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Control of oocyte meiotic maturation in *C. elegans*

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Abstract

In virtually all sexually reproducing animals, oocytes arrest in meiotic prophase and resume meiosis in a conserved biological process called meiotic maturation. Meiotic arrest enables oocytes, which are amongst the largest cells in an organism, to grow and accumulate the necessary cellular constituents required to support embryonic development. Oocyte arrest can be maintained for a prolonged period, up to 50 years in humans, and defects in the meiotic maturation process interfere with the faithful segregation of meiotic chromosomes, representing the leading cause of human birth defects and female infertility. Hormonal signaling and interactions with somatic cells of the gonad control the timing of oocyte meiotic maturation. Signaling activates the CDK1/cyclin B kinase, which plays a central role in regulating the nuclear and cytoplasmic events of meiotic maturation. Nuclear maturation encompasses nuclear envelope breakdown, meiotic spindle assembly, and chromosome segregation whereas cytoplasmic maturation involves major changes in oocyte protein translation and cytoplasmic organelles and is less well understood. Classically, meiotic maturation has been studied in organisms with large oocytes to facilitate biochemical analysis. Recently, the nematode *Caenorhabditis elegans* is emerging as a genetic paradigm for studying the regulation of oocyte meiotic maturation. Studies in this system have revealed conceptual, anatomical, and molecular links to oocytes in all animals including humans. This review focuses on the signaling mechanisms required to control oocyte growth and meiotic maturation in *C. elegans* and discusses how the downstream regulation of protein translation coordinates the completion of meiosis and the oocyte-to-embryo transition.

Keywords

oocyte meiotic maturation; meiosis; oogenesis; signaling; gap junction; soma-germline interactions; translational regulation

1 Overview

The oocytes of most sexually reproducing animals arrest in meiotic prophase I. This conserved mechanism may enable oocytes to stockpile cytoplasmic organelles, cellular constituents, and maternal determinants for the completion of embryogenesis. The final

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stage of oocyte development, meiotic maturation, entails the transition from prophase I to metaphase I in preparation for fertilization (Figure 1). Given the importance of oogenesis for sexual reproduction, how meiotic maturation is regulated in time and space has been of longstanding interest in the field of developmental biology (Wilson 1925). Oocyte meiotic maturation occurs in response to hormones and cues from somatic cells of the gonad. For example, it has long been known that removing mammalian oocytes from large antral follicles causes them to undergo meiotic maturation (Pincus and Enzmann 1935; Edwards 1965). Therefore, the somatic gonad plays an important role in maintaining oocytes in an arrested state. Hormones and cues from the somatic gonad interact to control a series of nuclear and cytoplasmic meiotic maturation events. Nuclear maturation involves nuclear envelope breakdown (NEBD; key abbreviations used are listed in Table 1), meiotic spindle assembly, and chromosome segregation. Cytoplasmic maturation encompasses the accumulation and reorganization of cytoplasmic organelles and ribonucleoprotein (RNP) complexes, cytoskeletal rearrangements, and changes in protein translation. Together, these processes ensure that the embryo inherits a proper maternal genome and the cytoplasmic milieu necessary to support embryonic development. The striking nuclear and cytoplasmic changes that occur during meiotic maturation are widely shared among divergent animals. Early studies of meiotic maturation focused on species with large oocytes, which enabled the biochemical characterization of the conserved master regulator of meiotic maturation, the maturation-promoting factor (MPF). These studies have been the subject of comprehensive reviews (Masui 2001; Kim et al. 2013; Li and Albertini 2013). MPF triggers M-phase entry, and consists of a regulatory cyclin B subunit and a protein kinase catalytic CDK-1/cdk1 subunit (Figure 2). The Wee1 or Myt1 kinases catalyze inhibitory CDK-1 phosphorylations in immature oocytes. Upon hormonal activation, Cdc25 phosphatase removes these inhibitory phosphorylations. When MPF is active, it phosphorylates substrates that function in the cellular events of oocyte meiotic maturation. An outstanding question in the field concerns how hormones and cues from the somatic gonad regulate MPF activation. In this review, we focus on studies undertaken in the nematode *Caenorhabditis elegans* to address this question. While *C. elegans* is a relative newcomer to the meiotic maturation field, the ability to combine genetic, molecular, and cell biological analyses has led to mechanistic insights into the control of meiotic maturation. To date, *C. elegans* is the only genetic model system for which the events of oocyte development, meiotic maturation, and ovulation are observable in living animals (Rose et al. 1997; McCarter et al. 1999) (Figure 3). Moreover, *C. elegans* is one of a few systems with a defined meiotic maturation signal and response pathway (Miller et al. 2001). Recent advances in gene editing combined with powerful genetic and biochemical techniques have enabled scientists to describe the essential roles of soma-oocyte communication as well as translational regulation in meiotic maturation.

