Oocyte Quality Control: Causes, Mechanisms, and Consequences

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Oocyte quality and number are key determinants of reproductive life span and success. These variables are shaped in part by the elimination of oocytes that experience problems during the early stages of meiosis. Meiotic prophase-I marks an extended period of genome vulnerability in which epigenetic reprogramming unleashes retroelements and hundreds of DNA double-strand breaks (DSBs) are inflicted to initiate the programmed recombination required for accurate chromosome segregation at the first meiotic division. Expression of LINE-1 retroelements perturbs several aspects of meiotic prophase and is associated with oocyte death during the early stages of meiotic prophase I. Defects in chromosome synapsis and recombination also trigger oocyte loss, but typically at a later stage, as cells transition into quiescence and form primordial follicles. Interrelated pathways that signal defects in DSB repair and chromosome synapsis mediate this late oocyte attrition. Here, I review our current understanding of early and late oocyte attrition based on studies in mouse and describe how these processes appear to be both distinct and overlapping and how they help balance the quality and size of oocyte reserves to maximize fecundity.

The common fate of a mammalian oocyte is an early death, with ~80% of human oocytes being lost before or shortly after birth (Fig. 1; Baker 1963; Kurilo 1981). The size and quality of the surviving pool of primordial follicles are important determinants of female fecundity and reproductive life span (Broekmans et al. 2007). Oogenesis begins during fetal development following the establishment of primordial germ cells in the undifferentiated gonads. The ensuing oogonia expand by mitosis such that very large numbers of primary oocytes enter meiosis, approximately six to seven million in humans. However, by birth, oocyte numbers have already crashed down to approximately one to two million and at the onset of puberty only approximately 200,000 to 300,000 remain (Fig. 1; Block 1953; Baker 1963; Forabosco et al. 1991). This finite ovarian reserve (Gleicher et al. 2011) comprises nongrowing primordial follicles arrested in the dictyate stage of meiosis, before the first meiotic division. Ovarian reserves are continually depleted through ongoing recruitment of primordial follicles to the growing follicle pool, and cyclical follicle-stimulating hormone (FSH)-dependent activation of cohorts of antral follicles to reenter meiosis (McGee and Hsueh 2000). For both recruitment and activation phases, the default outcome is again cell death through an apoptotic process termed atresia (Kaipia and Hsueh 1997), with only the dominant ovulatory follicle(s) completing the meiosis I division. Thus, only approximately 350 oocytes will escape cell death and be ovulated during the human reproductive life span, corresponding to <0.006% of the 6–7 million potential eggs initially formed during fetal development. Follicle depletion is associated with reduced production of the hormones estrogen and inhibin by the ovary, disrupting the hypothalamic–pituitary–gonadal (HPG) hormonal axis and eventually leading to menopause (Honour 2018). Thus, follicle depletion serves as a timer for the major landmarks of female reproduction (Broekmans et al. 2007). Moreover, genetic and environmental factors that influence the size of initial ovarian reserves and rates of follicle recruitment can significantly alter reproductive life span (Gleicher et al. 2011; Tilly and Sinclair 2013; Aiken et al. 2015; Findlay et al. 2015; Grive and Freiman 2015; Laven 2015, 2016; Laven et al. 2016).

The causes, mechanisms, and roles of the massive oocyte culling that occurs during fetal and early postnatal life have been the subject of much study and debate (Tilly 2001; Hartshorne et al. 2009). However, cumulative evidence from studies in mouse indicates that much of the oocyte death during this period is the result of quality control processes that eliminate potentially defective cells and nurture the cells that will survive (Di Giacomo et al. 2005; Lei and Spradling 2013, 2016; Malki et al. 2014). Two major stages of oocyte loss can be inferred in mouse (Fig. 2). Early oocyte attrition (EOA) occurs between embryonic days E15.5 and E8.5 and causes the loss of ~50% of all oocytes (Malki et al. 2014). Late oocyte attrition (LOA) follows in the early postnatal period as cells transition into quiescence to establish the pool of

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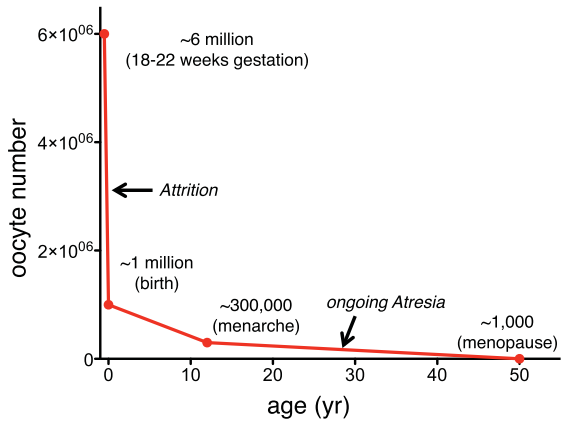

Figure 1. Oocyte decline in human fetal ovaries. Approximately 80% of the oocytes that enter meiosis are culled by birth and less than half of those remaining survive through puberty. Through ongoing atresia, following recruitment and hormonal activation, oocyte numbers continually decline until the hypothalamic–pituitary–gonadal (HPG) hormonal axis can no longer be supported and menopause ensues.

resting follicles (Di Giacomo et al. 2005; Klinger et al. 2015; Qiao et al. 2018). Not only are these two stages of oocyte death temporally distinct, but they also appear to have different underlying causes. In mouse, EOA is correlated with the activation of LINE-1 transposons (Malki et al. 2014), whereas LOA appears to be a response to errors in meiotic prophase I (Fig. 2; Di Giacomo et al. 2005; Bolcun-Filas et al. 2014; Rinaldi et al. 2017a). However, oocyte attrition is also generally associated with developmental processes in the nascent ovary (Pepling and Spradling 1998; Lei and Spradling 2013, 2016). These processes begin with the formation of clonal cysts comprising approximately 30 primordial germ cells interconnected in a syncytium. Coincident with meiotic prophase I, cysts then break down and reorganize into nonclonal nests. Concurrently, interconnected cells are differentiating into oocytes targeted for survival and nurse-like cells that nurture the developing oocytes by donating organelles and cytoplasm (Lei and Spradling 2016). Analogous to the well-characterized nurse cells of the *Drosophila* ovary (Jenkins et al. 2013), this self-sacrifice of mouse nurse-like cells concludes in programmed cell death prior to follicle formation.

