Parental Control Begins at the Beginning

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In this commentary, Diana Chu considers the findings of Ataeian et al. (2016) in this issue of GENETICS *in the context of parental contributions to development. This work reveals how molecular players contributed by oocyte and sperm coordinate early transitions in the embryo.*

New parents anticipate their job begins at birth. Little do they know they have been exerting control within the baby's first cell since fertilization. At that moment, sperm entry unleashes a torrent of molecular changes crucial for development. A key transition is forming the diploid DNA complement from paternal and maternal DNA. Sperm bring their haploid share to the oocyte; however, preparing the maternal haploid portion is carefully staged. Oocytes, which can be stored for years in some organisms, arrest prior to meiotic divisions until receiving a signal to begin meiotic maturation (Figure 1). Oocytes start meiotic divisions but arrest again until fertilization signals egg activation. At that point, meiotic divisions complete, and the cell transitions to mitosis. This transition from oocyte to embryo is vital—the cell must sense that the paternal DNA is in the house before completing the meiotic divisions. The molecules that coordinate these early events are largely mysterious in any organism, due in part to the difficulty of observing fertilization within living organisms. In this issue, Ataeian *et al.* (2016) exploit tools offered by the transparent model organism *Caenorhabditis elegans* to identify and characterize maternal and paternal molecular components that together convey that fertilization has occurred, and embryonic development is ready to proceed.

The maternal part of the story began with a classical temperature-sensitive genetic screen in *C. elegans* performed 20 years ago to identify genes important for embryonic development (Mitenko *et al.* 1997). Ataeian *et al.* (2016) focus on a dominant maternal effect lethal mutant called *sb41*. Examining an *sb41* strain expressing fluorescently tagged histone and tubulin proteins revealed that oocytes do not transition to embryos properly—they fail to complete the second meiotic division, do not form a second polar body, and enter mitosis with the wrong complement of maternal DNA. Subsequently, the cell fails to complete mitosis and dies. Based on this phenotype, the authors dub the affected gene *memi-1* (meiosis-to-mitosis transition defect).

Whole genome sequencing of the mutant allowed researchers to molecularly characterize *memi-1*. Database searches revealed two *C. elegans* paralogs, named *memi-2* and *memi-3*, that share 87% identity with *memi-1* but have no conserved domains. Genetic and RNAi analyses showed that single mutants or knockdowns of individual *memi* genes exhibit no phenotypes, whereas reducing expression of at least two *memi* paralogs together causes embryonic lethality, supporting the view that MEMI proteins work redundantly. This function is regulated in a cell cycle-dependent manner, as MEMI levels are high in oocytes but low in mitosis. The authors show that ubiquitin-mediated proteolysis, which is responsible for cell cycle progression, is also necessary for MEMI degradation. Consistent with this, the hypermorphic *sb41* mutation alters a putative target site in MEMI-1 for proline-directed kinases, possibly the cyclin-dependent kinase (CDK), and results in persistence of MEMI protein into mitosis.

A key question was whether the loss of *memi* function causes defects in the meiosis-to-mitosis transition. RNAi knockdown of *memi* in fact caused an earlier failure in meiosis I cytokinesis, and first polar body formation, after fertilization. These fertilized oocytes do not form a meiosis II spindle but instead begin mitosis, where chromosomes attempt to segregate but cytokinesis fails and embryos die. Importantly, this phenotype was similar to when fertilization itself fails. For example, *fer-1*(*ts*) mutants produce sperm that can signal to oocytes for maturation, but cannot fertilize oocytes (L'Hernault *et al.* 1988; McNally and McNally 2005). *fer-1*(*ts*) oocytes, which undergo meiotic maturation but not fertilization, also fail to form the first polar body and the meiosis II

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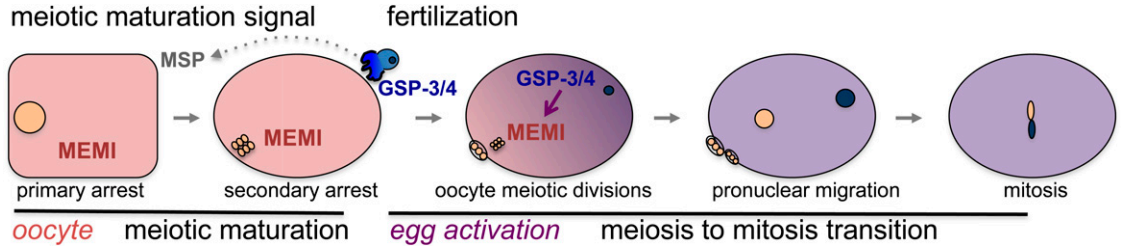

Figure 1 Oocytes are arrested prior to meiotic divisions until receiving a maturation signal. In *C. elegans*, this signal is the Major Sperm Protein (MSP), secreted from sperm. The cells pause until fertilization triggers egg activation. Ataeian *et al.* (2016) in this issue show that sperm deliver the paternal GSP-3 and GSP-4 PP1 phosphatase proteins that, directly or indirectly, activate maternal MEMI proteins. MEMI proteins enable the fertilized oocyte to complete meiotic divisions, and transition to the first mitotic division.

spindle (McNally and McNally 2005). This suggests that MEMI proteins inform the oocyte that fertilization has occurred. As such, they are one of the first maternal proteins identified as required to trigger proper completion of the oocyte meiotic divisions.