Diploid *C. elegans* animals with two X chromosomes are hermaphrodites, whereas those with only one X chromosome are males. The hermaphrodite animals produce sperm during the fourth larval stage, and they switch to producing oocytes during adulthood. In the absence of sperm, oocytes arrest in diakinesis I, as occurs in “female” animals (mutant for genes affecting germline sex determination), or in hermaphrodites that have used all their sperm. *C. elegans* sperm secrete the major sperm protein (MSP), which acts as a hormone to promote oocyte meiotic maturation. Thus, when oocytes become proximal to the

spermatheca, they progress to meiotic maturation (Figure 2A). Then, they are ovulated one by one into the spermatheca, where fertilization takes place.

The development and ultrastructure of the germline and the somatic cells of the gonad, which are important for the control of oogenesis and meiotic maturation, have been described (Hirsh et al. 1976; Kimble and Hirsh 1979; Hall et al. 1999; McCarter et al. 1999; Hall and Altun 2008). As an oocyte moves to the most proximal oocyte position adjacent to the spermatheca (called the -1 oocyte), its nucleus migrates distally (Figure 3). Then, the nuclear envelope breaks down as the prophase oocyte enters meiotic M phase (McCarter et al. 1999). As the nuclear envelope breaks down, microtubules gain access to the highly-condensed bivalents, and the acentriolar meiotic spindle begins to assemble (Müller-Reichert et al. 2010; McNally 2013). During meiotic maturation, the oocyte undergoes a cortical rearrangement, and its shape changes from cylindrical to ovoid (McCarter et al. 1999). These changes within the oocyte coincide with a sequence of contractions of the proximal gonadal sheath cells and the distal spermatheca resulting in ovulation. Ovulation occurs approximately five minutes after nuclear envelope breakdown. Fertilization occurs rapidly upon oocyte entry into the spermatheca (Ward and Carrel 1979; Samuel et al. 2001; Takayama and Onami 2016). The newly fertilized embryo enters the uterus approximately five minutes after ovulation, where the meiotic divisions are completed approximately 30 minutes after NEBD (McCarter et al. 1999). A challenge in the field has been to mechanistically link the signaling between sperm, oocytes, and the somatic gonad to the cellular responses. As discussed below, the involvement of conserved protein kinase signaling pathways and the regulation of protein translation within oocytes play important roles.

2 MSP: the sperm contribution to oocyte meiotic maturation

Oocyte meiotic maturation is under hormonal control. In *C. elegans*, MSP functions as a hormone to trigger oocyte meiotic maturation and gonadal sheath cell contraction independently of fertilization (Figure 4) (Miller et al. 2001). In addition, MSP has been found to be the chief cytoskeletal element underlying the actin-independent amoeboid motility of nematode spermatozoa (Nelson et al. 1982; Italiano et al. 1996).

The MSP signal controls and coordinates oocyte growth and meiotic maturation, thereby ensuring efficient reproduction when sperm are available for fertilization. Sperm release a small fraction of their MSP by a vesicle budding process (Kosinski et al. 2005). Following ovulation in a hermaphrodite or after mating, MSP exhibits a graded distribution in the gonad, with the highest concentration in the region most proximal to the spermatheca, where sperm are stored (Figure 1A; Kosinski et al. 2005). In addition to oocyte meiotic maturation, MSP promotes the actomyosin-dependent cytoplasmic flows that drive the oocyte growth process (Wolke et al. 2007; Nadarajan et al. 2009). MSP signaling appears to control oocyte growth and meiotic maturation in large part through the regulation of protein translation in oocytes (see below).

One of the molecular outcomes of MSP signaling is the activation of the mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is a conserved element of the

signaling mechanism that triggers oocyte meiotic maturation in invertebrates and vertebrates (Ferrell 1999; Liang et al. 2007). In *C. elegans*, the MPK-1/MAPK pathway is required for multiple processes during germline development, including oocyte meiotic maturation, morphogenesis and cellular organization of the gonad, oocyte growth control, and oocyte organization and differentiation (Lee et al. 2007; Arur et al. 2009). It is likely that MPK-1 regulates these diverse processes in the germline by phosphorylating multiple specific targets (Lee et al. 2007; Arur et al. 2009).

