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Long Non-Coding RNA Regulation of Reproduction and Development

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SUMMARY

Noncoding RNAs (ncRNAs) have long been known to play vital roles in eukaryotic gene regulation. Studies conducted over a decade ago revealed that maturation of spliced, polyadenylated coding mRNA occurs by reactions involving small nuclear RNAs and small nucleolar RNAs; mRNA translation depends on activities mediated by transfer RNAs and ribosomal RNAs, subject to negative regulation by micro RNAs; transcriptional competence of sex chromosomes and some imprinted genes is regulated in *cis* by ncRNAs that vary by species; and both small-interfering RNAs and piwi-interacting RNAs bound to Argonaute-family proteins regulate post-translational modifications on chromatin and local gene expression states. More recently, gene-regulating noncoding RNAs have been identified, such as long intergenic and long noncoding RNAs (collectively referred to as lncRNAs)—a class totaling more than 100,000 transcripts in humans, which include some of the previously mentioned RNAs that regulate dosage compensation and imprinted gene expression. Here, we provide an overview of lncRNA activities, and then review the role of lncRNAs in processes vital to reproduction, such as germ cell specification, sex determination and gonadogenesis, sex hormone responses, meiosis, gametogenesis, placenta-tion, non-genetic inheritance, and pathologies affecting reproductive tissues. Results from many species are presented to illustrate the evolutionary conserved processes lncRNAs are involved in.

While long noncoding RNAs are recognized as important mediators of cellular fate and function, their roles in the reproductive processes are only now being elucidated.

DISCOVERY OF lncRNAs

Initial efforts to comprehensively characterize the mammalian transcriptome revealed an abundance of RNAs that vastly exceeded what was expected from the coding genome. Many RNAs were identified as non-coding and distinct from previously known non-coding species, including small nuclear RNA, small nucleolar RNA, transfer RNA, ribosomal RNA, and Argonaute-family-associated small RNAs (Rinn et al., 2003; Shiraki et al., 2003; Bertone et al., 2004; Kampa et al., 2004; Carninci et al., 2005; Cheng et al., 2005; Kapranov

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et al., 2005). A very limited number of novel, noncoding RNAs had previously been characterized: *Xist* (X-chromosome inactive-specific transcript), transcribed from the inactive X-chromosome in female mammals (Borsani et al., 1991; Brockdorff et al., 1991; Brown et al., 1991) to regulate X-inactivation processes in *cis* (Penny et al., 1996; Marahrens et al., 1997); the imprinted transcripts *H19* (Brannan et al., 1990; Sleutels et al., 2002), *Airn* (antisense of insulin-like growth factor two non-protein-coding RNA), which regulates *IGF2R* (insulin-like growth factor 2) expression in *cis* (Lyle et al., 2000; Sleutels et al., 2002), and *Kcnq1ot1* (voltage-gated KQT-like potassium channel, subfamily Q member one opposite strand/antisense transcript 1), which controls the expression of genes in the *KCNQ1* (voltage-gated potassium channel KQT-like subfamily Q) cluster (Lee et al., 1999; Fitzpatrick et al., 2002); and *SRA* (steroid receptor RNA activator), which enhances steroid hormone receptor responses (Lanz et al., 1999; Lanz et al., 2002). Other long non-coding RNAs (lncRNAs) remained uncharacterized, and it was not clear if they had a function or were simply byproducts of transcriptional noise. In 2007, 231 additional lncRNAs from the human *HOX* (homeobox) clusters were discovered. One of these, *HOTAIR (HOX* transcript antisense RNA), transcribed from the *HOXC* cluster, was shown to regulate coding transcripts from the *HOXD* cluster in *trans* (Rinn et al., 2007), thus revealing functions of lncRNAs beyond *cis*-regulation of the silent X-chromosome and a few imprinted genes.

The development of genome-wide chromatin-state maps using chromatin immunoprecipitation followed by sequencing (ChIP-seq) revealed that known genes actively transcribed by RNA polymerase II carried specific histone 3 (H3) lysine methylation marks: H3K4me3 (trimethylation on lysine 4) at the promoter and H3K36me3 (trimethylation on lysine 36) across the transcribed region. These so-called K4-K36 domains were also found at sites not previously annotated as genes, leading to the discovery of more than 1,600 intergenic, spliced non-coding transcripts; that these regions were evolutionary conserved, with many exhibiting coordinated regulation, argued against the notion that they represented transcriptional noise (Guttman et al., 2009). More than 100,000 lncRNAs have since been described for human alone (Volders et al., 2015a).

Accepted lncRNA properties, and practices for their identification and naming, are evolving, but lncRNAs generally exhibit the following features (Mattick and Rinn, 2015): (1) Lengths are >200nt with a median size of ~500nt—generally smaller than mRNAs, although some exceed 100 kb; 98% are spliced, with 80% having 2–4 exons, and the majority exist as a single isoform. (2) Most are polyadenylated (Poly[A]$^{+}$), although proportionately more non-polyadenylated (Poly[A]$^{-}$) forms exist than for mRNAs. (3) Many show nuclear enrichment and chromatin association, albeit cytoplasmic forms exist; coding potentials are low, as assayed by codon-substitution frequency scores (Guttman et al., 2009, 2010; Cabili et al., 2011), low ribosome association (Guttman et al., 2013), and an absence of open reading frames >100nt. (4) Cumulative abundance is lower than for mRNAs, and expression is more tissue-specific. (5) Purifying selection is common, but occurs with weaker constraints than coding transcripts, and in some cases, structure rather than sequence might be under selection (Derrien et al., 2012; Smith et al., 2013). Finally, (6) some InRNAs are circular in

structure (Hansen et al., 2013; Memczak et al., 2013; Zhang et al., 2013; Petkovic and Muller, 2015).