But what paternal factors could the oocyte be sensing after fertilization? To find sperm factors that tie into the MEMI pathway, the authors used RNAi screening to identify two suppressors of the original *memi-1*(*sb41*) mutant: *gsp-3* and *gsp-4* (henceforth referred to as *gsp-3/4*), two nearly identical PP1 phosphatase homologs (Chu *et al.* 2006). GSP-3/4 are highly expressed during spermatogenesis, and required for sperm meiosis and motility (Wu *et al.* 2012). To rule out the possibility that oocytes contribute GSP-3/4, the authors treated *memi-1*(*sb41*) mutant hermaphrodites with *gsp-3/4* RNAi, and crossed them to wild-type males. They found no rescue, supporting the view that only reducing the paternally contributed GSP-3/4 suppresses the *memi-1*(*sb41*) mutant phenotype. Furthermore, the authors showed that coimmunoprecipitation of MEMI proteins could pull down GSP-3/4. Based on the genetic and physical interactions observed, the authors suggest that, once delivered, GSP-3/4 physically interact and activate MEMI proteins in the fertilized oocyte.

These results differ from another key paternal protein, SPE-11, required for embryogenesis in *C. elegans* (L'Hernault *et al.* 1988; Hill *et al.* 1989; Browning *et al.* 1996). *spe-11* mutant sperm are motile and can fertilize oocytes. However, oocytes fertilized by *spe-11* mutant sperm segregate chromosomes in meiosis I and II, but fail to complete cytokinesis for both events (Hill *et al.* 1989; McNally and McNally 2005). This phenotype is distinct from *fer-1*(*ts*) and *memi* loss-of-function mutants, suggesting paternally contributed SPE-11 mediates events important for meiotic cytokinesis. Still unknown are whether paternal factors like GSP-3/4 or SPE-11 function directly in oocyte meiosis, or indirectly through activating maternal factors. However, these results show that paternal factors influence distinct stages of the early meiosis-to-mitosis transition.

Sperm make other contributions important for early embryonic events. Sperm provide a centriole pair to oocytes, which eliminate theirs during oogenesis. Sperm entry also provides a cue that establishes the polarity of embryos in several organisms. Conversely, in *Drosophila*, a maternal factor, identified by the maternal effect mutation *sesame*, is required to decondense and prepare the paternal DNA for union (Loppin *et al.* 2000). However, the findings from Ataeian *et al.* (2016) are unique in that they identify one set of paternal and maternal molecular factors that may hand off information to coordinate events very early in embryogenesis, before embryonic transcription ramps us. The authors present a model in which the sperm-specific phosphatases GSP-3/4 enter the cell upon fertilization, and then activate MEMI proteins to signal the resumption of meiotic divisions—an important step in the transition from oocyte to embryo (Figure 1).

The evidence that paternal and maternal factors communicate leads to an intriguing possibility that other factors may be found in the sperm delivery package. Once released, these factors may then work with maternal proteins to likewise control other early events important for the oocyte-to-embryo transition. Thus, we have the potential to learn more about the earliest parental influences at work well before birth.

Literature Cited

Ataeian, M., J. Tegha-Dunghu, D. G. Curtis, E. M. Sykes, A. Nozohourmehrabad *et al.*, 2016 Maternal MEMI promotes female meiosis II in response to fertilization in *Caenorhabditis elegans*. Genetics 204: 1461–1477.

Browning, H., S. Strome, D. P. Hill, D. C. Shakes, S. Ward *et al.*, 1996 A sperm-supplied factor required for embryogenesis in *C. elegans*. Development 122: 391–404.

Chu, D., H. Liu, P. Nix, T. Wu, E. Ralston *et al.*, 2006 Sperm chromatin proteomics identifies evolutionarily conserved fertility factors. Nature 443: 101–105.

Hill, D. P., D. C. Shakes, S. Ward, and S. Strome, 1989 A sperm-supplied product essential for initiation of normal embryogenesis in *Caenorhabditis elegans* is encoded by the paternal-effect embryonic-lethal gene, *spe-11*. Dev. Biol. 136: 154–166.

L'Hernault, S. W., D. C. Shakes, and S. Ward, 1988 Developmental genetics of chromosome I spermatogenesis-defective mutants in the nematode *Caenorhabditis elegans*. Genetics 120: 435–452.

Loppin, B., M. Docquier, F. Bonneton, and P. Couble, 2000 The maternal effect mutation sesame affects the formation of the male pronucleus in *Drosophila melanogaster*. Dev. Biol. 222: 392–404.

McNally, K. L., and F. J. McNally, 2005 Fertilization initiates the transition from anaphase I to metaphase II during female meiosis in *C. elegans*. Dev. Biol. 282: 218–230.

Mitenko, N. L., J. R. Eisner, J. R. Swiston, and P. E. Mains, 1997 A limited number of *Caenorhabditis elegans* genes are readily mutable to dominant, temperature-sensitive maternal-effect embryonic lethality. Genetics 147: 1665–1674.

Wu, J. C., A. C. Go, M. Samson, T. Cintra, S. Mirsoian *et al.*, 2012 Sperm development and motility are regulated by PP1 phosphatases in *Caenorhabditis elegans*. Genetics 190: 143–157.

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