DEREPRESSION OF LINE-1 ELEMENTS AND EARLY OOCYTE ATTRITION

Long interspersed element 1, LINE-1 (L1), is the only autonomous retroelement that remains active in the human genome (Cordaux and Batzer 2009). It belongs to the non–

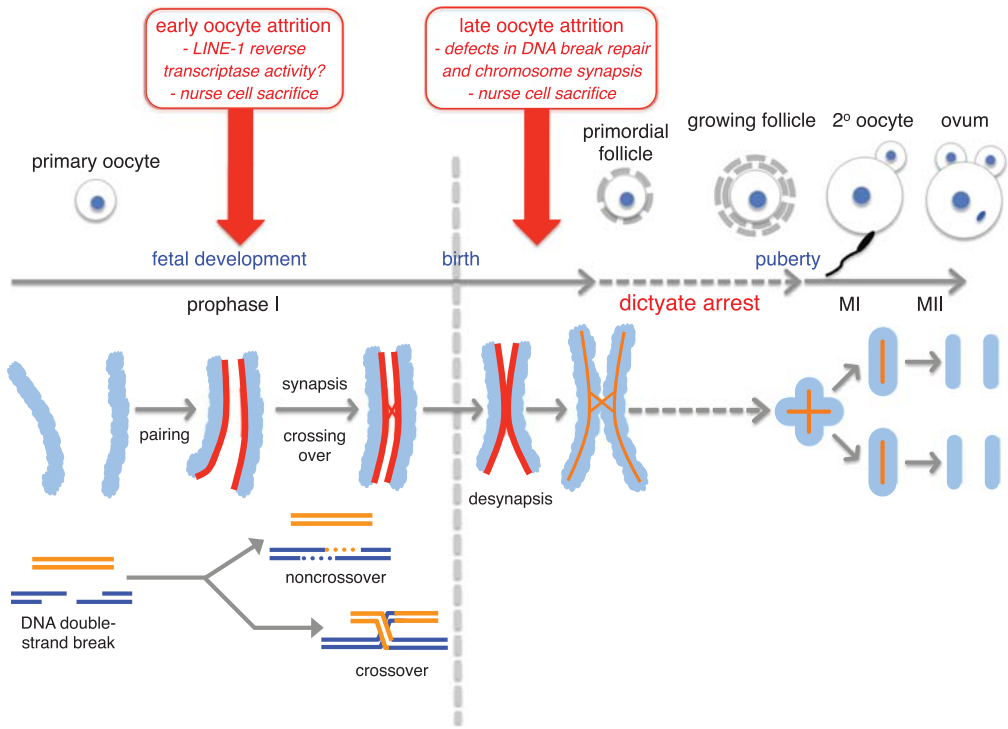

Figure 2. Time line of oocyte meiosis in mouse highlighting nuclear (*top*), chromosomal (*middle*), and recombination (*bottom*) landmarks. Pairing, synapsis, and crossing-over between homologous chromosomes are facilitated by programmed homologous recombination initiated by hundreds of DNA double-strand breaks. Early oocyte attrition (EOA) occurs during early meiotic prophase-I and is correlated with LINE-1 activity. Late oocyte attrition (LOA) occurs after homologs desynapse and oocytes begin to transition into dictyate arrest. LOA can be triggered by unrepaired DNA breaks and transcriptional silencing induced at sites where synapsis has failed. Meiosis only resumes in oocytes that have been recruited for growth and activated by follicle-stimulating hormone (FSH). Only the dominant ovulatory follicle will complete the meiosis-I division before arresting in metaphase II until fertilization.

long terminal repeat retrotransposon class of transposable elements that also includes nonautonomous *Alu* and SVA elements and makes up around one-third of the human genome. L1 alone accounts for ∼17% of the human genome—more than 500,000 copies—but less than 100 copies are thought to remain functional (Brouha et al. 2003). These full-length L1 elements are ∼6 kb in length and comprise a 5′ UTR containing an RNA Pol II promoter, two open reading frames (ORFs), and a 3′ UTR that terminates with a poly(A) tail and contains a polyadenylation signal (Babushok and Kazazian 2007). The ORFs encode activities required for transposition: ORF1 is a nucleic acid chaperone, and ORF2 has endonuclease and reverse transcriptase activities.

L1 transcripts are exported from the nucleus and translated. The ORF1 and ORF2 proteins bind with a strong *cis* bias to the mRNA that encoded them, assembling into ribonucleoprotein (RNP) complexes that reenter the nucleus to mediate transposition. In a process termed target-site-primed reverse transcription, the ORF2 endonuclease nicks the target-site DNA at the consensus sequence (5′-TTTT/AA-3′). The resulting 5′-TTTT-3′-OH strand anneals to the poly(A)-tail of the associated L1 mRNA to prime the ORF2 reverse transcriptase (Cost et al. 2002). Nicking of the second DNA strand of the target DNA is thought to provide a primer for second strand synthesis to complete L1 integration. Although the ORF1 and ORF2 proteins tend to bind to their cognate L1 mRNA, transactivation of abundant *Alu* and SVA nonautonomous retroelements and other cellular mRNAs can occur (Esnault et al. 2000; Dewannieux et al. 2003; Ostertag et al. 2003; Beck et al. 2011).

Consequences of LINE-1 Activity

The activities of L1 and other transposable elements have had profound effects on cellular function, genome stability, and evolution. *Cis* and *trans* activity of L1 is a major source of insertional mutagenesis, both somatic and germline, and is implicated in numerous diseases including cancer (Cordaux and Batzer 2009). Over the course of human evolution, insertion of more than 8000 human processed pseudogenes and more than a million nonautonomous retroelements are attributed to L1 activity (Zhang et al. 2003; Vinckenbosch et al. 2006).

ORF2 endonuclease activity can serve as a source of genome instability by generating DNA double-strand breaks (DSBs) uncoupled from successful transposition (Belgnaoui et al. 2006; Gasior et al. 2006). L1 insertion can also bypass the need for the ORF2 endonuclease by hijacking endogenous DSBs (Morrish et al. 2002). Although this endonuclease-independent insertion may facilitate DSB repair, it also has the potential to interfere with endogenous repair pathways as well as causing potentially deleterious insertions. Both endonuclease-dependent and -independent insertion has been associated with local DNA rearrangements including deletions, duplications, inversions, and translocations (Belancio et al. 2008). L1 itself is a source of unstable microsatellite sequences and insertion generates additional poly(A) microsatellites de novo (Grandi and An 2013).