MPK-1 is expressed throughout the gonad, but is only active in two distinct regions: (1) mid- to late-pachytene stages and (2) late-stage diakinesis oocytes in the proximal gonad (from -5 to -1). MPK-1 activation in the pachytene region is necessary for the oocytes to progress through pachytene (Church et al. 1995; Lee et al. 2007). MPK-1/MAPK activation in proximal oocytes seems to be important for oocyte growth, cellular organization, and meiotic maturation. MPK-1 activation in this proximal region depends on MSP signaling (Miller et al. 2001). In fact, the presence of MSP is sufficient to generate diphosphorylated MPK-1 (dpMPK-1) in these oocytes; unmated females exhibit dpMPK-1 shortly after the injection of MSP into their uteri (Miller et al. 2001). Interestingly, as the -1 oocyte undergoes maturation, there is a rapid decrease in dpMPK-1 levels (Lee et al. 2007). While the exact functions of MAPK in meiotic maturation are not fully defined at a mechanistic level, the identification of MAPK substrates has already provided multiple handles on this problem (Arur et al. 2009, 2011; Drake et al. 2014).

Meiotic spindle assembly occurs as part of the response to MSP signaling. The meiotic spindles of most animal oocytes have distinct assembly mechanisms from those of mitotic spindles. Female meiotic spindles are both acentriolar and anastral in many animal species (Albertson and Thomson 1993). During mitotic spindle formation, long radial microtubules nucleate at the periphery of centrosomes. In contrast, centrioles, which serve as the organizing center for centrosomes, are eliminated during oogenesis in many species including *C. elegans* (Schatten 1994; Mikeladze-Dvali et al. 2012). The elimination of centrioles at the diplotene stage during *C. elegans* oogenesis raises the interesting question of how microtubules are organized in oocytes. Interestingly, microtubules are extensively nucleated at the plasma membrane in the hermaphrodite gonad (Zhou et al. 2009). The Klarsicht/Anc-1/Syne-1-homology domain-containing protein ZYG-12 is required for microtubule organization in the gonad and the proper cellularization of oocytes. ZYG-12 plays an important role at the outer nuclear envelope by recruiting dynein (Zhou et al. 2009). The acentriolar meiotic spindles, which form during meiotic maturation, rely on chromatin to nucleate short microtubules that ultimately coalesce into a bipolar structure (Severson et al. 2016). Thus, assembly of the meiotic spindle occurs upon the onset of NEBD when cytoplasmic microtubules gain access to chromatin. Interestingly, MSP signaling might play a role in promoting meiotic spindle assembly through its effects on microtubule dynamics that occur prior to NEBD (Harris et al. 2006). When MSP is absent, microtubules are cortically enriched in oocytes. By contrast, MSP triggers microtubule reorganization such that cytoplasmic microtubules become evenly dispersed in a net-like configuration. MSP signaling was shown to remodel cytoplasmic microtubules by affecting the localization and density of growing plus ends, as well as affecting their directionality of movement. In addition to cytoskeletal reorganization, MSP signaling affects the organization of oocyte

RNPs. In unmated females, oocyte RNPs are cortically localized (Schisa et al. 2001; Jud et al. 2007, 2008). MSP was shown to be sufficient to promote the dissolution of these large RNP foci in oocytes (Jud et al. 2008). The large RNPs that accumulate in arrested oocytes might function to translationally repress and preserve messenger RNAs (mRNAs) that are needed for meiotic maturation and early embryonic development. Results described below on the characterization of oocyte RNP components with major roles in regulating meiotic maturation and the oocyte-to-embryo transition are consistent with this possibility.

3 The role of the somatic gonad

The essential roles for soma-germline interactions in regulating oocyte meiotic maturation have been revealed by a combination of laser ablation and genetic analyses, including the analysis of genetic mosaics (McCarter et al. 1997, 1999; Govindan et al. 2006, 2009; Kim et al. 2012; Starich et al. 2014). In *C. elegans*, the gonadal sheath cells function as the main MSP sensors, enabling oocytes to complete meiosis only when sperm are present. In the absence of sperm, and therefore MSP, the sheath cells inhibit meiotic maturation (Hall et al. 1999; Govindan et al. 2006, 2009; Whitten and Miller 2007; Nadarajan et al. 2009). The sheath cells form gap junctions with oocytes (Hall et al. 1999) (Figure 5B and D). The formation of gap junctions between oocytes and their closely apposed somatic counterparts appears to be an ancient conserved feature of oogenesis. For example, mammalian cumulus granulosa cells form gap junctions with oocytes at transzonal projections (Anderson and Albertini 1976) (Figure 5A and C).

