Meiosis is a fundamental process that underpins sexual reproduction. In mammals, the execution of meiosis is tightly integrated within the complex processes of oogenesis and spermatogenesis, and elucidation of the molecular mechanisms regulating meiotic initiation remains challenging. We have recently developed in vitro culture strategies to induce mouse pluripotent stem cells into germ cells, which successfully contribute to both oogenesis and spermatogenesis and to fertile offspring. The culture strategies faithfully recapitulate transcriptional and epigenetic dynamics as well as signaling principles for germ cell specification, proliferation, and female sex determination/meiotic induction, providing a valuable platform for studies to illuminate the molecular mechanisms underlying such critical processes. Here, we review mammalian gametogenesis with a focus on the implementation of meiosis and, based on our recent studies, discuss new insights into the mechanisms for meiotic initiation and germ cell sex determination in mice.

For most eukaryotic lineages, the creation of haploid gametes through meiosis and fertilization constitutes the foundation for sexual reproduction that assures continual succession of life (Wilkins and Holliday 2009). Through evolution, the regulatory components for meiotic recombination and chromosome segregation have been highly conserved (Marston and Amon 2004; Handel and Schimenti 2010; Watanabe 2012; Baudat et al. 2013); however, the mechanisms controlling meiotic initiation are divergent and involve species-specific and sex-specific developmental contexts (Harigaya and Yamamoto 2007; Lesch and Page 2012). In mammals, the implementation of meiosis is embedded within the complex oogenesis and spermatogenesis processes, and elucidating the molecular mechanisms pertaining to meiotic initiation remains a challenge.

Recently, we devised strategies to successfully reconstitute germ cell specification pathways from pluripotent stem cells (embryonic stem cells [ESCs] and induced pluripotent stem cells [iPSCs]) in mice (Hayashi et al. 2011). The transcriptional and epigenetic constitution of the resultant germ cells closely resembles those of primordial germ cells (PGCs) (Hayashi et al. 2011; Ohta et al. 2017), a group of sexually uncommitted precursor cells that give rise to either oocytes or spermatozoa. Remarkably, the in vitro–derived PGCs (PGC-like cells [PGCLCs]) possess a robust capability to differentiate into functional oocytes and spermatozoa in mice and contribute to fertile offspring (Hayashi et al. 2011, 2012; Hikabe et al. 2016; Ishikura et al. 2016; Ohta et al. 2017). The establishment of robust in vitro germ cell derivation strategies presents unprecedented opportunities for studies to illuminate the mechanisms of epigenetic reprogramming, sex determination, and meiotic initiation during mammalian germ cell development (Kurimoto et al. 2015; Shirane et al. 2016; Miyauchi et al. 2017; Ohta et al. 2017). In this review, we highlight the key components of mammalian germ cell development, the current understanding of the mechanisms of sex determination and meiotic initiation, new findings emerging from the studies using PGCLCs, and outstanding areas of studies that await further investigation.

GERM CELL SPECIFICATION IN MAMMALS

In metazoan lineages, germ cell fate is conferred via two major mechanisms. In model organisms such as Drosophila melanogaster and Caenorhabditis elegans, the germ cell fate is specified by a mechanism called “pref ormation,” in which the segregation and inheritance of maternal determinants from the egg specifies the future germ cell lineages in developing embryos (Ex tavour and Akam 2003). On the other hand, in mice and likely in other mammals, germ cell fate is specified by “epigenesis,” in which pluripotent embryonic cells are induced to confer the germ cell fate through the actions of inductive and restrictive signals from surrounding tissues and the embryo itself (Ex tavour and Akam 2003; Saitou and Yamaji 2012). In mice, in which the mechanism has been exten-
sively studied, the germ cell fate is induced in the most proximal posterior epiblast in response to bone morphogenetic protein (BMP) signaling emanating from neighboring extraembryonic ectoderm tissues and WNT signaling from the proximal posterior epiblast itself, beginning at around embryonic day 5.5 (E5.5) (Lawson et al. 1999; Saitou et al. 2002; Ohinata et al. 2009). Inhibitory molecules of BMP signaling, such as CER1, are secreted from the anterior visceral endoderm and inhibit germ cell induction in the anterior epiblast, restricting the emergence of the germ cells in the posterior region of the epiblast (Perea-Gomez et al. 2002; Ohinata et al. 2009). Consequently, by E7.25, a cluster of 30–40 PGCs is established within the extraembryonic mesoderm at the base of the allantois, which constitutes the founding population of the germ cell lineages (Fig. 1; Ginsburg et al. 1990; Lawson et al. 1999; Saitou et al. 2002; Ohinata et al. 2009).