Databases established to describe lncRNAs include lncRNA Disease (Chen et al., 2013), LncRBase (Chakraborty et al., 2014), NONCODE(Xie et al., 2014), LNCipedia (Volders et al., 2015b), lncRNAdb (Quek et al., 2015), lncRNAWiki (Ma et al., 2015), and RNAcentral (RNAcentral-Consortium, 2015). As with many similar databases, these examples are likely to include mis-annotated mRNAs. For example, some RNAs classified as lncRNAs associate with ribosomes (Ingolia et al., 2009; Chew et al., 2013; Ruiz-Orera et al., 2014). Additionally, mass spectrometry analyses of peptides in two cell lines revealed 69 of 9,640 so-called lncRNAs encode detectable peptides (Banfai et al., 2012; Derrien et al., 2012), and similar proteomic analysis of rat male germ cells identified peptide sequences derived from previously annotated lncRNAs (Chocu et al., 2014). It is not clear if these peptides are functional or represent translational noise. Nevertheless, the presence of a functional reading frame within an RNA does not exclude a non-coding function; indeed, *SRY* (sex-determining region Y), *SRA*, and *oskar* RNAs have both coding and non-coding functions.

lncRNA FUNCTIONS

It is likely that lncRNA classifications will be refined and that subtypes of lncRNAs will be identified (Tuck and Tollervey, 2013). Currently, distinctions may be made according to lncRNA interacting partners; their functioning in *cis versus trans;* whether they influence chromatin modification or organizational states; if activities are cytoplasmic or nuclear; lncRNA structural properties; or the kinds of sequences from which they originate. One example of the latter classification is represented by enhancer RNAs (eRNAs), which are enhancer-derived noncoding RNAs (ncRNAs) that are typically less than 2 kb in length and operate in *cis* (De Santa et al., 2010; Kim et al., 2010). Regulate transcript elongation by interacting with mediator complex (Lai et al., 2013) and recruiting NELF (negative-elongation factor) from RNA polymerase II pause sites (Schaukowitch et al., 2014). They also affect chromatin looping associated with enhancer function (Pefanis et al., 2015) and can regulate nucleosome remodeling (Mousavi et al., 2013). Impaired enhancer RNA accumulation, on the other hand, attenuates enhancer activity (Lam et al., 2013). lncRNAs *ncRNA-a3, 4, 5*, and 7 have enhancer-like functions (Oram et al., 2010), whereas other enhancer RNAs, such as *LED* (Leveille et al., 2015) and *LUNAR1* (Trimarchi et al., 2014), augment enhancer activity in *trans* by mechanisms that include recruiting mediator and RNA Polymerase II to enhancers. Additional examples of this classification include extra-coding RNAs, which are Poly-$(A)^-$ RNAs that extend beyond the gene bodies of coding genes (Di Ruscio et al., 2013), and promoter-associated noncoding RNAs (Hamazaki et al., 2015). The following four sections provide details of various molecular processes controlled by lncRNAs (see also Table 1 and Fig. 1).

lncRNA Control of Histone States

A common theme with lncRNAs is their regulation of chromatin states, including histone and DNA modifications, nucleosome positioning, and placement of histone variants. The HOXD-silencing lncRNA *HOTAIR* binds poly-comb repressive complex 2 (PRC2), the major H3K27 histone methyltransferase-containing complex, and is needed for deposition of

H3K27me3 at *HOXD* (Rinn et al., 2007). The *RepA* (repeat A of *Xist*) lncRNA encoded within *Xist*, as well as *Xist* itself, also binds PRC2, and is necessary for initial deposition of H3K27me3 on the inactive X-chromosome (Zhao et al., 2008); conversely, maintenance of H3K27me3 on the inactive X-chromosome requires additional lncRNAs other than *Xist*. PRC2 seems to bind RNA promiscuously (Davidovich et al., 2013; Kaneko et al., 2013), yet some specificity exists according to immunoprecipitation experiments revealing that only 20% of ~3,300 lncRNAs queried were observed to bind PRC2 (Khalil et al., 2009); indeed, subsequent studies identified lncRNAs with a high affinity for PRC2 (Herzog et al., 2014; Davidovich et al., 2015). PRC2-interaction partners may further control specificity, as demonstrated by the partial regulation of *Xist*-PRC2 interaction by the nucleosome remodeler ATRX (alpha thalassemia/mental retardation syndrome, X-linked) (Sarma et al., 2014). PRC2 is a heterogeneous complex (Margueron and Reinberg, 2011), and various components were found to recruit it to lncRNAs: for example, lncRNA-PRC2 binding can occur through its component proteins JARID2 (Jumonji, AT Rich Interactive Domain 2) (Kaneko et al., 2014) or EZH2 (enhancer of Zeste 2 PRC2, subunit 2) (Zhao et al., 2008; Kaneko et al., 2014).

