocyte development and arrest periods. Active MAP kinase (*red*) and Maturation Promotion Factor (CDK1/cyclin B) are regulated dynamically during the various stages of mammalian oocyte development

In addition to triggering an entry of germ cells from early to mid-pachytene, MPK-1 signaling also regulates multiple aspects of cell biology during oogenesis, including control of cellular morphogenesis and membrane organization (Arur et al. 2009, 2011; Lee et al. 2007). Active MPK-1 is required for the gonadal tube arrangement of pachytene cells on the surface and an interior cytoplasmic rachis (a process termed "pachytene cellular organization"), forming a single row of

cylindrically shaped oocytes in the proximal gonad (oocyte organization and differentiation), oocyte growth control, and migration of the oocyte nucleus to the distal surface. Genetic analysis as well as the pattern of activation indicates that these MPK-1 functions are largely or completely germ line autonomous. MPK-1 regulates these events that occur contemporaneously or simultaneously in the germ line via coordinated control of multiple distinct substrates that are phosphorylated and regulated in distinct regions, cell biological compartments, and times during germ line development. Currently, 31 novel MPK-1 substrates have been identified to regulate each of the eight processes (Arur et al. 2009). Analysis of each substrate in detail is shedding light into how MPK-1 regulates any given processes and the redundant mechanisms that drive the robustness in the germ line (Arur et al. 2009). However, it currently remains unknown, as to how MPK-1 mediates a switch from distal to proximal pachytene. The current model is that a number of MPK-1 substrates (currently unidentified) are likely involved in coordinating progression from distal to proximal pachytene.

4.2.3 Oocyte Growth and Development

Oocytes can achieve sizes >1000 times that of diploid somatic cells. Normal oocytes attain large sizes compared to their pachytene progenitors via influx of yolk protein and cytoplasmic constituents (Wolke et al. 2007). Clearly, sizes that oocytes achieve prior to undergoing a meiosis I arrest are stereotypical in all organisms. But mechanisms underlying their control remain unknown in most species. In *C. elegans*, large oocytes are observed under conditions of reduced MPK-1 activity (such as loss of *daf-2* insulin receptor signaling, *mpk-1* signaling, or loss of the phosphatase *ptp-2* null (Church et al. 1995; Gutch et al. 1998; Lopez et al. 2013). Conversely, small oocytes are generated under a condition where MPK-1 signaling is increased; *let-60 ras* gain of function alleles (Lee et al. 2007). Thus, the RAS/ERK signaling cascade appears to act as a rheostat to control oocyte size, with low MPK-1 activity promoting growth, high MPK-1 activity inhibiting growth, and presumably normal size oocytes produced at intermediate activity levels. Activated MPK-1 in diplotene, where it is normally downregulated appears to be involved in oocyte growth control. Multiple MPK-1 phosphorylation substrates have been identified that regulate the event of oocyte growth; however, mechanisms both cellular and mechanistic need to be delineated (Arur et al. 2011; Drake et al. 2014). It is likely that oocyte growth is controlled autonomously through each individual oocyte; however, a more likely possibility is that the flow of cytoplasmic contents from the central rachis of the gonad drives cytoplasmic constituents into each growing oocyte [connected with the rachis via a cytoskeletal bridge, much like a ring canal in *Drosophila melanogaster* oocytes (Robinson et al. 1994)], until the oocyte reaches a critical mass and completely buds off the central rachis. The signaling pathway thus likely regulates the growth of the oocyte through controlling either the cytoplasmic flow or the length of connection of the

cytoplasmic bridge in each oocyte with the rachis. In case of the former, activation of MPK-1 in pachytene is likely critical for enabling the cytoplasmic flow; the latter likely relies on the activation of MPK-1 in the oocytes.

Besides the RAS/ERK signaling pathway, loss of proliferation in the germ line stem cell population (discussed in Chaps. 1–3) via loss of the GLP-1/Notch signaling also results in generation of large oocytes (Nadarajan et al. 2009). Phenomenologically, this could occur due to loss of the progenitor stem cell-based populations that can no longer sustain the development of the germ line, and thus likely result in misregulation of multiple signaling pathways due to loss of tissue architecture. It could, however, also be a direct effect of Notch signaling itself, wherein Notch pathway generates a specific signal in the distal stem cell region, which is later transported to the oogenic germ line, and directly affects oocyte size. Blocking the connection of the oogenic germ line with the progenitor population via injection of a droplet of oil results in the generation of large oocytes lending support to the model that a physical connection between the progenitor population and oogenic germ cells may be involved in regulating normal oocyte growth and development (Nadarajan et al. 2009). Molecules and cellular events that mediate these events, however, remain to be defined.