**SEX DETERMINATION AND MEIOTIC INITIATION IN MAMMALS**

After specification, PGCs migrate through the hindgut endoderm toward developing gonads. Concurrently with the completion of PGC migration, the embryonic gonads undergo sex determination and initiate sex-specific developmental programs based on their sex chromosome constitutions. In gonadal somatic cells in XY individuals, the expression of the sex determination gene on the Y chromosome, *Sry*, initiates the formation of testicular structures essential for spermatogenesis (Sinclair et al. 1990; Koopman et al. 1991; Brennan and Capel 2004; Eggers et al. 2014). On the other hand, in the absence of *Sry*, a concerted activation of several ovary-specification genes, such as *Wnt4*, *Rspo1*, and *Fosl2*, drives the development of ovaries (Brennan and Capel 2004; Eggers et al. 2014). Importantly, once the decision is made, networks of activating and repressing signals actively maintain the sexual fate of gonads into adulthood (Uhlenhaut et al. 2009; Matson et al. 2011; Capel 2017).

In contrast to the sex determination mechanisms of the gonadal somatic cells, for germ cells, the commitment to a particular sex is dependent on the surrounding environment regardless of their sex chromosome constitutions (McLaren 1984, 1988; Kimble and Page 2007; Spiller et al. 2017). Intriguingly, in the fetal gonads, sex determination is coupled with the decision to initiate meiotic programs (McLaren 1984, 1988; Kimble and Page 2007; Spiller et al. 2017). In fetal ovaries, after several rounds of mitotic divisions, germ cells (now called oogonia) initiate meiotic prophase. The implementation of chromosomal events of meiotic prophase marks the first visible divergence between female and male germ cells, and it is classically considered as the onset of oogenesis (Hilscher et al. 1974; Speed 1982; McLaren 1984, 1988; Kimble and Page 2007; Spiller et al. 2017). In fetal testes, on the other hand, germ cells (now called spermatogonia or gonocytes) are actively suppressed from prematurely ini-

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**Figure 1.** (Top) A schematic representation of germ cell development in mice. (Bottom) Key events associated with each stage of germ cell development are shown along with the dynamics of the 5mC levels. ICM, inner cell mass; TE, trophectoderm; SSC, spermatogonial stem cell; PGC, primordial germ cell.
tiating meiosis, and this suppression appears critical for the commitment to the male germ cell pathway (Bowles et al. 2006; Koubova et al. 2006; MacLean et al. 2007; Saba et al. 2014b).

For the sexual commitment and meiotic induction, differential availability of retinoic acid (RA) between embryonic ovariess and testes is instrumental in setting up the sexually dimorphic development. RA is an active metabolite of vitamin A that is used in multiple developmental processes, including reproduction (Wilson et al. 1953; Huang and Hembree 1979; Morales and Griswold 1987; Niederreither and Dolle 2008; Li and Clagett-Dame 2009; Griswold et al. 2012; Cunningham and Duester 2015), and the actions of RA are controlled at the level of tissue distribution by the expressions of synthesizing and metabolizing enzymes and also at the molecular level by the actions of RA receptors and a cohort of interacting proteins (Bastien and Rochette-Egly 2004; Niederreither and Dolle 2008; Dolle 2009; Mark et al. 2009; Cunningham and Duester 2015). Developing gonads are capable of synthesizing RA (Bowles et al. 2016), but the predominant sites of RA synthesis appear to be at mesonephroi that develop adjacent to the gonads, with RA likely diffusing into gonads (Bowles et al. 2006; Koubova et al. 2006; Griswold et al. 2012; Feng et al. 2014).