L1 insertion also influences transcription, both positively and negatively. An antisense promoter in the 5′ UTR can drive transcription of flanking cellular genes and appears to be broadly used in tissue-specific gene regulation (Nigumann et al. 2002). Oppositely, as targets of heterochromatin formation, L1 elements can locally silence gene expression (Slotkin and Martienssen 2007). Intragenic L1 elements can impede transcription (Han et al. 2004) and serve as sense and antisense promoters (Faulkner et al. 2009), alternative splice junctions (Belancio et al. 2006, 2008), and termination sites (Lee et al. 2008). More generally, L1 expression is associated with cellular responses such as activation of the innate-immune response (Crow 2010; Goodier et al. 2015) and the DNA-damage response (Belgnaoui et al. 2006) and their downstream effects such as cell cycle arrest, senescence, and apoptosis (Belgnaoui et al. 2006; Gasior et al. 2006; Wallace et al. 2008).

Multiple Layers of LINE-1 Repression

Given the potentially catastrophic effects of L1 activity, cells have evolved defense mechanisms to interfere with each step of its life cycle (Goodier 2016; Pizarro and Cristofari 2016; Liu et al. 2018). At the level of initiation, the L1 promoter is suppressed by CpG DNA methylation (Hata and Sakaki 1997; Bourc'his and Bestor 2004) and the 5′ UTR has come under the control of host transcription factors (Tchenio et al. 2000; Yang et al. 2003; Athanikar et al. 2004). Consistently, L1 transcriptional repression also involves a variety of histone modifications (Castañeda et al. 2011) including de novo H3 Lys9 trimethylation by the "human silencing hub" complex (Liu et al. 2018). Involvement of the SMC complex condensin in restricting retotransposons, including L1, also indicates a repressive role for higher-order chromatin structure (Schuster et al. 2013; Ward et al. 2017). piwi-interacting small RNA (piRNA) biogenesis is a particularly important mechanism for silencing transposable elements, including L1, in the germline and is also required for their de novo remethylation (Aravin et al. 2008; Kuramochi-Miyagawa et al. 2008; Castañeda et al. 2011). Posttranscriptionally, RNA interference, degradation, premature polyadenylation, and editing can attenuate LINE-1 activity (Perepelitsa-Belancio and Deininger 2003; Yang and Kazazian 2006; Schumann 2007; Zhang et al. 2014; Hamdorf et al. 2015; Orecchini et al. 2018).

At the posttranslational level, the ubiquitin-proteasome system targets the L1ORF1 protein via TEX19.1 and the E3-ligase UBR2 (MacLennan et al. 2017). A DNA exonuclease, TREX1, is thought to destroy the reverse transcribed cDNA strand of L1 (Stetson et al. 2008). TREX1 also has an exonuclease-independent function that reduces L1 ORF1 protein levels (Li et al. 2017). SAMHD1, a dNTP triphosphohydrolase, is inferred to impede nuclear import of L1 RNPs by enhancing their sequestration in stress granules (Hu et al. 2015), cytoplasmic structures that accumulate untranslated mRNAs when cells

are stressed (Sheinberger and Shav-Tal 2017). TREX1, SAMHD1, and several other repressors of L1 activity are downstream components of the interferon (IFN) response pathway (Goodier et al. 2015). Involvement of these innate restriction factors implies that L1 induces an innate immune response, perhaps through detection of L1 RNA: DNA hybrids or L1 encoded proteins (Crow 2010; Rigby et al. 2014). Host DNA repair factors have also been implicated in suppression of late steps of L1 integration (Pizarro and Cristofari 2016; Servant et al. 2017; Liu et al. 2018). Notably, the ERCC1-XPF endonuclease has been proposed to remove the branched intermediates of L1ORF2 reverse transcription (Gasior et al. 2008).

Epigenetic Reprogramming Is Coincident with Meiosis in Females

As primordial germ cells migrate, DNA methylation (5 mC) is removed throughout the genome as a primary step in the global epigenetic reprogramming required for gametogenesis and ensuing embryogenesis (Seisenberger et al. 2012; Messerschmidt et al. 2014). In oocytes, the demethylated state is sustained throughout fetal development and only restored after birth. As such, meiotic prophase-I in females occurs in the context of a globally hypomethylated genome. In contrast, males restore DNA methylation at the prospermatogonial stage during the perinatal period, long before meiosis initiates. Hypomethylation causes a burst of L1 expression. In mouse, although LINE-1 RNA is detectable in primordial germ cells, it may not be translated until oocytes are in meiotic prophase (Trelogan and Martin 1995; Seisenberger et al. 2012). Also, intriguingly, although L1 expression peaks during meiosis, retrotransposition appears to occur mainly during embryogenesis and may be mediated by L1 RNA that was transmitted via the gametes (Kano et al. 2009).

Along with DNA demethylation, the global changes in chromatin organization and transcriptional reprogramming that characterize meiotic prophase may render primary oocytes uniquely disposed to high levels of L1 expression. Early meiotic prophase is characterized by interactions between pairs of homologous chromosomes (homologs) and their physical connection by crossovers (Fig. 2; Hunter 2015). Following S phase, meiotic chromosomes organize into stereotypic structures comprising linear arrays of chromatin loops, the bases of which organize into cores or axes that defines the interfaces for homologous interactions (Zickler and Kleckner 1999, 2015). Importantly, this global, semicompact loop-axis organization supersedes the higher-order structures (chromatin loops, topologically associating domains, and epigenetic compartments) that mediate transcriptional regulation in somatic cells (Dekker and Mirny 2016; Hansen et al. 2018). Other chromatin changes such as nucleosome composition and histone modifications, including those associated with meiotic recombination, could also enhance L1 activity during meiosis (Saitou et al. 2012; Ng et al. 2013; Székvölgyi et al. 2015; Izquierdo-Bouldstridge et al. 2017).