lncRNAs also bind a variety of writers, erasers, and readers of histone modifications, as well as other chromatin regulatory factors. In many cases, a given lncRNA can bind multiple chromatin regulatory factors (Guttman et al., 2011), although it is not yet known what the hierarchy of binding events is. Early findings reported that *Airn* (Nagano et al., 2008) and *Kcnq1ot1* (Pandey et al., 2008) bind the H3K9 methyltransferase EHMT2/G9A (euchromatic histone-lysine N-methyltransferase 2), with *Kcnq1ot1* also binding PRC2 (Pandey et al., 2008). By binding EHMT2/G9A, *Airn* directs this enzyme to the linked *SLC22A3* (solute carrier family 22, member 3) promoter to silence it (Sleutels et al., 2002; Nagano et al., 2008). *HOTTIP (HOXA* distal transcript antisense RNA) is brought into proximity to other sites in the *HOXA* cluster by looping; it promotes H3K4me3 deposition and gene transcription within the *HOXA* cluster through its recruitment of WRD5-containing KMT2A/MLL (histone-lysine N-methyltransferase 2A/mixed-lineage leukemia) complexes (Wang et al., 2011). *HOTAIR* binds PRC2, and the KDM1A/LSD1 (lysine-specific demethylase 1A) through distinct domains (Tsai et al., 2010). It is possible that these two factors are functionally coordinated, with KDM1A/LSD1 removing activating marks on H3K4 and PRC2 placing silencing marks on H3K27.

In addition to promoting or removing chromatin modifications, lncRNAs can restrict them to specific domains. A lncRNA from a pericentromeric region in *Schizosaccharo-myces pombe* limits the spreading of H3K9me3 and binding of HP1 (heterochromatin protein 1), a reader of H3K9me3, beyond the centromeric region (Keller et al., 2013)—centromeric transcripts are the sources of small interfering RNAs (siRNAs) required for local placement of H3K9me3 (Hall et al., 2002; Volpe et al., 2002). Furthermore, *Xist* binds SMART/SPEN (SMART/HDAC1-associated transcriptional repressor protein), HNRNPU/SAF-A (heterogeneous nuclear ribonucleoprotein U/scaffold-attachment factor A), and LBR(lamin B receptor)—three factors necessary for X-inactivation. SHARP/SPEN interacts with NCOR2/SMRT (nuclear receptor corepressor 2) to activate HDAC3 (histone deacetylase 3),

which likely participates in restricting silencing of the inactive X-chromosome (McHugh et al., 2015).

Beyond their influence on covalent modifications to histone proteins, lncRNAs can control nucleosome position and placement of histone variants. The lncRNA *SCHLAP1* (Switch/Sucrose non-fermenter [SWI/SNF] complex antagonist-associated with prostate cancer 1) controls the localization and activity of SMARCB1/SNF5 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1), a component of the SWI/SNF complex that repositions nucleosomes in an ATP-dependent manner (Prensner et al., 2013). The heart-specific lncRNA *MHRT (Myheart;* myosin heavy chain-associated RNA transcript) interacts with the nucleosome remodeler SMARCA4A/BRG1, restricting its activity at target sites (Han et al., 2014). Additionally, a centromeric lncRNA interacts with and is necessary for recruitment of the centromeric H3 variant, CENPA (centromere protein A) and its chaperone HJURP (Holliday junction recognition protein) to human centromeres (Quenet and Dalal, 2014).

lncRNA Control of DNA Methylation States

In addition to their effects on histone states, lncRNAs can provide signals for deposition of DNA methylation in *cis*. At the ribosomal DNA (rDNA) locus, a promoter-spanning antisense lncRNA forms an R-loop, a triplex structure between double-stranded DNA and a hybridized RNA, which recruits DNMT3B (DNA methyltransferase 3B) to the locus, leading to local methylation and rDNA silencing (Schmitz et al., 2010). At the imprinted *RASGRF1* (Ras protein-specific guanine nucleotide-releasing factor 1) locus, P element-induced wimpy testes (piwi)-interacting RNA (piRNA)-targeted RNA, a lncRNA spanning the domain carrying the methylation imprint, is required for local DNA methylation (Watanabe et al., 2011). These piRNA-targeted RNA normally functions in *cis* (Park et al., 2012), but DNA methylation occurred in *trans* at the homologous locus when expression patterns were perturbed (Herman et al., 2003).

lncRNAs can also prevent the deposition of DNA methylation. In contrast to their role in placing DNA methylation at the rDNA locus, R-loops that form at CpG islands of other promoters have been implicated in preventing CpG island methylation (Ginno et al., 2012). The Poly(A)$^-$ extra-coding RNA that extends across the *CEBPA* (CCAAT/enhancer-binding protein [C/EBP], alpha) locus binds to DNMT1 (DNA methyltransferase 1). This binding sequesters DNMT1, limiting DNA methylation of the transcribed locus and enabling expression of the coding form of the Poly(A)$^+$ mRNA (Di Ruscio et al., 2013). Many other Poly(A)$^-$ transcripts were identified by RNA immunoprecipitation studies using antibody against DNMT1, suggesting that extra-coding RNA control of DNMT1 might be commonplace. The domains from which extra-coding RNAs are transcribed tend to harbor less methylation and have more transcription relative to domains producing Poly(A)$^-$ transcripts that are unbound to DNMT1 (Di Ruscio et al., 2013); such observations are consistent with the notion that DNMT1 sequestration by extra-coding RNAs frequently limits DNA methylation.