In the germ cells of developing ovaries, the activation of RA signaling leads to the induction of meiotic genes and meiotic prophase (Baltus et al. 2006; Bowles et al. 2006; Koubova et al. 2006; MacLean et al. 2007; Le Bouffant et al. 2010; Childs et al. 2011; Saba et al. 2014b; Soh et al. 2015). Additionally, RA signaling suppresses the activation of several male germ cell specification genes (Bowles et al. 2010; Saba et al. 2014b), thus reinforcing the commencement of the female pathway. In male gonads, on the other hand, SRY and its immediate downstream target, SOX9, up-regulate the expression of CYP26B1, an enzyme that catabolizes RA (Kashimada et al. 2011; Li et al. 2014), thereby suppressing the onset of RA signaling and premature initiation of meiosis in the male germ cells (Bowles et al. 2006; Koubova et al. 2006; MacLean et al. 2007; Saba et al. 2014b). In addition to the suppression of the RA signaling, FGF9, secreted from Sertoli cells, as well as the expression of a translational regulator specific to male germ cells, NANOS2, promote the male germ cell pathway and repress the meiotic program (Suzuki and Saga 2008; Sada et al. 2009; Barrios et al. 2010; Bowles et al. 2010; Saba et al. 2014a; Kato et al. 2016). More recently, activin and nodal signaling have also been shown to reinforce the commitment to the male fate by activating Nanos2 and other male germ cell genes as well as suppressing the induction of meiosis (Spiller et al. 2012; Wu et al. 2013, 2015).

**THE IMPLEMENTATION OF MEIOSIS DURING OOGENESIS AND SPERMATOGENESIS**

As discussed above, in females, oogonia initiate meiotic programs and begin meiotic prophase in fetal ovaries, and all the major chromosomal events of meiotic prophase—synapsis between homologous chromosomes, programmed DNA double-strand break formation, and formation of meiotic recombination—take place in the developing embryo (Gerton and Hawley 2005; Handel and Schimenti 2010; Baudat et al. 2013). Upon completion of the recombination processes, the oocyte enters the dictyate stage and the progression of meiosis becomes suspended (Fig. 1; Handel and Schimenti 2010). Concurrently, oocytes begin to establish intimate associations with surrounding granulosa cells and develop into primordial follicles (McGee and Hsueh 2000; Pepling and Svardling 2001; Matzuk et al. 2002; Li and Albertini 2013). The growth and maturation of the follicle take place postnatally, and intricate bidirectional signaling between the oocyte and granulosa cells is integral for successful folliculogenesis (Matzuk et al. 2002; Albertini 2015). During the growth, oocytes acquire maternal imprinting (Lucifero et al. 2002; Kobayashi et al. 2012) and undergo cytoplasmic maturation to establish the competence for fertilization and embryogenesis (Matzuk et al. 2002; Li and Albertini 2013). As the follicle completes its maturation, the surge of luteinizing hormone induces ovulation and releases the meiotic arrest. During the first meiotic division (also known as the reductional division), crossovers between homologous chromosomes, the product of mitotic recombination during the fetal stage, play a vital role in the segregation of homologous chromosomes (Gerton and Hawley 2005; Handel and Schimenti 2010; Nagaoka et al. 2012). Fertilization triggers the onset of second meiotic division and the production of a haploid egg (Handel and Schimenti 2010; Clift and Schuh 2013). Finally, the fusion between maternal and paternal pronuclei restores diploidy, and the life of a new individual begins. Thus, meiosis encompasses the entire duration of oogenesis in mammals, and intricate control mechanisms at various stages must be in place in order to coordinate the chromosomal events of meiosis and the execution of the developmental programs for generating a competent ovum.