LINE-1 Derepression during Oogenesis Is Associated with Multiple Defects

The major events of meiotic prophase—homolog pairing, synapsis, and crossing-over—are mediated by programmed homologous recombination initiated by DNA breakage (Fig. 2; Lam and Keeney 2014; Hunter 2015). During the leptotene stage, SPO11 protein catalyzes DSB formation, inflicting on the order of 200–300 DNA DSBs per nucleus in mouse and human (Cole et al. 2012; Gruhn et al. 2013). Ensuing interhomolog DNA pairing and strand exchange bring chromosomes into close juxtaposition, enabling formation of synaptonemal complexes (SCs), densely packed transverse filaments that connect homologous chromosomes along their lengths (Zickler and Kleckner 1999). SCs form during zygotene and crossovers form in the context of fully synapsed SCs during the pachytene stage. Crossover formation is tightly regulated such that each pair of chromosomes becomes connected by at least one exchange, as required for accurate segregation at the meiosis-I division. Homologs then desynapse and cells enter diplotene. At this stage, oocytes then transition onto the protracted dictyate stage and become surrounded by a single layer of supporting granulosa cells to establish the reserve of primordial follicles (Fig. 2). After puberty, meiosis resumes in FSH-activated follicles and meiosis-I ensues in the dominant ovulatory cell.

L1ORF1 protein is readily detected in the nuclei of mouse fetal oocytes during early prophase stages, and striking cell-to-cell variation is observed implying stochastic variation in L1 activity (Malki et al. 2014). However, cytoplasmic transfer from syncytial nurse-like cells could help lower L1 activity in differentiating oocytes and contribute to the observed variation in L1ORF1 levels (Lei and Spradling 2016). Several lines of evidence point to a causal role for L1 in EOA and imply that oocytes with excessive L1 expression are targeted for killing (Malki et al. 2014): (i) EOA is enhanced when the piRNA pathway is defective; (ii) ORF1 protein levels correlate with oocyte survival; (iii) expression of an L1 transgene enhances EOA; and (iv) the nucleoside analog azidothymidine AZT, which presumptively inhibits of L1ORF2 reverse transcriptase activity (Jones et al. 2008; Dai et al. 2011), prevents EOA at normal times (between embryonic day E13.5 and E18.5), suggesting that a reverse transcriptase intermediate triggers EOA during this period (Fig. 3). However, oocyte death is not permanently rescued by AZT, and by 2 days postpartum (dpp), numbers drop to levels seen in untreated controls, suggesting that reverse transcriptase–independent activities of L1 can contribute to LOA (see below).

L1 expression during meiosis is associated with the formation of SPO11-independent DSBs (Soper et al. 2008; Carofiglio et al. 2013) and provokes a variety of prophase errors including persistent DNA damage, synapsis defects, reduced crossing-over, and elevated chromosome missegregation (Fig. 3; Malki et al. 2014). The DNA repair and synapsis defects are not relieved by AZT treatment consistent with the possibility that they result from

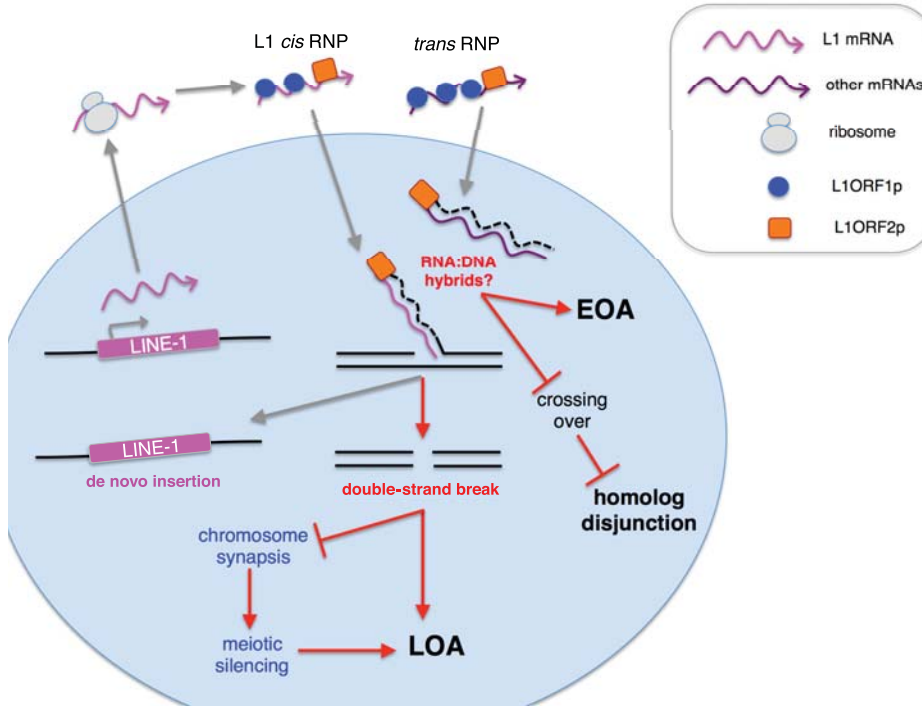

Figure 3. LINE-1 activities during early prophase-I perturb meiosis and may trigger early oocyte attrition (EOA) and late oocyte attrition (LOA). DNA demethylation leads to derepression of full-length LINE-1 (L1) elements during oocyte meiosis. L1ORF1 and ORF2 proteins are translated and assemble into RNP complexes, showing a string *cis* bias for the encoding L1 mRNA, but transactivation of non-L1 mRNAs can also occur. Target site nicking by the L1ORF2 enodonuclease primes the L1ORF2 reverse transcriptase to synthesize an RNA:DNA hybrid intermediate. Nicking of the other strand and second-strand synthesis leads to L1 integration. RNA:DNA hybrids trigger EOA and interfere with crossing-over, elevating the risk of chromosome missegregation. Aberrant L1 activity may also lead to double-strand break formation and defective synapsis leading to LOA.

DNA damage inflicted by the L1ORF2 endonuclease. Intriguingly, AZT does suppress the crossover deficit associated with excessive L1 expression. In fact, wild-type oocytes make ~10% more crossovers when treated with AZT, indicating that L1ORF2 reverse transcriptase activity somehow interferes with the process of meiotic crossing-over (Malki et al. 2014).