3.1 Gap junctions

Somatic cells function to promote the development of the germline and enable its reproductive functions. Gap junctions mediate direct communication between cells and play essential roles in development and physiology (Nielsen et al. 2012). Innexins and connexins, which mediate gap-junctional communication in invertebrates and vertebrates, respectively, are unrelated by sequence but are topologically similar and thought to function analogously (Nielsen et al. 2012; Simonsen et al. 2014). Gap junction channels are comprised of two hemichannels docked in two membranes (Figure 6). It was previously hypothesized that innexins formed hexameric hemichannels as connexins do (Oshima et al. 2013). However, recent protein 2D crystallization and cryo-EM of innexin 6 demonstrate that each one of the *C. elegans* gap-junction hemichannels is composed of eight subunits (Oshima et al. 2016a,b). Hence, innexin octameric hemichannels assemble in opposing cells and associate at sites of close apposition to form channels through which small molecules and ions move (Oshima et al. 2016a).

In *C. elegans* there are two classes of gap junction channels mediating essential soma-germline interactions. In both classes of gap junctions, the hemichannels in the somatic gonad are composed of the nearly identical INX-8 and INX-9 subunits (Figure 6). In contrast, the hemichannels in the germ cells are composed of a combination of INX-14 with INX-21 or INX-22 (Figure 6) (Starich et al. 2014). Gap junctions localize to punctate structures throughout the germline, including distal regions of the gonad (Govindan et al. 2009). Nevertheless, INX-21-containing gap junctions seem to be expressed at higher levels

in the distal region, whereas INX-22-containing gap junctions are enriched in the proximal region of the gonad (Starich et al. 2014). The gap junctions formed by INX-8/INX-9:INX-14/INX-22 function to negatively regulate oocyte meiotic maturation (Govindan et al. 2006, 2009; Whitten and Miller 2007; Starich et al. 2014) (Figure 6). In addition, *inx-14* seems to have a role in promoting germline proliferation (Govindan et al. 2009; Starich et al. 2014) and in the production of a cue that guides sperm from the uterus to the spermatheca (Edmonds et al. 2011).

The other class of gonadal gap junctions, formed by INX-8/INX-9:INX-14/INX-21, is required for germ cell proliferation, meiotic differentiation of germ cells, and for early embryonic development (Figure 6). Genetic epistasis experiments established a major essential role for this class of channels in promoting germline proliferation that is independent of the GLP-1/Notch pathway. INX-8/INX-9:INX-14/INX-21 gap junctions are also required later for the viability of early embryos, as shown by studies using distal tip cell-specific expression experiments to rescue germline proliferation, which resulted in embryonic lethality (Starich et al. 2014). In addition to facilitating intercellular passage of small molecules, connexin and innexin family members have been proposed to function also as hemichannels distinct from intercellular channels and to contribute to cell adhesion. Because the aforementioned somatic gonadal and germline innexins exhibit comparable mutant phenotypes, a hemichannel role is unlikely. Further, genetic analysis suggests that a strictly adhesive role is unlikely. Therefore, a major unanswered question for the field concerns the nature of the small molecules and ions that transit through these junctions to mediate their multiple essential functions.

3.2 G-protein pathways

In the absence of sperm, as occurs in germline of genetic “females” or in sperm depleted hermaphrodites, oocytes arrest in the diakinesis stage of meiotic prophase I. This arrest in diakinesis, as well as all described MSP responses in the germline, are regulated by protein kinase A (PKA) signaling in the somatic gonadal sheath cells (Govindan et al. 2006, 2009; Harris et al. 2006; Cheng et al. 2008; Jud et al. 2008; Nadarajan et al. 2009; Kim et al. 2012) (Figure 4). Importantly, genetic mosaic analysis (see Yochem and Herman 2003) established that conserved components of the stimulatory G-protein pathways such as GSA-1 (the stimulatory G-protein G_{α_s}), ACY-4 (adenylate cyclase), and KIN-1 (the PKA catalytic subunit) are required in the gonadal sheath cells for oocytes to undergo meiotic maturation. By contrast, these proteins are dispensable in the germline. For example, mosaic animals whose somatic gonad was *gsa-1^{-/-}* but whose germline was *gsa-1^{+/+}* failed to undergo meiotic maturation and were sterile. Conversely, mosaic animals whose somatic gonad was *gsa-1^{+/+}* but whose germline was *gsa-1^{-/-}* produced oocytes that underwent meiotic maturation and could be fertilized but ultimately developed into arrested larvae with the phenotypic characteristics of *gsa-1* null mutants (Govindan et al. 2009).