In developing gonads of male embryos, pro spermatogonia proliferate through several rounds of mitotic divisions, while actively suppressing the entry into meiosis (Bowles et al. 2006; Koubova et al. 2006; MacLean et al. 2007; Saba et al. 2014b). Subsequently, they enter into a quiescent state of G0/G1 mitotic arrest (Manku and Culry 2015; Spiller et al. 2017) and acquire androgenetic epigenome, including paternal imprints (Fig. 1; Davis et al. 2000; Ueda et al. 2000; Kato et al. 2007; Seisenberger et al. 2012; Kobayashi et al. 2013; Kubo et al. 2015). After birth, although many spermatogonia initiate the first wave of spermatogenesis in mice (Yoshida et al. 2006), a small pool establish a spermatogonial stem cell (SSC) population with a lifelong capacity to perform numerous rounds of spermatogenesis (Outley and Brinster 2008; Yoshida 2012; Kanatsu-Shinohara and Shinohara 2013). At each round of spermatogenesis, SSCs give rise to differentiating spermatogonia, which undergo several rounds of mitotic cell divisions and then initiate meiosis (Griswold 2016). In contrast to meiosis in females, meiotic prophase and the two meiotic divisions in males proceed without a halt and result in the generation of four haploid spermatids (Fig. 1). Subsequently, spermatids un-
dergo morphological transformation, as well as chromatin compaction in the form of histone-to-protamine replacement, and develop into highly motile and fertilization-capable spermatozoa (Toshimori and Eddy 2015). Remarkably, throughout the seminiferous epithelium within the testes, new waves of spermatogenesis are constantly initiated from SSCs, which concurrently and successively mature to haploid spermatozoa, providing a continuous supply for the lifetime of a male (Griswold 2016).

Considering the integration of meiosis within sex-specific gametogenesis steps involving key functions of gonadal somatic cells, the establishment of experimental means that can resolve the intricate interactions between germ cells and somatic cells will be crucial for efforts to understand the mechanism for meiosis.

IN VITRO DERIVATION OF PRIMORDIAL GERM CELLS

The tantalizing capability of the germ cells to create new organisms has been inspiring developmental and stem cell biologists alike to attempt to recreate gametogenesis processes from pluripotent stem cells (Daley 2007; Saitou and Miyauchi 2016). In recent years, the realization of robust in vitro derivation strategies was finally achieved (Hayashi et al. 2011, 2012). This feat was largely attributable to the accumulation of knowledge about germ cell specification (Ginsburg et al. 1990; Lawson et al. 1999a; Saitou et al. 2002; Ohinata et al. 2009), refined understanding of different pluripotent states among stem cells propagated in vitro (Hackett and Surani 2014; Martello and Smith 2014), and the development of reproductive technologies that can convincingly test the potency of the derived germ cells (Brinster and Avarbock 1994; Brinster and Zimmermann 1994; Chuma et al. 2005). The successful derivation strategies generate germ cells that closely resemble PGCs in their transcriptional and epigenetic characteristics. Importantly, the derived PGCLCs possess a robust capability to perform successful oogenesis and spermatogenesis that contribute to fertile offspring when transplanted into surrogate animals (for spermatogenesis and oogenesis) (Hayashi et al. 2011, 2012; Ishikura et al. 2016; Ohta et al. 2017) or when cultured in appropriate in vitro growth conditions (IVG) and in vitro maturation (IVM) conditions (for oogenesis) (Fig. 2; Hikabe et al. 2016; Morohaku et al. 2016). Thus, the in vitro germ cell derivation strategy provides a valuable platform for studies to elucidate mechanisms underlying critical processes during mammalian germ cell development.