Interestingly, however, in a female germ line that lacks the sperm signal, and thus is unable to activate MPK-1 in oocytes via the Ephrin receptor, the oocytes are formed normally and arrest prior to oocyte maturation. The growth of these oocytes is equivalent to oocytes from hermaphroditic animals with robust sperm-dependent MPK-1 activation, suggesting that oocyte growth per se maybe regulated via events occurring more distally in the gonad, specifically in pachytene stage of gonadal development. These models remain to be tested.

4.2.4 Events Controlling Oocyte Meiotic Maturation

The oocytes of most sexually reproducing animals arrest in diplotene or diakinesis of meiotic prophase (Greenstein 2005). Species-specific hormonal signals trigger the resumption of meiosis termed meiotic maturation. Meiotic maturation is defined by the transition to metaphase I (M phase) and is accompanied by nuclear envelope breakdown (NEBD), rearrangement of the cortical cytoskeleton, and meiotic spindle assembly. In vertebrates, hormonal signaling activates cyclin-dependent kinase (CDK1) to promote M-phase entry (see below). Somatic cells of the gonad also function to maintain meiotic arrest in many species, see the section on mammalian oocyte arrest. Meiotic maturation of oocytes arrested in prophase I is under the control of signaling and translational events, since these oocytes are transcriptionally quiescent. Current studies are investigating the mechanisms that link signaling to translational control and how those regulate meiotic maturation.

In *C. elegans*, MPK-1 activation is also correlated with oocyte maturation/ovulation (Drake et al. 2014; Lee et al. 2007; Miller et al. 2001), but functionally, MPK-1 activity seems required mainly for initiation of the transition from

prophase I, as timely activation of maturation/ovulation. MPK-1 activity is clearly required for the initiation of meiotic maturation such as nuclear translocation from the center of the cell to the anterior and cortical rearrangement of the oocyte (Harris et al. 2006; Kim et al. 2013; Lee et al. 2007). In accordance with this, in a female, where there is no sperm-dependent activation of MPK-1, oocytes do not initiate the process of meiotic maturation and remain arrest in prophase I (Harris et al. 2006; Kim et al. 2013; Lee et al. 2007). The sperm-dependent MPK-1 activation in zone 2, comprising of the most proximal ~five oocytes appears to be responsible for MPK-1's function in maturation/ovulation (Govindan et al. 2009; Greenstein 2005; Harris et al. 2006; Kim et al. 2013; Lee et al. 2007; Miller et al. 2001). However, because only the −1 oocyte undergoes maturation it suggests that MPK-1 activation alone is not sufficient and additional regulatory mechanisms, such as inhibition of CDK1 from proximal oocytes and/or inhibition from somatic gonadal sheath cells, must block maturation of the −2 through −5 oocytes (Govindan et al. 2006; McCarter et al. 1999).

The major sperm protein (MSP) that serves as a ligand to active MPK-1 signaling initiates the events of oocyte meiotic maturation (Miller et al. 2001). MSP likely acts both on the oocyte and the surrounding sheath cells; injection of purified MSP is sufficient to induce resumption of meiosis. Work from Govindan et al. established the role for Gαs-based activation of adenylate cyclase to elevate cAMP levels (Govindan et al. 2006, 2009). Blocking adenylate cyclase results in loss of cAMP signaling and blocks oocyte maturation, indicating a direct role of the adenylate cyclase and cAMP to regulate meiotic maturation in *C. elegans* oocytes. Mechanistically, activation of Gαs counteracts the inhibitory signals from Gαi/o that block meiotic maturation in the absence of MSP. Although MSP can act both on the oocyte and the sheath cells, the function of MSP directly on the oocytes remains to be determined. MSP regulates the functions described above via a communication between the somatic sheath cells and the oocyte. Interestingly, other regulators of oocyte meiotic maturation have been identified such as CEH-18 (A POU domain transcription factor) that also act in the soma to repress MPK-1 activation in the oocyte and mediate meiotic arrest (Govindan et al. 2009; Yamamoto et al. 2006). However, their exact mechanism of action remains to be defined.

Activated MPK-1 levels drop dramatically as the −1 oocyte undergoes maturation (Drake et al. 2014; Lee et al. 2007). This inactivation of MPK-1 is distinct from that in vertebrates where active ERK is present from maturation until release of the meiosis II arrest by fertilization (see below). Unlike in vertebrates though, in *C. elegans* sperm signal initiates ovulation and fertilization of a mature oocyte, and the events of both the events of meiosis are completed after fertilization. Thus, the evolutionary reasons for these differences are both intriguing and challenging to define.