In contrast to stimulatory G-protein signaling, inhibitory G-protein signaling in the gonadal sheath cells is required to prevent PKA signaling and meiotic maturation when sperm are absent (Govindan et al. 2006, 2009). For example, in *goa-1* mutant females (*goa-1* encodes the inhibitory G_{α_i} subunit) oocytes undergo meiotic maturation constitutively despite the

absence of MSP. Likewise, mutations in *kin-2*, which encodes the cAMP-binding regulatory PKA subunit, result in constitutive meiotic maturation in females. The involvement of multiple G-protein pathways in the regulation of meiotic maturation has led to the suggestion that the MSP receptors in the sheath cells are G protein-coupled receptors (GPCRs). The *C. elegans* genome encodes more than 1000 GPCRs (Fredriksson and Schlöth 2005). Thus, potential redundancy may have complicated their identification through forward and reverse genetics. Work thus far has identified the VAB-1 Eph receptor as an oocyte MSP receptor for meiotic maturation. VAB-1 plays a non-essential modulatory role in the regulation of meiotic maturation, in contrast to the stimulatory G-protein pathway, which is required for meiotic maturation. Interestingly the trafficking and function of the VAB-1 Eph receptor as a negative regulator of meiotic maturation in oocytes is regulated by the stimulatory G-protein pathway in sheath cells (Cheng et al. 2008). The stimulatory G-protein pathway regulates VAB-1 Eph receptor trafficking through a mechanism involving the sheath-oocyte gap junctions. Genetic analysis suggests that the inhibitory sheath-to-oocyte INX-8/INX-9:INX-14/INX-22 gap junctions are targets of PKA signaling (Figure 4), but how this might be achieved at a biochemical level is uncertain.

3.3 Soma-to-germline signaling: an ancestral feature of meiotic maturation

The requirement for a somatic stimulatory G-protein (G_s) pathway appears to be an ancient conserved feature of meiotic maturation signaling (Figure 5E and F). Although MSP and luteinizing hormone (LH) are unrelated in their protein sequence, they both promote meiotic maturation in a process utilizing a stimulatory G-protein pathway and soma-to-germline gap-junctional communication. In mammals, mural granulosa cells of the follicles express the LH receptor, which is a GPCR. The cumulus granulosa cells form gap junctions with oocytes at specialized cellular extensions called transzonal projections, which penetrate the zona pellucida. In both *C. elegans* and mammals, interfering with the function of soma-to-germline gap junctions permits meiotic maturation to occur in the absence of hormonal stimulation. Meiotic maturation encompasses a series of cellular and molecular responses, which are conserved from nematodes to mammals. At the cellular level, the responses include NEBD, cortical cytoskeletal rearrangement, assembly of the acentriolar meiotic spindle, and chromosome segregation. At a molecular level, the meiotic maturation responses involve the control of conserved protein kinase pathways and post-transcriptional gene regulation in the oocyte. A major difference between the mammalian and nematode systems is that PKA signaling has an additional function within the oocyte to maintain meiotic arrest only in mammals and other vertebrates. This function is absent in *C. elegans*, in which oocytes lacking PKA (i.e., *kin-1* mutants) undergo meiotic maturation normally, as shown by genetic mosaic analysis (Kim et al. 2012). In meiotically arrested mammalian oocytes, cAMP generated in the oocyte maintains oocyte PKA activity, which is important for keeping MPF in an inactive state (Jaffe and Egbert 2017). cGMP generated in the granulosa cells enters the oocyte through gap junctions where it inhibits the PDE3A phosphodiesterase that degrades cAMP. Upon LH stimulation of the mural granulosa cells, cGMP levels decline throughout the follicle and cGMP diffuses out of the oocyte via gap junctions. This enables PDE3A to degrade cAMP, resulting in decreased PKA activity, which causes MPF to become active and meiotic maturation to occur.

4 Translational regulation in the oocyte

About 100 years ago, it was recognized that the final stages of oogenesis involve nuclear and cytoplasmic events, called nuclear and cytoplasmic maturation, respectively (Wilson 1925). This conclusion was reached by careful examination of oocytes from a variety of organisms. At present, nuclear maturation is defined by the striking events of meiotic chromosome condensation, NEBD, and meiotic spindle assembly. Nuclear maturation is crucial for ensuring the faithful segregation of meiotic chromosomes. MPF promotes many of these nuclear events through the phosphorylation of protein substrates. Cytoplasmic maturation, though less saliently observable and biochemically defined, is no less important. Cytoplasmic maturation includes i) reorganization of cytoplasmic organelles and RNP complexes, ii) cytoskeletal rearrangements, and iii) changes in protein translation (Li and Albertini 2013).