lncRNA Control of Transcriptional States

lncRNAs can modify gene expression by influencing local chromatin states as well as through non-chromatin means. For example, lncRNAs such as *GAS5* (growth arrest-specific 5) (Kino et al., 2010) and *PANDA* (promoter of CDKN1A antisense, DNA damage activated) (Hung et al., 2011) can limit access of transcription factors to their DNA targets by directly binding to these factors. Alternatively, the lncRNA *BCAR4* (breast cancer anti-estrogen resistance 4) can enable transcription factor recruitment to DNA (Xing et al., 2014). In some cases, such transcription factor interactions are sensitive to extracellular signaling molecules (Trimarchi et al., 2014; Xing et al., 2014) or involve histone modifiers that affect local chromatin states (Wang et al., 2008; Xing et al., 2014). In addition to binding and recruiting EHMT2/ G9A to some target sites, *Airn*, the lncRNA that regulates imprinted *IGF2R* expression (Sleutels et al., 2002), exerts its effect by transcriptional interference at the silenced paternal *IGF2R* allele (Latos et al., 2012). At other loci, transcriptional interference by lncRNAs appears to be sufficient to control local gene expression (Martianov et al., 2007; Latos et al., 2012; Santoro et al., 2013).

lncRNAs may also respond to changes in chromatin and gene expression states. For example, the lncRNAs *NEAT1* (nuclear paraspeckle assembly transcript 1) and *MALAT1* (metastasis-associated lung adenocarcinoma transcript 1) bind chromatin, but exhibited novel patterns of chromatin localization following treatments with the transcription elongation inhibitor flavopiridol. Thus, lncRNA localization can respond to and influence RNA polymerase II activity (West et al., 2014). Alternatively, lncRNAs might maintain chromatin or expression states, once they are established, as is the case for the lncRNA *FIRRE* (Firre intergenic repeating RNA element), which is required to maintain previously established H3K27me3 on the inactive X-chromosome (Yang et al., 2015).

lncRNA Control of Other Functions

lncRNAs influence a variety of other cellular functions beyond control of chromatin and transcriptional states, including nuclear architecture, splicing, and mRNA translation. In addition to its role in maintaining H3K27me3 on the inactive X-chromosome, *FIRRE* is required for nucleolar localization of the inactive X-chromosome in mammals. This occurs through a mechanism involving its own interaction with CTCF (CCCTC-binding factor zinc finger protein) (Yang et al., 2015). *FIRRE* also binds HNRNPU (heterogeneous nuclear ribonucleoprotein U), a nuclear matrix protein, through a sequence repeated within the lncRNA, and localizes to distinct regions in the genome in a manner dependent on HNRNPU expression (Hacisuleyman et al., 2014).

The lncRNA *MALAT1* binds SRSFs (serine-arginine splicing factors) and influences their localization within nuclear speckles (Tripathi et al., 2010). *MALAT1* also interacts with pre-messenger RNAs (Engreitz et al., 2014), and its depletion causes changes in alternative splicing (Tripathi et al., 2010). An additional example of splicing control by lncRNAs involves intron-encoded lncRNAs that are processed by small-nucleolar-RNA-dependent mechanisms. These so-called *sno-lncRNAs* influence splicing by their association with memberse of the FOX family of splicing factors (Yin et al., 2012). An anti-sense lncRNA

from the human *FGFR2* (fibroblast growth factor receptor 2) locus controls local alternative splicing choices by affecting local histone methylation state (Gonzalez et al., 2015).

A lncRNA corresponding to an antisense transcript from the coding gene *UCHL1* (ubiquitin carboxyl-terminal esterase L1) regulates *UCHL1* translation (Carrieri et al., 2012). Interestingly, this lncRNA exerts its translational control through sequences with similarity to the *SINEB2* (short interspersed nuclear element B2) repetitive element. Long intergenic noncoding RNA *p21* also regulates translation of specific transcripts, likely by a mechanism that involves physical interaction with its targets (Yoon et al., 2012). Although not controlling translation, the lncRNA *TINCR* (tissue differentiation-inducing non-protein coding RNA) can also affect protein levels after transcription and splicing by regulating mRNA stability (Kretz et al., 2013).

Effects of lncRNA may involve functional interactions with other regulatory ncRNAs as well. Micro RNAs (miRNAs) can be sequestered by lncRNAs, which are referred to as competing-endogenous RNAs, some of which are circular (Hansen et al., 2013; Memczak et al., 2013; Tay et al., 2014). Competing-endogenous RNAs limit the capacity of miRNAs to regulate translation of their mRNA targets. Originally reported in Arabidopsis (Franco-Zorrilla et al., 2007), this phenomenon was also found to occur in mammalian livercancercells (Wang et al., 2010), myoblasts (Cesana et al., 2011), and embryonic stem cells (Wang et al., 2013). Interestingly, *H19* was shown to act as a miRNA sink as well (Kallen et al., 2013), yet also serves as a precursor for distinct miRNAs (Gao et al., 2012; Keniry et al., 2012). This is in addition to *H19's* ability to bind the methylated DNA binding protein MBD1 (methyl-CpG binding domain protein 1) and to regulate other imprinted genes, both in *cis* and *trans* (Monnier et al., 2013). miR-9 can also target the lncRNA *MALAT1* for degradation (Leucci et al., 2013). Beyond miRNAs, the piRNA pathway is necessary for lncRNA-mediated control of DNA methylation at the imprinted locus *RASGRF1* (Watanabe et al., 2011).