Notably, meiosis in human females shows a high degree of heterogeneity relative to males, with frequent synaptic errors and highly variable crossover numbers (Hassold and Hunt 2001; Lenzi et al. 2005; Tease et al. 2006; Hassold et al. 2007; Hunt and Hassold 2008; Gruhn et al. 2013). Moreover, crossover patterning in females is suboptimal, producing outcomes that are at risk for chromosome missegregation, such as nonexchange chromosomes and chromosomes with a single crossover located close to a centromere or telomere (Cheng et al. 2009; Nagaoka et al. 2012; Herbert et al. 2015). A key factor underlying this defect is inefficient maturation of crossovers, which is inferred to occur with only ~75% efficiency in females (Wang et al. 2017). The association between L1 activity, increased synaptic errors, and decreased crossover formation in mouse (Malki et al. 2014) raises the possibility that L1 and/or other transposable elements contribute to the inefficient crossover maturation and elevated aneuploidy seen in human females.

In sum, analysis in mouse suggests that L1 activity induces EOA via a reverse transcriptase–dependent intermediate, although direct evidence for this inference remains an important goal (Fig. 3; Malki et al. 2014). One possibility is that L1-catalyzed RNA:DNA hybrids trigger an innate immune response. Alternatively, L1-mediated RNA:DNA hybrids may interfere with protein translation as observed in human platelets (Schwertz et al. 2018). Also, whether EOA occurs via canonical apoptotic pathways and its relationship to nurse cell sacrifice remain unclear.

By inflicting additional DNA damage on top of the hundreds of programmed DSBs, L1 activity could push damage signaling above a threshold not normally reached during early prophase and sufficient to induce cell death. However, the AZT sensitivity of EOA suggests that L1-induced DNA damage is not the cause of early oocyte death. In fact, the early prophase period of oocyte meiosis appears to be relatively insensitive to DNA damage–induced apoptosis. For example, recombination mutants that fail to repair DSBs, even those with elevated DSB levels such as $Atm^{-/-}$, induce oocyte culling at the pre-follicle stage (Di Giacomo et al. 2005), not during early prophase as seen for L1-associated EOA. Also, zygotene/pachytene-stage oocytes are relatively resistant to irradiation-induced apoptosis compared to those in diplotene (Hanoux et al. 2007; Kim and Suh 2014; Hunter N, unpubl. data). It makes sense that oocytes should suppress DNA damage–induced apoptosis pathways during these stages while hundreds of programmed meiotic

DSBs are processed. Consistently, oocyte culling in AZT-treated fetal ovaries now occurs in the early postnatal period (Fig. 3; Malki et al. 2014), during the diplotene-to-dictyate transition when programmed DSBs have mostly been repaired and cells become sensitive to DNA damage–induced apoptosis (Hanoux et al. 2007). This observation raises the possibility that L1-induced DNA lesions are not efficiently repaired by the meiotic recombination machinery, or that some other AZT-independent activity of L1 interferes with meiotic DSB repair.

Advantages of EOA

In early meiotic prophase, the high background of ongoing DSB repair may make it unfeasible for oocytes to monitor L1 activity based on L1-inflicted DNA damage. The ability of oocytes to detect excessive L1 activity independently of DNA damage overcomes this challenge, enabling selective early culling of oocytes with high L1 activity. Despite the associated payoff of massive oocyte loss, follicles selected for low L1 activity likely experience a several-fold advantage because they have (i) a lower probability to experience de novo insertion; (ii) fewer SPO11-independent DSBs that could lead to LOA and other defects (see below) (Carofiglio et al. 2013; Rinaldi et al. 2017a); (iii) fewer synapsis defects and associated meiotic silencing, which can also cause oocyte death (see below) (Royo et al. 2013); (iv) higher crossover levels and thus a lower chance of homolog missegregation at meiosis I and aneuploidy in the resulting zygote; (v) a lower probability to transmit L1 RNA to the zygote and inflict insertion during embryogenesis (Kano et al. 2009); and (vi) possibly, a higher capacity to silence L1 postnatally and in the next generation. It should be noted that EOA occurs around the time of cytoplasmic transfer between interconnected sister oocytes and the breakdown of cysts (Lei and Spradling 2013, 2016). The relationship between the level of L1 activity and the differentiation of oocytes that will survive and the nurse cells that will nurture them and then die is unknown and an important question for the future.

Potential Advantages of L1 Derepression in the Germline

It is also speculated that DNA demethylation and the resulting derepression of L1 elements play positive roles for germ cell differentiation, meiosis, and genotype diversity during development (Kano et al. 2009; van der Heijden and Bortvin 2009; Castañeda et al. 2011; Chuma 2014; Malki et al. 2014). For example, transcriptional regulation mediated by insertionally inactive L1 elements could be important for the meiotic program. The sheer abundance of L1 elements and their enriched association with chromosome axes and SCs (Pearlman et al. 1992; Hernández-Hernández et al. 2008) raises the possibility they help organize meiotic chromosome structure and facilitate homolog recognition and pairing (van der Heijden and Bortvin 2009).

DNA DAMAGE AND SYNAPSIS DEFECTS TRIGGER LOA

LOA was originally delineated in meiotic mutants defective for DSB repair and/or homolog synapsis (Di Giacomo et al. 2005). Such mutants are typically born with large oocyte pools (at least 50% of wild type), which rapidly decline in the first few days after birth, as cells transition into the dictyate stage, arrest, and establish the reserve of primordial follicles (Di Giacomo et al. 2005; Kogo et al. 2012a; Wojtasz et al. 2012; Kerr et al. 2013; Bolcun-Filas et al. 2014; Malki et al. 2014; Cloutier et al. 2015; Rinaldi et al. 2017a; Hunter N, unpubl. data). The severity of LOA can vary between mutants. For example, in *Spo11* mutants, which lack programmed DSBs, chromosome synapsis is severely defective, but ∼15% of oocytes survive LOA. However, this small reserve is rapidly depleted because of recruitment, ensuing atresia, and ovulation (Di Giacomo et al. 2005). In contrast, in mutants such as *Dmc1, Msh4*, *Msh5, Atm, Trip13*, and *Mcmdc2*, recombination is initiated, but DSB repair and/or synapsis are defective, and wholesale culling of oocytes is observed within 2–5 d of birth (Di Giacomo et al. 2005; Li and Schimenti 2007; Finsterbusch et al. 2016; McNairn et al. 2017; Hunter N, unpubl. data). *Spo11* mutation is epistatic to DSB repair mutants with respect to the severity of oocyte loss, indicating that defective repair of SPO11-dependent DSBs is a potent trigger of LOA.