EXPANSION CULTURE OF PGCs/PGCLCs AND RECONSTITUTION OF THE EPIGENETIC BLANK SLATE OF THE GERM CELLS

Coculturing strategies with embryonic gonadal somatic cells are instructive in promoting the sex determination of PGCLCs and their differentiation toward oocytes or spermatogonia; however, the complexity of germ–soma interaction precludes the elucidation of the precise molecular mechanisms underlying sex determination. To overcome this obstacle, we have recently developed a culturing system to propagate sexually uncommitted PGCs/PGCLCs without the use of gonadal somatic cells (Ohta et al. 2017). By using the PGCLC system, we conducted systematic chemical screenings to identify compounds that can enhance the proliferative capacity of PGCs/PGCLCs. The screening revealed that cyclic AMP signaling plays a pivotal role in the expansion of PGCs/PGCLCs in culture, as previous studies reported using isolated PGCs (De Felici et al. 1993; Farini et al. 2005). Global transcriptome and cell cycle kinetics of the expanded PGCLCs showed that they maintained characteristics of sexually uncommitted PGCs. Importantly, functional testing upon transplantation into neonatal testes showed their robust capability to contribute to spermatogenesis. The proliferation of PGCLCs was accompanied with a steady decrease in global 5-methylcytosine (5mC) level, presumably driven by progressive dilution of methylation upon DNA replication (Seisenberger et al. 2012; Kagiwada et al. 2013; Kobayashi et al. 2013). At the end of the expansion culture, the global 5mC level of the PGCLCs was comparable to that of gonadal germ cells at E13.5 in mice, a stage at which the genome-wide DNA methylation level reaches its nadir during the germine cycle (Fig. 1; Seisenberger et al. 2012; Kobayashi et al. 2013). It is notable that the demethylation process showed differential kinetics at distinct genomic regions (i.e., promoters of demethylation-resistant “germline genes,” ICRs of imprinted genes, and repetitive elements), in a manner reminiscent of PGCs (Seisenberger et al. 2012; Kobayashi et al. 2013). Further, we found that “escapees” that evade DNA demethylation (5mC > 20%) during PGCLC derivation and the expansion culture largely overlapped with those found in E13.5 germ cells (Seisenberger et al. 2012; Ohta et al. 2017). Thus, the induction of PGCLCs and subsequent expansion culture recapitulated the DNA methylation reprogramming events of PGCs. Remarkably, this global hypomethylation state was accompanied by apparent upregulation of histone H3K27me3 at promoters of genes that showed substantial demethylation during the expansion culture, plausibly compensating for the hypomethylation state and preventing aberrant gene expression from such loci. Nonetheless, we observed a partial activation of key gonadal germ cell genes that took place concurrently with the erasure of DNA methylation and reorganization of the histone modification landscape, implying that such epigenetic reorganization leads to a basal activation of some germline genes and might prime the germ cells for the eventual reception of the sex determination signals (Ohta et al. 2017). Taken together, these findings show that expansion culture recapitulates a global epigenetic reorganization process that forms an epigenetic “blank slate” of the germ cells upon which either an androgenetic or a gynogenetic epigenome can be established. The global epigenetic reorganization in the PGCs occurs cell-autonomously, without the guidance from gonadal somatic cells, and thus the reorganization process is an event genetically dissociable from the germ cell sex determination program.
The PGCLC expansion system described above, in which the sexual fate of the germ cells remains uncommitted, provides a valuable platform for studies to reconstitute the processes of germ cell sex determination and meiotic initiation. Using this culture system, we examined the effects of a panel of cytokines that might have an impact on sex determination with or without the treatment of RA (Miyauchi et al. 2017). Among the combinations of molecules we assayed, the combined provision of BMPs and RA resulted in the up-regulation of transcriptional programs for oogenesis and initiation of meiotic prophase. Notably, the transcriptional and cytological progression faithfully recapitulated the events of fetal oocytes, and the initiation of meiosis occurred in a highly synchronous manner within germ cell cysts (Miyauchi et al. 2017), demonstrating a coordinated developmental progress within the oocyte cysts (Fig. 1; Pepling and Spradling 1998). It has previously been shown that developing embryonic ovaries strongly express Bmp genes, particularly Bmp2 under the influence of Wnt4 (Yao et al. 2004; Ross et al. 2007; Jameson et al. 2012), and germ cell–specific deletion of Smad4, a gene coding for an essential signal transducer of BMP/TGFβ signaling, negatively affects the induction of female germ cell fate and meiotic onset (Wu et al. 2016). When considered together with our current results and those of other groups (Farini et al. 2005), these findings clearly show that BMP signaling plays a pivotal role in the induction of female germ cell fate. To our surprise, although RA signaling was proved to be essential for meiotic induction and oogenesis commitment, the addition of RA alone was not sufficient to confer the female fate (Miyauchi et al. 2017). Specifically, treatment with RA alone resulted in the up-regulation of known RA-regulated genes that are involved in meiosis (i.e., Stra8 and Rec8) (Oulad-Abdelghani et al. 1996; Mahony et al. 2011; Koubova et al. 2014; Soh et al. 2015), but the activation of these genes was not sufficient to initiate meiosis. Instead, the RA-only treatment up-regulated genes involved in other developmental programs (e.g., “embryonic organ development”), indicating that the cross talk with BMP
signaling is essential not only to activate the transcriptional cascades for the induction of meiosis and oogenic programs but also to repress unnecessary developmental programs elicited by RA. In the absence of \textit{Stra8}, a gene essential for premeiotic DNA replication, combined treatment of BMP and RA failed to fully activate meiotic genes and to repress unnecessary developmental programs (Miyauchi et al. 2017). Notably, however, \textit{Stra8} knockout did not prevent the activation of many fetal oocyte genes, including those involved in oocyte development (e.g., \textit{Figla} and \textit{Sohlh2}), demonstrating that the oocyte developmental program is independent from STRA8 and the chromosomal events of meiotic prophase, as reported recently (Dokshin et al. 2013).