Besides MSP, cyclin-dependent kinase CDK1 (Boxem et al. 1999) and the polo-like Kinase-1, PLK-1, dependent (Chase et al. 2000), each positively regulates events of oocyte meiotic maturation. The zinc finger domain-containing proteins OMA-1 and OMA-2 are redundantly required for oocyte maturation and ovulation

(Detwiler et al. 2001). In *oma-1* and *oma-2* double mutants, MPK-1 activation is not sustained and NEBD is suppressed. OMA-1 and OMA-2 may function upstream of two conserved cell cycle regulators, the MYT1-related kinase WEE-1.3 and CDK1 (Detwiler et al. 2001; Spike et al. 2014b). Additionally, recently the NHL1 domain protein LIN-41 has been identified to work antagonistically with the OMA-1 and OMA-2 proteins to control the prophase to metaphase transition in *C. elegans* (Spike et al. 2014a). Chapter 6 discusses the role of these proteins in mediating the events of oocyte meiotic maturation in further detail.

4.3 *Drosophila* Female Germ Line Development

Drosophila melanogaster germ cells, much like *C. elegans*, are specified in the embryo as primordial germ cells (PGCs) (Forbes and Lehmann 1999; Lehmann 1992). However, primordial germ cell specification from this point on is very different between these two species. In one cell embryo, right after fertilization of male and female pronuclei, nuclear divisions, in the absence of cytokinesis, give rise to a syncytial embryo. Of these early nuclear divisions, ~10 nuclei migrate to the posterior pole and become the first to be surrounded by a plasma membrane. These cells then undergo symmetric, but asynchronous divisions to give rise to a total of about 40 cells. These 40 cells are termed the pole cells and are the early primordial germ cells. Much like in *C. elegans*, these cells are transcriptionally quiescent (reviewed in Lehmann 1992).

During early embryogenesis, pole cells remain positioned at the posterior end of the embryo; however, as the germ layers form, and midgut starts to invaginate, the pole cells along with the midgut travel inside the embryo. Once inside the embryo, at day 10 of embryogenesis, the pole cells start to migrate through the midgut epithelium. These processes have been extensively reviewed in McLaughlin and Bratu (2015) and Williamson and Lehmann (1996). The migration and colonization of the embryonic gonad occur by the time the embryogenesis is complete. At the end of embryogenesis, another process starts to take place: the somatic gonadal cells begin to encapsulate the pole cells and form the embryonic gonads on either side of the embryo. The germ line stem cells continue to stay connected to the somatic gonadal cells through the rest of germ cell development (Forbes and Lehmann 1999; Williamson and Lehmann 1996).

These two cell types, the somatic gonadal cells and the pole cell precursors, form the major progenitors of the *D. melanogaster* female germ line or the ovary. The ovary comprises of two main stem cell populations, the germ line (GSC) and the follicle stem cells (FSC) (reviewed in Chaps. 1 and 3). These two cells give rise to the nurse cells, oocyte, and follicle cells of the mature egg chamber. Each stem cell population resides in a unique, specialized niche containing several types of somatic gonadal precursor cells (Fig. 4.2a). The somatic gonadal cells also harbor the germ line stem cell "niche" necessary for regulated balance between stem cell self-renewal and differentiation, reviewed in Chaps. 1–3.

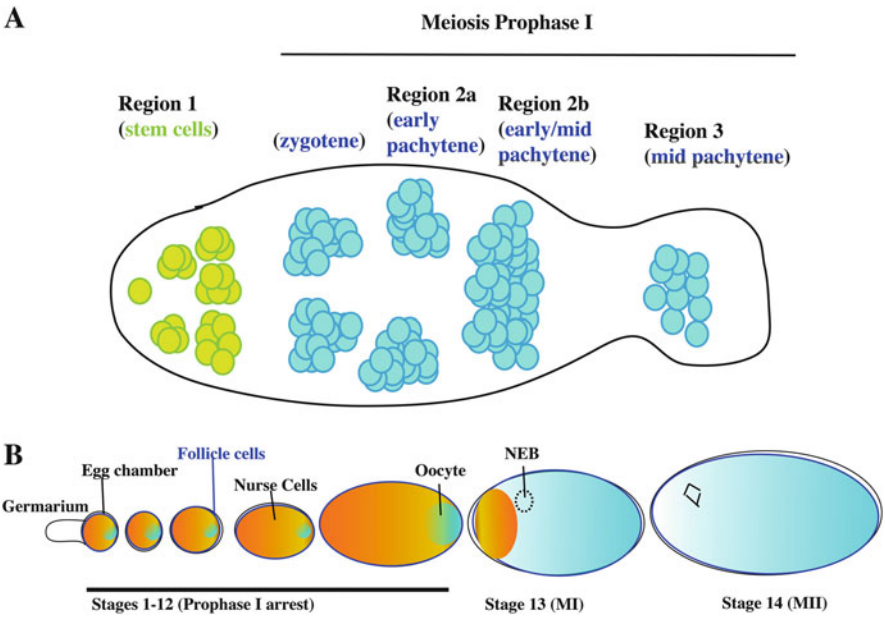

Fig. 4.2 Stages in *Drosophila* oogenesis. (**a**) Mature germarium with the various regions containing cells in differing stage of mitosis (*left*, *green*) or meiotic prophase I. (**b**) Once a germarium matures, it is surrounded by follicle cells (*blue line*, *orange*) that surround the maturing oocyte (*green*). A mature oocyte surrounded by the follicle cells makes an egg chamber. As newer oocytes are born, the older egg chambers progress through different stages of meiosis. At stage 13, the oocyte starts to undergo the process of meiotic maturation, marked by the nuclear envelope breakdown. The oocyte arrests in meiosis II at stage 14, until it passes through the oviduct, during which time the oocyte undergoes maturation in the absence of sperm