The examples of genomic regulation provided here are illustrative of known lncRNA activities; additional studies are likely to reveal further activities and the necessity of individual lncRNAs for physiological processes in vivo. In one study of mice deficient for 18 lncRNAs, three were found to be essential for viability and two affected growth (Sauvageau et al., 2013). Important questions, whose answers are beginning to emerge, include the following: By what mechanisms are the lncRNAs themselves regulated (Amin et al., 2015)? What are the details of the mechanisms by which lncRNAs exert their effects? What health and disease-relevant phenotypes are controlled by lncRNAs? Understanding mechanisms of lncRNA action will require further knowledge of lncRNA structure and its impact on function (Brown et al., 2014a; Somarowthu et al., 2015); interacting factors, including proteins, other RNAs, and possibly metabolites; factors controlling lncRNA subcellular localization; and for chromatin-based phenomena, determining how lncRNAs localize to and/or restrict their activities at specific genomic domains. Many *cis*-acting lncRNAs are likely to function co-transcriptionally, while still tethered to their DNA template. On the other hand, how *trans*-acting lncRNAs become targeted to and act at specific loci is less clear. The transcription factor YY1 (yin and yang 1), for example, is important for recruiting *Xist* to the inactive X-chromosome(Jeon and Lee, 2011), buthow

Xist is excluded from othergenomic locations is not clear. This might involve licensing enabled by X-chromosome pairing prior to X-inactivation (Xu et al., 2006), a mechanism that could be limited to X-inactivation. *HOTAIR* has many binding sites in the genome that are enriched for a GA-rich DNA motif, indicating DNA sequence-specific binding factors might recruit the RNA (Chu et al., 2011). In human cells, transcriptional targets of the lncRNA *ANRIL/CDKN2B-AS1* (cyclin-dependent kinase inhibitor 2B antisense RNA 1) both contain and require *Alu* elements for their *ANRIL/CDKN2B-AS1* response—yet not all *Alu* elements respond to *ANRIL/CDKN2B-AS1*, so it is not clear what provides specificity for *Alu* elements at *ANRIL/CDKN2B-AS1* target genes (Holdt et al., 2013). Additional issues requiring more study include the functional importance, if any, of post-transcriptional modifications to lncRNAs (Kiani et al., 2013; Zheng et al., 2013b; Batista et al., 2014; Fu et al., 2014; Schwartz et al., 2014; Wang and He, 2014; Liu et al., 2015a), and the roles transposable elements have played in lncRNA diversity (Kelley and Rinn 2012; Liang et al., 2012; Kapusta et al., 2013). Approaches that systematically characterize proteins bound to specific lncRNAs will continue to be informative (McHugh et al.,2015).

lncRNAs IN REPRODUCTION AND DEVELOPMENT

Many excellent and recent reviews describe the discovery, cataloging, and activities controlled by lncRNAs, as well as approaches toward functional analysis (Wang and Chang 2011; Hu et al., 2012; Troy and Sharpless, 2012; Batista and Chang, 2013; Geisler and Coller, 2013; Ghosal et al., 2013; Sun and Kraus, 2013; Ulitsky and Bartel, 2013; Cech and Steitz, 2014; Fatica and Bozzoni, 2014; Flynn and Chang, 2014; Morris and Mattick, 2014; Quinodoz and Guttman, 2014; Chu et al., 2015; Engreitz et al., 2015; Holoch and Moazed, 2015; Iyer et al., 2015). Additional reviews focus on mechanisms of lncRNA control of sex-chromosome dosage compensation (Lee and Bartolomei, 2013; Autuoro et al., 2014; Briggs and Reijo Pera, 2014; Deng et al., 2014; Galupa and Heard, 2015), and control of development, including stem cell maintenance and differentiation (Batista and Chang, 2013; Ghosal et al., 2013; Fatica and Bozzoni, 2014; Flynn and Chang, 2014; Yao and Jin, 2014). Given the diverse roles lncRNAs play in essential biological processes common to many cell types, it should come as no surprise that lncRNAs play a vital role in reproduction, which is the focus of the remainder of this review. Though many ongoing studies are descriptive, functional and mechanistic studies exist and will be highlighted (see Table 2 and Fig. 2). Observations from a diversity of species will be presented, as they help define evolutionary conserved processes.