A Single DNA Damage Response Pathway May Trigger LOA Caused by Meiotic Defects

The observations described above led to the concept of two distinct checkpoint processes that can lead to LOA, one that monitors DSB repair and another that responds to defective synapsis (Di Giacomo et al. 2005; Wojtasz et al. 2012; Bolcun-Filas et al. 2014; Cloutier et al. 2015). However, more recent studies have revealed the existence of a significant population of SPO11-independent DSBs that can also trigger oocyte death via the DNA damage response (Carofiglio et al. 2013; Rinaldi et al. 2017a). This class of DSBs is highly variable in number, mirroring the variable expression of the L1ORF1 protein and consistent with the idea that a possible source of SPO11-independent DSBs is DNA cleavage initiated by the L1ORF2 endonuclease (Malki et al. 2014). Thus, a single pathway that signals persistent DNA breaks, regardless of their cause, may account for the majority of LOA (Rinaldi et al. 2017a). This meiotic DNA damage response pathway is mediated by a chromosome axis-based, kinase-signaling cascade whose key components include the proximal kinase ATR and the effector kinase CHK2 (Fig. 4; Bolcun-Filas et al. 2014; Subramanian and Hochwagen 2014; Rinaldi et al. 2017a). CHK2 activates the apoptotic regulators p53 and an isoform of p63 (a p53 paralog) called TAp63 (the Trans-Activation isoform), which appear to trigger apoptosis through canonical pathways (Morita et al. 1999; Kerr et al. 2012; Bolcun-Filas et al. 2014; Klinger et al. 2015; Omari et al. 2015). TAp63 is first expressed in late pachytene and diplotene oocytes and re-

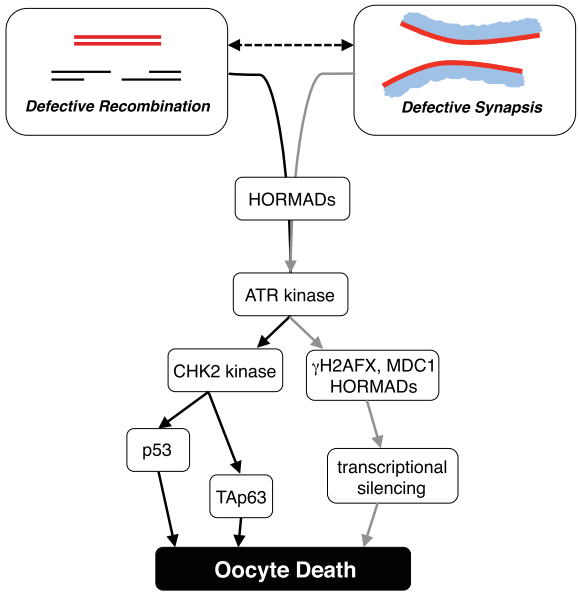

Figure 4. Meiotic DNA damage response and transcriptional silencing pathways. Double-strand breaks and defective synapsis are signaled via the HORMADs and the ATR kinase. ATR activates the effector kinase CHK2 to induce apoptosis via p53 and TAp63. ATR also mediates transcriptional silencing by nucleating and amplifying H2AFX phosphorylation in conjunction with MCD1 and the HORMAD proteins. The dashed line indicates the interdependence between defective recombination and defective chromosome synapsis.

mains constitutively expressed in resting follicles conferring exquisite sensitivity to DNA damage (Suh et al. 2006; Livera et al. 2008; Bolcun-Filas et al. 2014; Kim and Suh 2014). p53 may be the primary mediator of apoptosis during the diplotene-to-dictyate transition, with TAp63 largely superseding this function in quiescent oocytes. However, a more complex regulatory relationship between p53 and TAp63 is also suggested (Bolcun-Filas et al. 2014).

A key observation implicating the meiotic DNA damage response in LOA is the striking rescue of oocyte death and infertility in *Trip13* mutant females by *Chk2* mutation (Bolcun-Filas et al. 2014). However, rescue is incomplete, suggesting that other kinases may partially substitute for CHK2 function, especially when residual DSB levels are high; candidates include CHK1, DNA-PK, or direct signaling by ATR or the related PI3K-like kinase, ATM. Notably, the efficiency of oocyte rescue by *Chk2* mutation negatively correlates with the number of residual DSBs present in different mutant backgrounds and/or as a result of ionizing irradiation (Rinaldi et al. 2017a). These observations point to a damage-threshold model for oocyte elimination in which oocytes with at least 10 residual DSBs are culled.

Meiosis-Specific HORMA-Domain Proteins Facilitate LOA

Other key players in LOA include HORMAD1 and HORMAD2, two members of a conserved family of meiosis-specific HORMA (Hop1, Rev7, and Mad2)-domain proteins (HORMADs) (Daniel et al. 2011; Kogo et al. 2012b; Shin et al. 2013). HORMADs play central roles in regulating the major events of meiotic prophase-I, including meiotic DSB formation, homolog pairing, and synapsis, checkpoint signaling, transcriptional silencing (described below), and biasing meiotic recombination to occur between homologs by impeding intersister DSB repair (Carballo et al. 2008; Shin et al. 2010; Royo et al. 2013; Vader and Musacchio 2014; Stanzione et al. 2016; Rinaldi et al. 2017a). As discussed below, the latter two functions appear to be central to the role of the HORMADs in promoting LOA (Rinaldi et al. 2017a; Hunter N, unpubl. results).