4.3.1 Meiotic Prophase I Progression

The basic unit of the ovary in *Drosophila* is the ovariole; there are 16–20 ovarioles per ovary, each being autonomous with its own stem cell populations and egg chambers at varying developmental stages (Fig. 4.2a). The ovariole can be divided into three principal regions (from anterior to posterior): the terminal filament, germarium, and vitellarium (also see Chap. 3). The germarium is the site of germ line stem cell (GSC) division, differentiation, and germ line cyst formation and is divided into four regions (1, 2a, 2b, and 3) (Fig. 4.2a). In germarium region 3, the germ line cyst, containing nurse cells and oocyte, is ensheathed by a somatic cell layer, together forming a structure named the "egg chamber" before being passed into the vitellarium. Here, I discuss the process of meiotic prophase progression and maturation, which primarily occurs in germarium region 2a (Fig. 4.2a).

The oocyte undergoes both developmental maturation and meiosis throughout the course of oogenesis, and these processes are intimately linked. The balance of oocyte differentiation and progression through meiosis is achieved by two major

meiotic arrests during oogenesis. Prophase I of meiosis begins in region 2a of the germarium, where the events of synaptonemal complex can be visualized (reviewed in Lake and Hawley 2012; McLaughlin and Bratu 2015), and arrests in diplotene stage of prophase I at the beginning of stage 5 in the egg chamber. The remaining 15 cells develop into the nurse cells and enter an endocycle to become highly polyploid. Determination of the oocyte fate seems to be dictated by the accumulation of the cyclin-dependent kinase inhibitors p21 CIP/p27 KIP/p57 KIP2 that prevent endoreduplication via repressing the CDK2/cyclin E such that the oocyte maintains its meiotic state (Hong et al. 2003). While much is known about the signaling and molecular events underlying meiotic I arrest and progression in *C. elegans*, relatively little is understood in *D. melanogaster* regarding events that surround meiotic I arrest. Additionally, events such as gap junction-mediated germ line communications between somatic follicle cells and developing oocytes have not been established. While gap junction proteins have been identified in *D. melanogaster* oocytes (Stebbings et al. 2002), loss of gap junction proteins in the oocyte did not result in any developmental arrest phenotypes in the oocytes (Bohrmann and Zimmermann 2008), suggesting that the gap junction proteins do not play a major role in mediating meiotic I arrest in *D. melanogaster* unlike in *C. elegans* and mammals.

Likewise, unlike *C. elegans* where the MAPK pathway is central to meiotic I progression and meiotic maturation, in *D. melanogaster*, while the MAPK pathway is activated in the oocyte by a Mos (MAPK kinase kinase) homolog, loss of either MAPK or Mos does not result in meiotic arrest or any developmental defects in oocytes (Ivanovska et al. 2004), suggesting that MAPK activation plays a nonessential role in *D. melanogaster* development. Thus, currently much remains to be determined about the signaling and molecular events that regulate and sustain the prophase I arrest in flies (Fig. 4.3).

4.3.2 Oocyte Meiotic Maturation

The cyclin-dependent kinase signaling pathway CDK1/cyclin B regulates the process of meiotic maturation in the *D. melanogaster* oocyte at stage 13 of oogenesis (Von Stetina et al. 2008; Xiang et al. 2007). Loss of the active CDK1/cyclin B in *D. melanogaster* results in a delay in the process of meiotic maturation, including the process of NEBD (Von Stetina and Orr-Weaver 2011; Von Stetina et al. 2008). The Polo-like kinase, Polo, regulates the activity of CDK1/cyclin B. Polo binds to Matrimony (MTRM, a sterile alpha motif-containing protein that is expressed from the end of pachytene until the completion of meiosis I) in prophase. Phosphorylation of Matrimony, by a currently unknown kinase, results in generation of Polo binding site. Binding of Matrimony to Polo results in inactivation of Polo activity towards cell division cycle 25 (CDC25 or Twine). Activation of Polo results in activation of CDC25 phosphatase and thus activation of CDK1/cyclin B. Besides Matrimony, the Great Wall Kinase (Gwl) (Yu et al. 2004) also antagonizes Polo