Germ Cell Specification

Formation of the animal germ line begins with specification of primordial germ cells (PGCs), pluripotent cells that, in mammals, are derived from a cluster of cells posterior to the definitive primitive streak in the extraembryonic mesoderm of mid-primitive-streak-stage embryos (7–7.5 days post-coitum in mouse). PGCs later migrate along the genital ridge, where they contribute to the developing gonad (Ginsburg et al., 1990). Three proteins required for PGC specification include BLIMP1/PRDM1 (PR domain-containing 1, with a zinc-finger domain), TFAP2C/AP2γ (transcription factor AP-2 gamma), and PRDM14 (PR domain-containing 14) (Magnusdottir et al., 2013). In mouse PGCs, BLIMP1/PRDM1 acts

as a transcriptional repressor to block the expression of genes involved in somatic development (Keller and Maniatis, 1991; Gyory et al., 2003), but it also binds near other genes that are activated and important for PGC specification, such as *Tcfap2c/Ap2γ* and *Cbx7* (chromobox homolog 7). Among the 5,046 BLIMP1/PRDM1 binding sites in mouse PGCs, 313 are associated with noncoding genes (Magnusdottir et al., 2013) whose functions in PGC specification are unknown. Given that lncRNAs are known to directly repress transcription, it is possible that BLIMP1/PRDM1 indirectly activates targets by negatively regulating repressive lncRNAs; further profiling of germ-line lncRNAs, and their interacting factors, could help resolve this.

The RNA-binding proteins DAZ1 (delete in azospermia 1), DAZL (deleted in azospermia-like), and BOLL/BOULE (Boule-like RNA-binding protein) are important for PGC specification and meiotic progression (Kee et al., 2009). These proteins bind RNA in the cytoplasm, regulating translation initiation (Collier et al., 2005), and have also been shown to translocate into and out of the nucleus during germ line development (Reijo et al., 2000). Within the nucleus, these proteins might functionally regulate coding and/or noncoding RNAs that are important for PGC formation or differentiation. These dual functions could be addressed by identifying and functionally characterizing RNAs associated with DAZ family members at different time points during germ line differentiation.

lncRNAs may also be involved in PGC specification via the mechanisms cited above. For example, *Bvht (Brave-heart)* is a lncRNA that controls the expression of *MesP1* (mesoderm posterior basic helix-loop-helix transcription factor 1), a master regulator controlling differentiation of mesodermal precursors into cardiomyocytes (Klattenhoff et al., 2013). It is therefore possible that master regulators of PGC fate, like BLIMP1/PRDM1 or DAZL, may also be under the control of an unknown lncRNA. Thus, lncRNA regulation might be active at every level of PGC development, both as an initiator and as a downstream response element.

Sex Determination and Gonadogenesis

Several lines of evidence suggest the importance of lncRNAs for sex determination and sex-specific patterns of development. The number or identity of sex chromosomes is typically the genetic determinant of sex—although lncRNA involvement in this process is documented as well. For example, Drosophila become female upon the early expression of the X-encoded *Sxl* (Sex-lethal) gene. *Sxl* expression is dependent upon the ratio of X chromosomes to autosomes (A), involving a complex chromosome-counting mechanism that requires the competition of gene products from each chromosome. If X≥A, then the X transcription factors Sisterless-a and Sisterless-b activate *Sxl* expression; if X<A, then proteins including Deadpan and Extramacrochaetae directly or indirectly block binding to the *Sxl* promoter, resulting in male determination (Schutt and Nothiger, 2000). Interestingly, expression of a panoply of lncRNAs located ~1 kb upstream of the promoter add to the complexity of this counting mechanism, with RNAs from the R1 region repress whereas RNAs from the R2 region activate *Sxl* (Mulvey et al., 2014). These RNA species were also shown to recruit chromatin modifiers like Polycomb and Trithorax, indicating that *Sxl* expression is regulated by a complex interaction network involving many lncRNAs.

In mice, expression of the Y-chromosome-encoded *Sry* gene is sufficient to drive male sex determination (Koopman et al., 1991). SRY protein activates transcriptional cascades specific for male development (Kashimada and Koopman,2010), but its RNA independently functions as a circular-RNA miRNA sponge that competitively binds miR-138 in vitro, which can further positively regulate male specification (Hansen et al., 2013).

DMRT1 (Doublesex and Mab-3 related transcription factor 1) has been implicated in sex determination in a variety of vertebrate and invertebrate species, including humans, and acts both as a transcriptional repressor and activator (reviewed in Matson and Zarkower, 2012). In mice, the *Dmrt1* transcript participates in *trans* splicing with the lncRNA *Dmr*, producing a transcript that encodes a protein with an altered carboxyl terminus. Overexpressing *Dmr* in primary Sertoli cell cultures increased the abundance of this altered form of DMRT1 protein, reduced the abundance of the cannonical DMRT1 isoform, and led to impaired expression of DMRT1 targetgenes, mimicking the *Dmrt1* loss-of-function phenotype. It is clear that *trans* splicing negatively regulates DMRT1; what is unclear is whether or not the non-cannonical isoform has its own regulatory activity. Interestingly, reporters carrying a 3' untranslated region (UTR) from *Dmr* exhibit enhanced expression (Zhang et al., 2010). It is not known if these contrasting results are due to idiosyncrasies of the specific assay system or if they reflect the range of regulation controlled by *Dmr*.

Sex Hormone Responses

The study of lncRNA activity in the context of sexhormone response has largely been restricted to the steroid sex hormones, which utilize nuclear receptors, including ESR1 (estrogen receptor 1), AR (androgen receptor), and PGR (progesterone receptor). On the other hand, roles for lncRNAs have not been demonstrated for signaling by follicle-stimulating hormone and luteinizing hormone, which utilize G-protein coupled receptors and cytosolic signal transduction cascades—although the cytosolic localization and activity of many lncRNAs still leave such roles plausible.