During the expansion culture, PGCLCs globally erase 5mC in a comprehensive manner to a level comparable to E13.5 germ cells in mice (Ohta et al. 2017), a stage immediately preceding meiotic onset in females, and we tested whether such epigenetic states play a permissive role in sex determination and meiotic initiation. The combined BMP and RA treatment failed to induce meiotic genes in PGCLCs immediately after the inception from epiblast-like cells, but the treatment resulted in a robust activation of meiotic genes and commitment to the female fate after PGCLCs completed epigenetic reprogramming, indicating that the global epigenetic changes might make the germ cells more receptive to signals for sex determination and initiation of meiosis (Miyauchi et al. 2017). Interestingly, spermatagonia undergo significant DNA demethylation at promoters of relevant meiotic genes before meiotic initiation (Kubo et al. 2015; Miyauchi et al. 2017). This demethylation occurs despite the global re-acquisition of high 5mC level during male germ cell development (Fig. 1; Kubo et al. 2015), implying that epigenetic requirements for meiotic entry might be common between male and female germ cells (Miyauchi et al. 2017). Such competence acquisition could be partly explained by the erasure of DNA methylation marks at promoters of key germ cell genes (e.g., \textit{Dazl}). An evolutionarily conserved RNA binding protein, DAZL, has been shown to be a critical factor for sexual commitment and meiotic initiation in mice (although the influence of DAZL in sex determination and meiotic initiation varies among different genetic backgrounds) (Ruggiu et al. 1997; Lin et al. 2008; Gill et al. 2011). In our work, the reduction of 5mC level at \textit{Dazl} promoter was accompanied by a basal activation of \textit{Dazl} during the expansion culture, which likely contributed to the competence acquisition and thus to the commitment to the female germ cell fate upon activation of RA and BMP signaling (Lin et al. 2008; Gill et al. 2011; Kato et al. 2016; Miyauchi et al. 2017). Collectively, our works show that meiotic initiation requires a delicate coupling between extrinsic inputs and intrinsic molecular circuitry within the germ cell: Germ cell–autonomous epigenetic remodeling is instrumental in initiating the meiotic program and also in inducing female fate upon concerted activation of BMP and RA signaling (Fig. 3). Elucidation of downstream effector(s) of BMP signaling and investigation of the mechanisms by which BMP signaling, in concert with RA signaling, orchestrates

![Figure 3. A schematic representation of a potential signaling network controlling the sex determination processes for germ cells.](image-url)
the onset of female fate and meiotic initiation will be key challenges for the future.