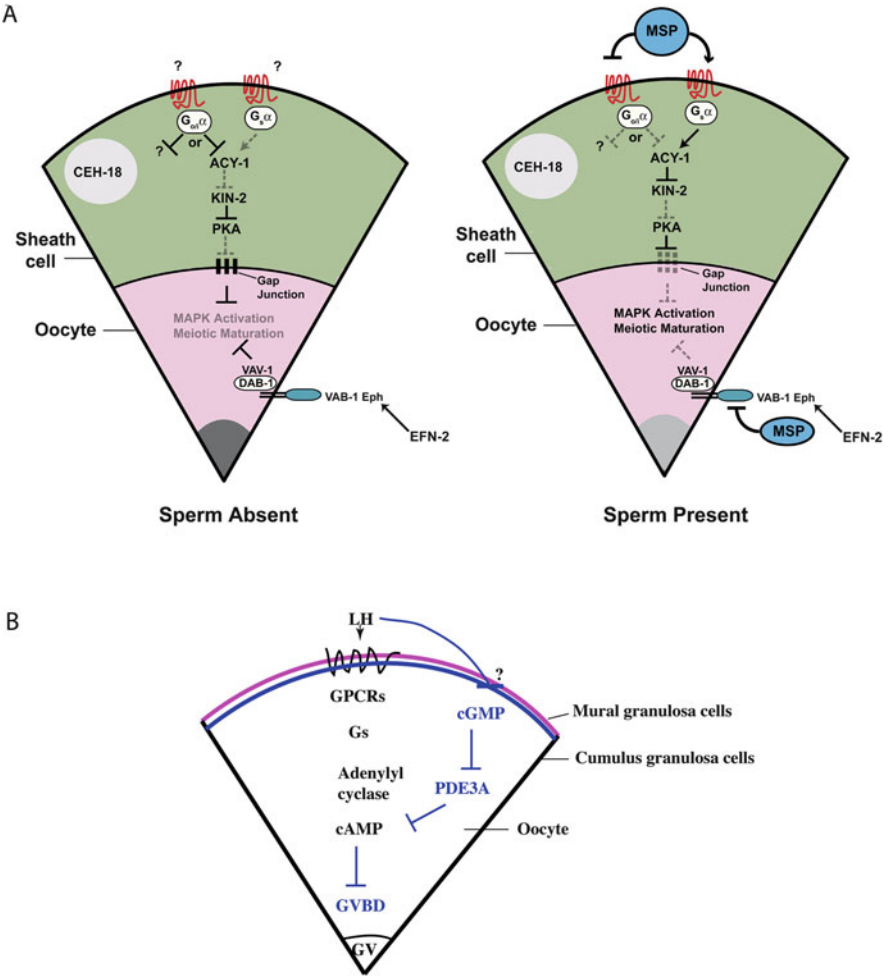

Fig. 4.3 Cell–cell communication and cyclic AMP coordinates oocyte meiotic maturation in worms and mammals. (**a**) In *C. elegans*, in the absence of the sperm signal, the Gαo/i pathway in somatic sheath cells surrounding the oocyte (*pink*) leads to the inactivation of adenylate cyclase 4 (ACY-4) and protein kinase A (PKA). This inhibition blocks MAP kinase (MAPK) activation and oocyte meiotic maturation. Additionally, the VAB-1/Ephrin Receptor in the oocyte also inhibits MAPK and oocyte maturation. Presence of the major sperm protein (MSP) antagonizes both the somatic Gαo/i and oocyte VAB-1 signaling pathways and activates Gαs pathway in the somatic sheath cells resulting in MAPK activation and meiotic maturation. (Adapted from Govindan et al. 2006 reprinted with express permission from David Greenstein and Current Biology.) (**b**) Cyclic AMP in the oocyte inhibits meiotic maturation in mammals. cGMP produced by the cumulus somatic cells enters the oocyte via the gap junctions (via currently unknown mechanisms) to inhibit PDE3A. PDE3A hydrolyses cAMP. Binding of luteinizing hormone (LH) to its G protein-coupled receptor (GPCR) (*blue*) activates the cAMp pathway and enables meiotic maturation via promoting GVBD

(Archambault et al. 2007) and maintains meiotic arrest. Activation of CDC25 allows cyclin-dependent kinase 1 (CDK1) to activate and promote germinal vesicular breakdown (GVBD) in prometaphase.

Besides, Polo and matrimony, α-endosulfine homolog is also thought to control CDK1/cyclin B activity and almost all aspects of meiotic maturation (Von Stetina et al. 2008). The endos encodes a conserved phosphoprotein; endos mutant oocytes display a severe delay in NEB, spindle formation, and chromosome congression defects very similar to twine mutants. The Endos protein appears to regulate CDK1/cyclin B activity, likely via novel substrates of CDK1/cyclin B (Von Stetina et al. 2008). On meiotic maturation at stage 13, Polo proteins overcome the inhibition of Matrimony, by sheer increase in their number, thus effectively inactivating CDC25 and activating CDK1/cyclin B and mediating meiotic resumption.