Functional studies of noncoding RNA involvement in AR and ESR1 responses include roles for enhancer RNAs and other lncRNAs. For example, enhancer RNAs transcribed from ESR1-bound enhancers recruit transcriptional activators to drive expression of nearby ESR1-responsive genes. Loss of the enhancer RNAs, by siRNA knockdown, reduced transcription of targetgenes without affecting ESR1 recruitment; moreover, tethering specific enhancer RNAs to a reporter gene enabled reporter activation(Li et al.,2013). In a similar manner, the lncRNAs *PCGEM1* (prostate-specific transcript) and *PRNCR1* (prostate cancer-associated non-coding RNA 1) associate with the AR. Knockdown of *PCGEM1* or *PRNCR1* reduced transcription of a number of canonical AR-targeted genes while enhancer-promoter interactions were reduced, based on chromatin-conformation capture assays (Yang et al., 2013). AR binds to an enhancer cluster 4 kb upstream of the AR-driven promoter of *KLK3* (Kallikrein-related peptidase 3) in a hormone-dependent manner (Hsieh et al., 2014). This enhancer RNA acts as part of a scaffolding apparatus, which includes Mediator and AR, that enhances transcriptional activity at the endogenous *KLK3* locus and at the downstream *KLK2* locus. Additional AR and ESR1 target genes might also be influenced by lncRNAs.

The lncRNA *SRA* was originally identified in a yeast two-hybrid screen for human PGR-interacting factors, indicating it has a functional reading frame. Yet, its steroid-hormone-receptor-activator activity does not require *SRA* translation or an open reading frame (Lanz et al., 1999,2002). SRA has since been shown to modulate the activity of AR, ESR1, and PGR through direct association with hormone receptors (Lanz et al., 1999) and through recruitment of a variety of transcriptional activators and repressors (Shi et al., 2001; Watanabe et al., 2001; Hatchell et al., 2006). Furthermore, this lncRNA can be spliced and translated into SRAP/SRA1 (SRA protein 1), which also enhances steroid hormone-mediated gene expression (Kawashima et al., 2003). In breast cancer cells, *SRA1* has also been shown to associate with a repressive histone-modifying complex containing unliganded PGR and with chromatin-binding and modifying factors, including CBX5/HP1 (chromobox homolog 5/het-erochromatin protein 1), KDM1A/LSD1, HDAC1 and 2 (histone deacetylase one and 2), and RCOR1/CoREST (RE1-silencing transcription factor corepressor 1). Unliganded PGR localizes this complex to approximately 20% of steroid-responsive genomic loci. Depletion of *SRA* led to destabilization of the complex and aberrant gene expression. Upon progesterone treatment, the repressive complex is evicted and replaced by ligand-bound PGR and basal transcription factors (Vicent et al., 2013). Yet, even though SRAP/SRA1 can enhance the activity of various steroid receptors—including, but not limited to, the steroid sex hormones—the regulation of *SRAP/SRA1* transcription itself is unknown. Similarly, the factors that determine its differential splicing to become a transcript coding for SRAP/ SRA1 are also unknown.

Meiosis

lncRNAs have been implicated in the control of meiosis from studies in both plants and yeasts. In several plant species, seeds can form asexually through a variety of processes collectively referred to as apomixis (Koltunow and Grossniklaus, 2003). Shared features include female gamete formation in the absence of recombination or reductive division, which are normally seen in meiosis, followed by parthenogenic embryo development in the absence of fertilization. The resulting plants harbor their maternal genotype. In several apomictic species of the genus Boechera, microarray analyses identified a conserved lncRNA, *UPGRADE2*, that is present and highly upregulated in pollen mother cells. No homolog was found in sexually reproducing species of the same genus (Mau et al., 2013), so it remains to be determined if this lncRNA is simply associated with or is required for apomixis in Boechera.

In the budding yeast *Saccharomyces cerevisiae*, *IME1* (inducer of meiosis 1) is kept transcriptionally silent by the repressor RME1 (regulator of meiosis 1) in vegetative cells growing in a nutrient-rich environment and in haploid cells encountering no partners of the opposite mating type. RME1 induces expression of a lncRNA, *IRT1 (IME1* regulatory transcript), which spans the *IME1* promoter and works in *cis* to increase local nucleosome occupancy and to recruit the SET3 complex that deposits repressive histone modifications at the promoter (van Werven et al., 2012). Interestingly, many SET3-repressed genes have overlapping lncRNA transcripts (Kim et al., 2012).