In *C. elegans*, as in many species, full-grown oocytes are transcriptionally quiescent (Starck 1977; Gibert et al. 1984; Schisa et al. 2001; Walker et al. 2007). Nonetheless, large-scale changes in protein translation occur during oocyte meiotic maturation and the oocyte-to-embryo transition (Chen et al. 2011; Kronja, I. et al. 2014). In this section, we review what is known about how protein translation is regulated in the germline to temporally and spatially restrict meiotic maturation to the most proximal (–1) oocyte.

4.1 LIN-41 and OMA RNA-binding proteins regulate the activation of the Maturation-Promoting Factor

As in other species, in *C. elegans* MPF functions as the master regulator of M-phase entry, and is formed by cyclin B, the regulatory subunit, and CDK-1/cdk1, the catalytic subunit (Figure 2) (Kim et al. 2013). Before the onset of meiotic maturation CDK-1 is inactivated by the conserved WEE-1.3 kinase. WEE-1.3 catalyzes the CDK-1 inhibitory phosphorylations at Thr14 and Tyr15 (Burrows et al. 2006). At the onset of meiotic maturation, members of the CDC-25-family of protein phosphatases activate CDK-1 by removing the inhibitory phosphorylations.

CDK-1 activation appears to be under translational regulation by the redundant OMA-1 and OMA-2 zinc-finger RNA-binding proteins (collectively referred to as the OMA proteins) and the antagonistic NHL-TRIM protein LIN-41 (Detwiler et al. 2001; Spike et al. 2014a, b; Tsukamoto et al. 2017). In *oma-1; oma-2* double mutants, oocytes fail to activate CDK-1 and do not undergo meiotic maturation, resulting in sterility (Detwiler et al. 2001). In contrast, in *lin-41* null mutants, CDK-1 is prematurely activated in developing oocytes at the end of the pachytene stage, causing sterility. The defective features of *lin-41* mutant oocytes include premature cellularization and CDK-1 activation at the end of the pachytene stage, followed by disassembly of the synaptonemal complex. *lin-41* null mutant oocytes do not progress to the diplotene stage during which the centrioles are eliminated. Consequently, when CDK-1 is prematurely activated, the oocytes aberrantly assemble spindles and attempt to segregate chromosomes (Spike et al. 2014a). In addition, oocytes in *lin-41* null mutants aberrantly express genes normally expressed by a variety of differentiated cell types, likely as an indirect consequence of premature CDK-1 activation (Spike et al. 2014a, b; Tocchini et al. 2014). LIN-41 inhibits CDK-1 activation in part through the 3'-UTR-dependent

translational repression of the CDK-1 activator, CDC-25.3 phosphatase (Spike et al. 2014b; Tsukamoto et al. 2017). The OMA proteins are also required for translational repression of *cdc-25.3* in oocytes (Spike et al. 2014b; Tsukamoto et al. 2017). This finding posed a paradox of how the OMA proteins and LIN-41 mediate the translational repression of common mRNA targets despite having opposite null phenotypes. LIN-41 and the OMA proteins also affect oocyte growth in opposing fashion. In *lin-41* null mutants, pachytene-stage oocytes prematurely cellularize and fail to grow; whereas *oma-1*; *oma-2* double mutant oocytes grow abnormally large in the presence of sperm (Detwiler et al. 2001; Spike et al. 2014a). Thus, oocyte growth and meiotic maturation are coordinately controlled by both MSP signaling and translational regulation. This observation is consistent with the suggestion that oocytes of many species arrest in meiosis to enable the growth process.