Interestingly, a recent report showed that PGCLCs can initiate meiosis and develop into spermatid-like cells if cocultured with dissociated testicular cells of neonatal mice in the presence of RA, BMP2/4/7, and activin A for 6 days, followed by treatments of follicle stimulating hormone, bovine pituitary extract, and testosterone in the subsequent 8 days (Zhou et al. 2016). Surprisingly, the reported “in vitro spermatogenesis” procedure skips a period of more than 2 weeks of male germ cell development in vivo—that is, the period from PGCs at around E9.5 to spermatogonia before meiotic onset at postnatal day 10 (Bellvé et al. 1977). It is important to note that, during this period, male germ cells undergo epigenetic reprogramming, acquire the androgenetic epigenome, and differentiate into spermatogonia (Davis et al. 2000; Ueda et al. 2000; Kato et al. 2007; Seisenberger et al. 2012; Kobayashi et al. 2013; Kubo et al. 2015; Manku and Culity 2015). Furthermore, the reported procedure was conducted entirely at 37°C, a nonpermissive temperature for spermatogenesis (Steinberger et al. 1964; Sato et al. 2011). Thus, we consider it important to re-examine the validity of this study, including a precise analysis of the induced intermediate cells.

CONCLUSION

In this review, we have provided a brief outline of mammalian germ cell development with a focus on the implementation of meiosis and the latest findings from in vitro germ cell derivation studies. Meiosis is a process that can be conserved from unicellular organisms to multicellular organisms, and species-specific gametogenic strategies have evolved for successful execution of meiosis (Harigaya and Yamamoto 2007; Lesch and Page 2012). Recent advances have begun to provide a blueprint of how mammals execute meiosis in the context of epigenetic (Yokobayashi et al. 2013; Miyauchi et al. 2017), transcriptional (Soh et al. 2015; Miyauchi et al. 2017), extracellular signaling (Bowles et al. 2006; Koubova et al. 2006; MacLean et al. 2007; Saba et al. 2014b; Miyauchi et al. 2017), and post-transcriptional regulations (Zheng et al. 2013; Abby et al. 2016; Kato et al. 2016; Hsu et al. 2017; Soh et al. 2017). Moving forward, considering our rudimentary understanding of how sex determination and meiotic onset are coupled in the fetal gonads (Hilscher et al. 1974; McLaren 2000; Kato et al. 2007; Seisenberger et al. 2012; Kobayashi et al. 2013; cubed et al.), pp. 59–97. Elsevier/Academic, New York. Baltus AE, Menke DB, Hu YC, Goodheart ML, Carpenter AE, de Rooij DG, Page DC. 2006. In germ cells of mouse embryonic ovaries, the decision to enter meiosis precedes premeiotic DNA replication. Nat Genet 38: 1430–1434. Barrios F, Filipponi D, Pellegrini M, Paronetto MP, Di Siena S, Geremia R, Rossi P, De Felici M, Jannini EA, Dolci S. 2010. Opposing effects of retinoic acid and FGF9 on Nanos2 expression and meiotic entry of mouse germ cells. J Cell Sci 123: 871–880. Bastien J, Rochette-Egly C. 2004. Nuclear retinoid receptors and the transcription of retinoid-target genes. Gene 328: 1–16. Baudat F, Ihai Y, de Massy B. 2013. Meiotic recombination in mammals: Localization and regulation. Nat Rev Genet 14: 794–806. Bellvé AR, Cavicchia JC, Millette CF, O’Brien DA, Bhatnagar YM, Dym M. 1977. Spermatogonial cells of the prepuberal mouse. Isolation and morphological characterization. J Cell Biol 74: 68–85. Bowles J, Knight-D, Smith C, Wilkinson D, Richman J, Mamiya S, Yashiro K, Chawengsaksophak K, Wilson MJ, Rossant J et al. 2006. Retinoid signaling determines germ cell fate in mice. Science 312: 596–600. Bowles J, Feng CW, Spiller C, Davidson TL, Jackson A, Koopman P. 2010. FGF9 suppresses meiosis and promotes male germ cell fate in mice. Dev Cell 19: 440–449. Bowles J, Feng CW, Miles K, Ineson J, Spiller C, Koopman P. 2016. ALDH1A1 provides a source of meiosis-inducing retinoic acid in mouse fetal ovaries. Nat Commun 7: 10845. Brennan J, Capel B. 2004. One tissue, two fates: Molecular genetic events that underlie testis versus ovary development. Nat Rev Genet 5: 509–521.

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