HORMADs initially associate with unsynapsed chromosome axes during leptotene but are locally depleted at regions of synapsis during zygotene and excluded from fully synapsed chromosomes during pachytene (Fig. 5; Wojtasz et al. 2009; Fukuda et al. 2010). By analogy to the orthologous budding yeast Hop1 protein (Niu et al. 2005; Carballo et al. 2008; Goldfarb and Lichten 2010; Lao and Hunter 2010), and supported by indirect evidence, mammalian HORMADs are inferred to function in early meiotic prophase to impede DSB repair between sister chromatids and thereby promote interhomolog interactions (Fig. 6; Daniel et al. 2011; Kogo et al. 2012b; Shin et al. 2013; Rinaldi et al. 2017a). HORMAD depletion is coupled to synapsis via the AAA+ ATPase, TRIP13 (a.k.a. PCH2 in nonmammalian species) (Li and Schimenti 2007; Wojtasz et al. 2009; Roig et al. 2010), which likely disrupts protein–protein interactions at the homolog axis, including the ability of HORMADs to oligomerize (Ye et al. 2017; West et al. 2018). In asynaptic mutants and when TRIP13 function is compromised, HORMADs remain associated with the homolog axes and impede DSB repair (Fukuda et al. 2010; Shin et al. 2010; Daniel et al. 2011; Shin et al. 2013; Rinaldi et al. 2017a). Thus, oocyte culling in mutants defective for homolog synapsis and DSB repair can be suppressed to varying degrees by mutation of *Hormad1* or *Hormad2* (Daniel et al. 2011; Kogo et al. 2012b; Shin et al. 2013; Rinaldi et al. 2017a). However, the mode of suppression by *Hormad1/2* mutation appears to be distinct from that of *Chk2* and *p53/TAp63* mutations.

The high levels of DNA damage that persist in dictyate-stage oocytes from *Chk2 Trip13* double mutants are consistent with CHK2 acting as a bona fide checkpoint protein, allowing cells to progress but not affecting the efficiency of DSB repair (Bolcun-Filas et al. 2014). However, this damage is subsequently repaired, oocytes remain viable, and *Chk2 Trip13* mutants are fertile. This contrasts the effects of *Hormad1/2* mutation, which decrease DSB levels and accelerate DSB repair (Fukuda et al. 2010; Shin et al. 2010; Daniel et al. 2011; Shin et al. 2013; Rinaldi et al. 2017a). HORMAD1 has a twofold effect on DSB levels, facilitating the formation of SPO11-dependent DSB and impeding their repair until homologs have synapsed. HORMAD2 shares only the latter function and its localization to unsynapsed chromosome axes requires HORMAD1. Thus, absence of HORMADs is inferred to reduce DSB load (*Hormad1* mutation) and enhance DSB-repair capacity (*Hormad1* and *Hormad2* mutations) by allowing recombination between sister chromatids such that damage signaling is diminished

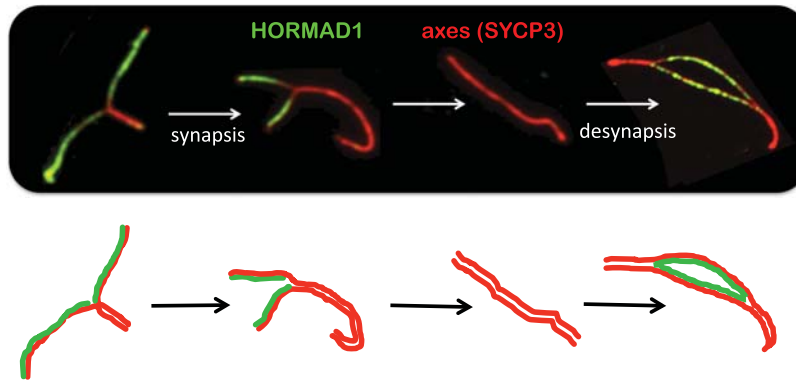

Figure 5. Dynamic localization of HORMADs during meiotic prophase I. Images show mouse oocyte chromosomes immunostained for the axes marker SYCP3 and HORMAD1.

(Daniel et al. 2011; Kogo et al. 2012b; Shin et al. 2013; Rinaldi et al. 2017a). Put another way, by blocking the repair of DSBs between sister chromatids, HORMADs help maintain damage signaling at levels required to trigger LOA. These observations indicate that CHK2 and the HORMAD proteins collaborate to signal defective interhomolog interactions and trigger LOA (Fig. 4).

Meiotic Silencing Is Mediated by HORMADs and Components of the DNA Damage Response

Chromosome asynapsis in *Spo11* mutants, and in a variety of other contexts that cause partial asynapsis, also triggers a distinct response termed meiotic silencing that results in transcriptional inactivation and is inferred to contribute to oocyte death by silencing genes required for survival (Mahadevaiah et al. 2008; Burgoyne et al. 2009; Garcia-Cruz et al. 2009; Kouznetsova et al. 2009; Blanco-Rodríguez 2012; Royo et al. 2013; Cloutier et al. 2015; Turner 2015). Sensing of asynapsis involves homolog axis components, the HORMAD proteins, and BRCA1. ATR and its activators ATRIP and TOPBP1 are then recruited to establish a reversible asynapsis signaling step that involves phosphorylation of the HORMADs (Fukuda et al. 2012; Royo et al. 2013). Silencing initiates via the ATR-catalyzed phosphorylation the histone variant H2AFX. This γH2AFX mark spreads throughout the unsynapsed region via a signal-amplification step mediated by ATR, HORMADs, and the γH2AFX binding factor

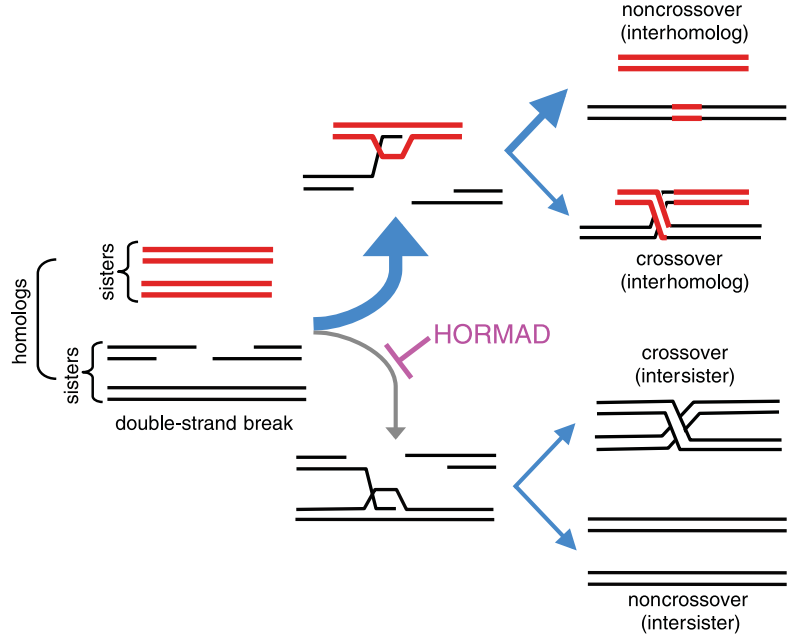

Figure 6. HORMADs bias recombination to occur between homologs rather than sister chromatids. Meiotic recombination must occur between homologs to achieve pairing, synapsis, and crossing-over. HORMADs promote interhomolog interactions through unknown mechanisms. One model posits that HORMADs create a barrier to intersister recombination (Hollingsworth 2010). Alternatively, HORMADs may prevent recombination from progressing beyond the initial nascent DNA strand-exchange step and couple progression to homolog synapsis (Goldfarb and Lichten 2010; Lao and Hunter 2010).