Interestingly, while there must be extrinsic signals that regulate oocyte maturation, not much is known about them. Some examples have, however, been defined. For example, the prostaglandin hormones or the steroid hormone ecdysone seem like likely stimulatory signals, since cyclooxygenase (COX), which results in prostaglandin synthesis, promotes early ovarian follicle maturation (Tootle and Spradling 2008). Similarly, ecdysone signaling is also required for progression of oogenesis and egg chamber maturation during mid-oogenesis (Buszczak et al. 1999). Because the follicles in mutants affecting either signaling pathways do not reach stage 13 (when meiotic maturation takes place), it is not known whether prostaglandins or ecdysone are required for meiotic maturation in flies.

4.4 Mammalian Female Germ Line Development

Mammalian females are born with differentiated oogenic germ cells arrested in meiosis I. Mammalian oocytes arrest in prophase during fetal development, an arrest that lasts for months in mice and years in women. In response to the leutenizing hormone signal from the pituitary at puberty, the oocyte transitions from prophase to metaphase II, where it remains arrested until fertilization causes the completion of meiosis. The prophase-to-metaphase transition is characterized by the breakdown of the nuclear envelope (NEBD, also known as germinal vesicle breakdown or GVBD) (Schuh and Ellenberg 2007). Because the oocytes are born under a condition of meiosis I arrest, not much is understood about earlier events leading up to the arrest in mammalian systems. This chapter will focus on signaling events that regulate meiosis I transition to metaphase and oocyte maturation. Events resulting in meiosis II resumption and fertilization are covered in Chaps. 7 and 8.

4.4.1 Hormonal Control of Prophase I Arrest in Mammalian Oocytes

4.4.1.1 cAMP and Luteinizing Hormone

Somatic cells surround mammalian oocytes, and these somatic cells are essential for maintaining prophase arrest in the oocyte. The somatic cells are made up of two layers, the outer layers or the mural granulosa and the inner cumulus layer. Oocytes or cumulus–oocyte complexes that are removed from the follicle resume meiosis spontaneously (Pincus and Enzmann 1935; Edwards 1965), suggesting that a meiosis inhibitory factor coming from the somatic cells helps maintain the arrest. Additionally, a physical continuity between the cellular layers connecting the somatic cells and the oocyte is essential for maintenance of prophase arrest. Gap junctions mediate the physical connection between the somatic cells and the oocyte; inhibition of gap junction proteins also results in resumption of meiosis, suggesting that gap junction-based communication is critical for oocyte meiotic arrest (Edry et al. 2006; Norris et al. 2008; Sela-Abramovich et al. 2006). The nature of the inhibitory signal that passes between the somatic cells and the oocyte currently remains undetermined.

Maintenance of prophase arrest in the fully grown mammalian oocyte requires high level of cyclic AMP (cAMP) in the oocyte. Inhibition of cAMP levels in the oocyte results in spontaneous resumption of oocyte progression to metaphase (Cho et al. 1974; Magnusson and Hillensjo 1977). cAMP is generated in the oocyte by the constitutively active Gs-linked receptor, GPR3 or GPR12, which act to stimulate adenylyl cyclase (Mehlmann et al. 2002 reviewed in Runft et al. 2002; Kalinowski et al. 2004; Mehlmann et al. 2004; Norris et al. 2007). Perturbing either the receptor, Gs, or adenylyl cyclase causes cAMP levels to decrease resulting in resumption of meiosis. Measurements of the cAMP concentration in isolated intact follicle-enclosed mouse oocytes reveal basal cAMP concentration of about ~700 nM (Norris et al. 2009). This cAMP concentration is sufficient to activate the cAMP-dependent kinase (PKA), PKAI and PKAII (Viste et al. 2005), both of which accumulate in the oocyte (Newhall et al. 2006). Cyclic AMP regulates meiotic prophase arrest by PKA-mediated phosphorylation of the phosphatase CDC25 (CDC25B in mouse) causing CDC25 inactive towards dephosphorylating CDK1; CDK1 remains phosphorylated and inactive (Lincoln et al. 2002; Oh et al. 2010; Zhang et al. 2008). Removal of the oocyte from its follicle (Vivarelli et al. 1983), or inhibition of the gap junction permeability within the follicle (Sela-Abramovich et al. 2006), causes cAMP to decrease in the oocyte, resulting in lack of PKA phosphorylation, which in turn activates CDC25, and CDC25 dephosphorylates CDK1 activating CDK1/cyclin B complex. Because inhibition of gap junctions results in initiation of meiosis, it is interesting to speculate that maybe the meiosis inhibitory signal that passes from the somatic cells to the oocyte through gap junctions is cAMP, which diffuses between the somatic cells and the oocytes and maintains itself at a high level in the oocyte. Interestingly, however, cAMP

from the somatic cells (despite being high) is insufficient to maintain cAMP in the oocyte at an inhibitory (high) level (Mehlmann et al. 2002) suggesting that the simple diffusion-based model is inaccurate. One likely possibility is that the somatic cells maintain oocyte cAMP at ~700 nM level via a signal that inhibits the oocyte cAMP phosphodiesterase PDE3A. In accordance with this hypothesis, chemical or genetic inhibition of PDE3A in the oocyte (Masciarelli et al. 2004) helps maintain the oocyte arrest in prophase even when removed from the follicle. Further studies remain to be conducted, however, to understand the mechanisms underlying the control of PDE3A, the role of cAMP, and the mechanisms governing the control of cAMP in mediating prophase I arrest in oocytes.