4.2 LIN-41 and the OMA proteins mediate a translational repression-to-activation switch

Recently, biochemical purifications have begun to address the mechanisms by which LIN-41 and the OMA proteins antagonistically control the prophase-to-metaphase transition and growth of *C. elegans* oocytes. LIN-41 and the OMA proteins copurify in large molecular weight RNP complexes (Spike et al. 2014; Tsukamoto et al. 2017). Mass spectrometry and RNA-sequencing was used to characterize the protein and RNA components of these complexes, respectively. Protein constituents of LIN-41- and OMA-1-containing RNPs include essential germline RNA-binding proteins, the GLD-2 cytoplasmic poly(A) polymerase, the CCR4-NOT deadenylase, and translation initiation factors. These findings are consistent with a major role for LIN-41 and the OMA proteins in regulating protein translation in oocytes. Intriguingly, many important germline RNA-binding protein translational regulators are both protein and mRNA components of LIN-41 and/or OMA-1-containing RNPs, including GLD-1, MEX-3, SPN-4, POS-1, and LIN-41 and OMA-1/2. The finding that LIN-41 and/or the OMA proteins regulate the translation of several RNA-binding constituents of their RNPs suggests LIN-41 and the OMA proteins drive the assembly and maturation of the translational regulatory apparatus during oogenesis. mRNA components of these RNPs broadly fall into three classes: those that stably associate with LIN-41 and OMA-1 and those that associate selectively with either LIN-41 or OMA-1. LIN-41 and OMA-1 translationally repress several mRNAs that stably associate with both proteins, including *cdc-25.3*, *zif-1*, and *rnp-1*. Of particular interest are two transcripts that selectively associate with LIN-41, which encode the RNA regulators SPN-4 and MEG-1. LIN-41 was found to repress translation of *spn-4* and *meg-1*, whereas the OMA proteins were found to promote their expression (Figure 7). Upon their synthesis in proximal oocytes, SPN-4 and MEG-1 assemble into RNPs prior to their functions in late-stage oocytes and early embryos. This finding suggests that LIN-41 and the OMA proteins mediate a translational repression-to-activation switch to support cytoplasmic oocyte maturation.

LIN-41- and OMA-containing RNPs might function to toggle specific mRNA targets between translational repression and activation. The mass spectrometric identification of proteins associated with LIN-41 and OMA-1 suggests a possible model (Figure 8). The GLD-2 cytoplasmic poly(A) polymerase and its accessory cofactors GLD-3 and RNP-8 copurify with both LIN-41 and OMA-1 (Spike et al. 2014b; Tsukamoto et al. 2017). Studies in invertebrates and vertebrates suggest that GLD-2 cytoplasmic poly(A) polymerases

function as translational activators (Wang et al. 2002; Kwak et al. 2004; Ivshina et al. 2014). Indeed, GLD-2 was found to promote the expression of SPN-4 and MEG-1 in oocytes. On a more global scale, many transcripts that were found to selectively associate with LIN-41 exhibit shortened poly(A) tails in *gld-2* null mutants (Tsukamoto et al. 2017). This finding suggests that these transcripts might be normally poised with long poly(A) tails for translation in late-stage oocytes upon the disruption of LIN-41-mediated repression. LIN-41 activity, which includes the prevention of M-phase entry, appears to be inactivated sequentially during oocyte meiotic maturation (Figure 4 and Figure 8). In the first step, LIN-41 translational repression activity appears to be attenuated in the most proximal oocyte. For example, this enables the expression of SPN-4 in the most proximal two oocytes despite the expression of the LIN-41 repressor (Figure 7 and Figure 8). In the second step, LIN-41 is inactivated and degraded. The degradation of LIN-41, which commences upon the onset of meiotic maturation, requires CDK-1 activity (Figure 4; Spike et al. 2014a), indicating that a bistable switch regulates the all-or-none activation of CDK-1 for meiotic maturation. How MSP signaling leads to the apparent inactivation and degradation of LIN-41 to enable meiotic maturation is an important question for future work.

5 Conclusions

The regulation of oocyte meiotic maturation has been a longstanding question in developmental biology. In recent years, studies that use *C. elegans* as a model organism have yielded fundamental new insights into how intercellular signaling and translational regulation control this major developmental transition required for sexual reproduction of animals. An ever-expanding array of technologies—electron microscopy, proteomics, genomics, and genome editing—has driven progress in this system. In the context of these new technologies, classical genetics is becoming even more powerful as a way of achieving a comprehensive and rigorous understanding of complex biology. Studies of *C. elegans* oocytes in the future are expected to reveal additional conceptual, anatomical, and molecular links to oocytes in all animals including humans.

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Figure 1.

Oocyte meiotic maturation in *C. elegans*. (A) The *C. elegans* hermaphrodite gonad is composed of two U-shaped arms (one is shown here). The germline stem cells are located at the distal end of the gonad near the distal tip cell (DTC). The germline develops as a syncytium, with germ cell nuclei sharing a common core cytoplasm. As germ cells move proximally (closer to the spermatheca), they enter meiosis. In the gonad of the adult hermaphrodites, germ cells that enter meiosis differentiate into oocytes. Oocytes undergo meiotic maturation (entry into M phase of meiosis I from prophase), ovulation, and fertilization in an assembly-line-like fashion. Meiotic maturation is spatially restricted to the most proximal (−1) oocyte. (B) The most proximal (−1) oocyte undergoes meiotic maturation in response to MSP from sperm (purple).