MDC1 (Ichijima et al. 2011; Kogo et al. 2012a). Ensuing heterochromatinization results in exclusion of RNA Pol II. Persistent DSBs within unsynapsed regions, both SPO11-dependent and independent, are thought to serve as initiation sites for meiotic silencing (Carofiglio et al. 2013; ElInati et al. 2017). However, the enrichment of DSB markers observed within silenced regions is also likely to reflect the inhibitory role of HORMADs on DSB repair.

Physiological LOA and the Role of HORMADs

LOA was defined and is typically studied in a variety of pathological conditions that cause severe defects in DSB repair and/or synapsis and wholesale oocyte death. In these settings, initial association of HORMADs persists and promotes oocyte death by impeding DSB repair between sister chromatids (Rinaldi et al. 2017a). In contrast, in a physiological setting, DSBs engage in interhomolog interactions, synapsis generally occurs efficiently, and HORMADs dissociate, presumably enabling recombination to progress. HORMADs then reassociate with desynapsing homolog axes during diplonema when DSBs have been repaired and crossing-over has occurred (Fig. 5; Fukuda et al. 2010; Niu et al. 2005; Wojtasz et al. 2009). The role of HORMADs at this stage is unknown, but a role in signaling recombination defects can be envisioned. Residual DSBs present in diplotene may be the result of failed interhomolog recombination or de novo DSB formation (e.g., via L1 activity or aberrant processing of recombination intermediates by nucleases). Reassociation of HORMADs at this stage could block intersister repair to robustly signal such defects and enable a quality control decision to be made. Nascent meiotic silencing events could also be reinforced by HORMAD reloading. Thus, the reassociation of HORMADs is potentially a key event that primes oocytes for LOA specifically during the diplotene-to-dictyate transition and may explain why oocytes become sensitive to irradiation-induced apoptosis at this time (Hanoux et al. 2007; Hunter N, unpubl. data). Other events that may potentiate LOA during this transition include the onset of expression and ability to activate apoptotic factors, including TAp63 and caspase 2 (Suh et al. 2006; Hanoux et al. 2007; Livera et al. 2008; Kim and Suh 2014). Consequently, oocytes that have experienced defects in synapsis and/or recombination are eliminated before they become established in the ovarian reserve as primordial follicles, thereby minimizing nonproductive ovulation and the risk of meiotic errors.

CONCLUSION

Oocyte attrition occurs in response to L1 activity, meiotic errors, and self-sacrifice of nurse-like cells. These processes are estimated to cull up to 80% of all oocytes in mouse (Malki et al. 2014; Hunter N, unpubl. data), mirroring the dramatic reduction in oocyte numbers seen in human females between ~20 wk gestation and birth (Findlay et al. 2015). Thus, oocyte attrition in human females is presumed to occur via equivalent quality control processes. However, significant differences likely exist. For example, numbers of full-length, potentially mobile L1 elements differ between mouse and human, with an estimated 11,000 in mouse compared to just 100 in human (Goodier and Kazazian 2008). As such, the L1 load may be lower in humans. An important goal for the future is to attain a clearer understanding of the causes and mechanisms of oocyte culling in humans or nonhuman primates.

Studies of EOA and LOA described here raise many burning questions. What are the relationships between L1 expression, meiotic errors, and oocyte/nurse cell differentiation? Is EOA triggered by L1-mediated RNA:DNA hybrids and, if so, what is the mechanism? Does EOA occur via apoptosis or an alternative cell death pathway? Why is L1 expression so variable between oocytes and what factors influence this ostensibly cell-autonomous phenomenon? What is the contribution of the various suppressive mechanisms to L1 inhibition during meiosis? Does the L1ORF2 reverse-transcriptase activity interfere with crossing-over, and, if so, does this activity contribute to the crossover maturation defect seen in human females? Is L1ORF2 endonuclease activity responsible for SPO11-independent DSBs? What are the contributions of L1-dependent and independent prophase defects to LOA and to meiotic errors in oocytes that escape EOA? Can genetic and environmental factors be identified that specifically influence EOA and LOA? Is L1-regulated gene expression important for mammalian meiosis? Does treatment with reverse-transcriptase inhibitors during pregnancy impact EOA in humans? Do kinases other than CHK2 contribute to physiological LOA? What is the contribution of meiotic silencing to physiological LOA? How do HORMAD proteins impede DSB repair? How does synapsis trigger HORMAD dissociation and how are they reloaded onto diplotene chromosomes? Finally, can ovarian reserves be enlarged to extend reproductive life span, or can they be rescued from death induced by cancer therapeutic agents without sacrificing oocyte quality, fertility, and ovary function (Livera et al. 2008; Kerr et al. 2012; Bolcun-Filas et al. 2014; Rinaldi et al. 2017b)?

Despite these oocyte quality control processes, errors in meiosis are the leading cause of pregnancy miscarriage and congenital disease in humans (Hassold et al. 2007; Nagaoka et al. 2012; Hunter 2015). By interfering with the normal processes of meiotic prophase, the activities of L1 and other retroelements represent one source of meiotic errors. L1 insertion also poses a tangible threat to genomic integrity: The rate of insertion is estimated at greater than one in eight births in laboratory mice (Richardson et al. 2017), and at approximately one in 20 births in the humans (Kazazian 1999). Thus, it remains important to better understand the causes of meiotic errors, the processes that work to minimize them, and the quality-control processes that selectively eliminate defective gametes and nurture and protect those that survive.

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