Interestingly, high levels of cAMP are also necessary in the fetal ovary to enable the disassembly of synaptonemal complex during the development of mouse oocytes and for completion of prophase I until the arrest (Wang et al. 2015). These results suggest that cAMP needs to be high during early stages of oocyte development to enable normal oocyte growth and differentiation until arrest in prophase I. At which point it remains arrested for several weeks or years (if human), until a signal from LH results in downregulation of cAMP for resumption of meiosis.

4.4.1.2 Interplay Between cAMP and cGMP Regulates Prophase I Arrest

Besides cAMP, cyclic GMP is an additional key player in maintaining prophase I arrest in mammalian oocytes. cGMP is also thought to inhibit meiotic progression since the levels of cGMP in the oocyte decrease with time after removal from the follicle, and cGMP injection into an isolated oocyte delays spontaneous meiotic resumption (Tornell et al. 1990). Also, levels of cyclic GMP, much like cyclic AMP are also regulated by luteinizing hormone (Hubbard 1986). These observations together suggest that the prophase arrest is maintained by the coordinated function of cyclic nucleotide regulatory systems in both the somatic cells and oocyte, compartments that are connected by gap junctions. However, many unanswered questions remain. For example, it remains unknown as to exactly which guanylyl cyclases in the mural granulosa cells, and possibly in the oocyte, regulate cGMP, and in turn how they themselves are regulated. It also remains unknown whether like cAMP, cGMP has an additional role in oocyte growth and differentiation during meiosis prior to meiotic arrest.

4.4.2 The Role of Luteinizing Hormone in Mediating Progression of Meiosis I

Luteinizing hormone (LH) is released from the pituitary and is the primary stimulus for meiotic resumption in vertebrate oocytes. In mice, NEBD occurs ~2–4 h after exposure of isolated follicle containing oocytes to LH (Park et al. 2004). LH receptors are expressed both on the oocyte and the somatic cells suggesting that they likely act on one or the other cell type or both to mediate meiotic resumption (Amsterdam et al. 1975). The LH receptor is a G protein-coupled receptor that activates Gs, Gi, and Gq/11 (Herrlich et al. 1996; Rajagopalan-Gupta et al. 1998). Gs activation causes the production of cAMP in the granulosa cells, stimulating their PKA activity (Tsafriri et al. 1972). However, the effect of Gi or Gq stimulation on the function of the receptor remains undetermined.

How is LH conveyed from the somatic cells to the oocytes? In frogs and fish, unlike mice, LH stimulation of meiotic resumption is mediated by the synthesis of progesterone (Fortune 1983; Masui 1967; Nagahama and Yamashita 2008). However, while LH causes mammalian follicles to produce progesterone, which is essential for ovulation and subsequent implantation of the embryo, progesterone does not have a significant function in stimulating the prophase-to-metaphase transition in mammalian oocytes (reviewed by Tsafriri and Motola 2007). Thus, another process must account for how the LH signal is conveyed from the somatic cells to the oocyte.

4.4.3 LH-induced MAPK Activation and Meiotic Resumption

LH stimulates a key signaling pathway leading to meiotic resumption: MAP kinase (specifically the ERK MAPK) signaling pathway (Norris et al. 2008; Panigone et al. 2008). EGF receptor is expressed throughout the somatic cells (but not the oocyte), and current evidence suggests that synthesis and release of EGF receptor ligands from the somatic cells result in engagement of the EGF receptor and signaling to the oocyte. Within 30 min of exposure of the follicle to LH, EGF receptors are activated in the somatic cells in a manner dependent on phosphorylation and activation of PKA (Panigone et al. 2008). Application of EGF receptor ligands to follicles causes meiotic resumption (Dekel and Sherizly 1985; Nedachi and Conti 2004; Park et al. 2004), and loss of EGF receptor/Mos/MEK/ERK or any member of the EGFR/MAPK family results in loss of meiotic resumption, suggesting that LH signaling pathway leads to meiotic resumption via the EGFR pathway. Most importantly, studies of mutant mice with reduced EGFR activity and mice with genetic deletions of EGF ligands have shown that reducing EGFR activation largely, but not completely, inhibits meiotic resumption in response to LH (Hsieh et al. 2007).