Figure 2.

The Maturation-Promoting Factor is a conserved master regulator of oocyte meiosis maturation. MPF consists of a regulatory cyclin B subunit and a protein kinase catalytic CDK-1/cdk1 subunit. The Wee1 kinase catalyzes inhibitory CDK-1 phosphorylations in immature oocytes. Upon hormonal activation, Cdc25 phosphatase removes these inhibitory phosphorylations promoting meiotic maturation.

Figure 3.

C. elegans oocyte meiotic maturation and ovulation are observable in living animals. Time-lapse photomicrographs show the most proximal (–1) oocyte of an anesthetized adult hermaphrodite as it starts meiotic maturation and is ovulated. Lower panels show a schematic representation. Oocytes (light blue) and sperm (purple) are shown. The approximate timing of events is depicted, with the time of nuclear envelope breakdown (NEBD) corresponding to 0 min.

Figure 4.

A model for the regulation of *C. elegans* oocyte meiotic maturation. Somatic G_{α_s} -adenylate cyclase-protein kinase A signaling is required for oocyte meiotic maturation. G_{α_i} and sheath-oocyte gap junctions function as inhibitors of meiotic maturation. Grey thick lines are the lipid bilayers of the sheath cell and oocyte.

Figure 5.

Oocyte meiotic maturation is triggered by hormonal cues and signaling from somatic cells. The communication between somatic cells and oocytes through gap junctions is a conserved feature: mammalian cumulus granulosa cells form gap junctions with oocytes at transzonal projections (A and C), while in *C. elegans* the gonadal sheath cells form gap junctions with oocytes at multiple points of contact (B and D). Somatic $G\alpha_s$ -adenylate cyclase pathways regulate meiotic maturation in response to luteinizing hormone (LH) stimulation in mammals (E), and after MSP stimulation in *C. elegans* (F). Freeze-fracture electron micrographs of oocytes from rats (C) and *C. elegans* (D) are reprinted with permission from Anderson and Albertini 1976, and Hall et al. 1999, respectively. ZP, zona pellucida; gj, gap junction; O, oocyte; GP, cumulus granulosa cell process; E, E-face; P, P-face; p, sheath pore.

Figure 6.

Two classes of *C. elegans* gap junction channels mediate soma-germline interactions essential for germline proliferation and gametogenesis. In *C. elegans* there are at least two classes of gap-junction channels. The somatic hemichannels are comprised of INX-8 and INX-9 in both classes of gap junctions. The germ cell hemichannels are composed of (1) INX-14/INX-21 or of (2) INX-14/INX-22 (adapted from Starich et al. 2014).

Figure 7.

LIN-41 and the OMA proteins differentially regulate translation of the SPN-4/Rbfox1 RNA binding protein. (A) SPN-4 translation increases dramatically after meiotic maturation, paralleling the decline of LIN-41, which is degraded upon the onset of meiotic maturation. (B–G) LIN-41 represses and the OMA proteins promote SPN-4 translation (adapted from Tsukamoto et al. 2017).

Figure 8.

LIN-41 and OMA proteins regulate oocyte meiotic maturation and mediate a translational repression-to-activation switch. Several transcripts that stably associate with LIN-41 and OMA-1, such as the CDK-1 activator *cdc-25.3*, are translationally repressed in a 3'-UTR-dependent mechanism as shown in the oocyte in diakinesis (left). Transcripts that stably associate selectively with LIN-41, including *spn-4* and *meg-1*, are translationally repressed by LIN-41 (left) but are translationally activated by the OMA proteins (right). *spn-4* translation commences in the -2 oocyte (see Figure 7C). LIN-41 translational repression activity appears to be inactivated in two steps during the late stages of oogenesis: (1) the OMA proteins activate translation through another component of the RNP complex; and (2) LIN-41 is inactivated and degraded.

Table 1

Key Abbreviations *

Abbreviation	Definition
GPCR	G protein-coupled receptor
MAPK	Mitogen-activated protein kinase
MPF	Maturation-promoting factor
MSP	Major sperm protein
NEBD	Nuclear envelope breakdown
PKA	Protein kinase A
RNP	Ribonucleoprotein

* Abbreviations for many key gene discussed in this review are indicated in Figure 4.