EGF ligands that appear to be important for LH signaling are epiregulin and amphiregulin (Panigone et al. 2008). Granulosa cells from women as well as nonhuman primates also synthesize EGF ligands in response to LH (reviewed by Hsieh et al. 2009). EGF receptor activation results in the activation of MAP kinase in the cumulus cells, and this activation is necessary for activation in the oocyte. Interestingly, MAP kinase is also thought to be activated by an EGF receptor-independent pathway in the cumulus cells in a Src kinase-mediated manner in rat (Wayne et al. 2007). In this context MAP kinase activation may be a key link between LH stimulation and gap junction closure necessary for reinitiating meiosis. However, while very exciting, all of these models await rigorous experimental evidence.

4.5 Common Themes and Differences Across Evolution that Govern the Events of Meiotic Progression and Maturation

Despite the reproductive differences in the species reviewed in this chapter, varied signaling and molecular pathways function to regulate evolutionarily conserved events. The most striking of these is the communication between the somatic cells and the oocytes regulated via gap junctions in *C. elegans* and mammals. In both cases, high cyclic AMP levels along with adenylate cyclase activity in the somatic cells result in resumption of oocyte maturation. Although, in mammals, the high cAMP levels in the oocyte also assist in maintaining prophase I arrest. The signals that result in high cAMP levels in the somatic cells are the major sperm protein in *C. elegans* and luteinizing hormone in mammals, where they both engage the G protein-coupled receptors in the somatic cells. Major sperm protein, while produced by sperm, unlike LH produced by an endocrine system, can be thought of as a short range hormonal signal, since in essence the protein is secreted by the sperm very much like peptide hormones and elicits a robust signaling response even in the absence of physical sperm. Interestingly, in both *C. elegans* and mammals, meiotic maturation is associated with inactivation of the gap junctions between the oocyte and the somatic cells. It is therefore interesting to test whether in *D. melanogaster* gap junctions in the follicle cells play a role in regulating meiotic maturation. The source of a hormonal signal, however, maybe the key to understanding this regulation. In worms, MSP from the sperm seems to function as the hormonal signal to regulate the gap junctions and the cAMP levels; in flies it maybe a distinct mechanism that triggers this signaling event. Previously, these experiments have not been feasible; however, with the advent of genome editing technologies and continuous development of powerful imaging and genetic tools, in the future it will be interesting to test the function of gap junction proteins on the soma–oocyte communication in flies.

In vertebrates, ERK activation functions to promote oocyte meiotic maturation; events prior to this in prophase progression cannot be determined (Fan and Sun

2004; Liang et al. 2007). In *C. elegans*, ERK activation is necessary for meiotic prophase progression and is essential for onset of early events of meiotic maturation, such as NEBD and nuclear translocation. However, in *C. elegans*, active ERK levels are dramatically downregulated in the maturing oocyte before the completion of meiotic maturation. In fact, an inability to downregulate active ERK once meiotic maturation has begun results in early onset of mitosis and endocycles, rather a transition to metaphase I. This inactivation of ERK is distinct from that in mammals where active ERK is present from meiotic maturation until the release of the oocyte from meiosis II by fertilization. This difference is likely a reflection of the reproductive needs and architecture of the reproductive organs. In mammals, meiosis II arrest and meiosis I are spatially and temporally separated. Thus, a high active ERK signal in meiotic I maturation does not necessarily have an impact on meiosis II onset. However, in *C. elegans*, completion of meiosis I occurs only in the presence of the MSP signal from the sperm. The presence of the sperm ensures that meiosis I maturation is coupled with ovulation into the spermatheca, followed quickly by fertilization. This suggests that an inability to downregulate active ERK in the oocyte may result in an arrest in meiosis II, while in the spermatheca it results in aberrant fertilization and developmental defects. Currently, the phosphatase that mediates the downregulation of active ERK in the maturing oocyte in worms is unknown; identification of this phosphatase will enable us to directly test this model. It is also interesting to speculate that there maybe evolutionary intermediates where meiosis I arrest and transition while spatially and temporally separated from meiosis II may still occur in a relatively short time scale to enable cell biological and genetic dissection of the events. Interestingly, *D. melanogaster* would have served as such an intermediate; however, unlike worms and mammals, loss of Mos (the MAPK Kinase Kinase) or loss of ERK does not impact meiotic maturation or ovulation, although active ERK is robustly detected in the oocytes. This suggests that at least in flies ERK signaling and activity play a nonessential function during oocyte development.

While exciting, the regulatory events uncovered thus far suggest that we are barely scratching the surface in our understanding of the regulatory and signaling mechanisms that coordinate the various events underlying meiosis I progression, prophase arrest, and transition from prophase to metaphase. The parallels and differences between these model systems form a powerful foundation for uncovering common and novel principals underlying reproductive fitness in females.

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