Another inducer of meiosis, IME4 (Shah and Clancy, 1992), is regulated in *cis* by the lncRNA *RME2*, which is transcribed antisense relative to *IME4* and might block its expression by transcriptional interference rather than by recruiting chromatin-modifying factors (Hongay et al., 2006; Gelfand et al., 2011; van Werven et al., 2012). Antisense transcripts to these lncRNAs activate sporula-tion (van Werven et al., 2012). Interestingly, IME4 is a methyltransferase capable of placing N6-methyladenine (m6A) RNA modifications (Agarwala et al., 2012), a modification that makes the RNA that harbors it less stable than those lacking it (Batista et al., 2014). The Drosophila ortholog of IME4, METTL3 (methyltransferase-like 3), is essential for gametogenesis and embryo viability (Hongay and Orr-Weaver, 2011). These functions in Drosophila are mediated by IME4 through Notch signaling, although it is not clear how. Indeed, many RNAs with IME4-dependent m6A modifications have been described (Schwartz et al., 2013), and meiosis-specific lncRNAs beyond *RMA2* have been described in S. *cerevisiae*, raising the likelihood that additional lncRNA-dependent mechanisms exist that regulate meiosis (Lardenois et al., 2011).

lncRNAs have also been implicated in meiotic control in the fission yeast S. *pombe*. Mei2 (meiosis RNA-binding protein 2) is the master regulator of S. *pombe* meiosis (Watanabe and Yamamoto, 1994; Watanabe et al., 1997). It is recruited to the nucleus by the lncRNA *meiRNA* (Yamashita et al., 1998; Shichino et al., 2014), forming a nuclear dot (Shimada et al., 2003) that includes the lncRNAs *Mei2* and *Mmi1* (meiotic mRNA interception 1). This occurs at the *sme2* (suppressor of *Mei2v*) locus from which *meiRNA* is transcribed, which defines a *cis*-acting function for *meiRNA*. The nuclear dot promotes meiosis by sequestering Mmi1, an RNA-binding protein that degrades meiosis-promoting transcripts (Harigaya et al., 2006). Degradation requires polyadenylation and involves nuclear exosomes. Interestingly, Mmi1, whose function is antagonized by *meiRNA*, is required for *meiRNA* recruitment to *sme2* (Shichino et al., 2014); therefore, although *meiRNA* functions in *cis*, its localization involves *trans*-acting factors.

Additional lines of evidence indirectly suggest other mechanisms that potentially involve lncRNA in meiosis. Methyltransferases have been implicated in processes critical to RNA function in vertebrates, invertebrates, and plants (Zhong et al., 2008; Li and Mason 2014; Schwartz et al., 2013); the example of m6A controlled by IME4, cited above, is one. Indeed, more-thorough characterization of both m6A-modified RNAs and lncRNAs influencing meiosis may clarify the importance of m6A modifications to lncRNA function. Another potential mechanism influencing lncRNA action involves RNA-binding proteins known to be important in mammalian meiosis, including DAZL and DDX4/VASA (DEAD box polypeptide 4) (Medrano et al., 2012). The DAZ family of RNA-binding proteins, which are required for PGC specification, are found in the nucleus and cytoplasm of fetal germ cells, in the cytoplasm of developing oocytes, and in the nucleus of spermatogonia. Their translocation between the nucleus and cytoplasm during meiosis (reviewed in Brook et al., 2009; Smorag et al., 2014) implicates additional functions beyond translational control (Collier et al., 2005). DAZ and BOLL/BOULE are also required for later stages of meiosis (Kee et al., 2009). Immunoprecipitates of DAZL from rat testis homogenate contained many mRNAs, but as these data were detected by microarray, some recently characterized

lncRNAs may have been overlooked. Indeed, associations between DAZ-family proteins and lncRNAs might reveal important participants in meiosis. DDX4/VASA is an RNA helicase that regulates mRNA translation and piRNA production (reviewed in Kotov et al., 2014). DDX4/VASA immunoprecipitates from mouse testicular cells contained 858 mRNAs (Nagamori et al., 2011), as identified by microarrays designed to detect mRNAs. RNA-sequencing (RNA-seq) analysis, however, would more reliably reveal if DDX4/VASA also binds and functionally regulates lncRNAs associated with meiosis. MOV10L1 (Mov10 RNA-induced silencing complex RNA helicase-like 1) is another RNA helicase expressed at increasing levels in germ cells between the gonocyte and pachytene spermatocyte stages. It binds the PIWI (P-element induced wimpy testes) proteins PIWIL1/MIWI and PIWIL2/MILI (Frost et al., 2010; Zheng et al., 2010) and piRNA precursor transcripts (Vourekas et al., 2015), which may formally be considered a class of lncRNAs. MOV10L1 is required for primary piRNA biogenesis (Zheng et al., 2010; Zheng and Wang 2012; Vourekas et al., 2015) and silencing retrotransposons in the male germ line (Frost et al., 2010). Male mice lacking MOV10L1, or carrying a point mutation in the ATP-binding domain of the helicase, exhibit meiotic arrest in prophase I (Frost et al., 2010; Zheng et al., 2010; Zheng and Wang 2012; Vourekas et al., 2015); on the other hand, females deficient for the protein are fertile. Special requirements for helicases during piRNA biogenesis may relate to G-quadruplex structures present in precursor transcripts (Vourekas et al., 2015).

Gametogenesis

Spermatogenesis—lncRNAs are dynamically expressed and appear to be highly regulated in spermatogenesis. Several studies have profiled the transcriptomes of the developing male germ line, revealing a clear pattern. First, transcript levels dramatically increase as spermatogonia enter meiosis. These increase further as spermatocytes give rise to spermatids, but is followed by a rapid depletion of RNA in spermatozoa (Bao et al., 2013; Laiho et al., 2013; Soumillon et al., 2013; Chalmel et al., 2014; Liang et al., 2014; Margolin et al., 2014). These total-RNA profiling studies revealed novel lncRNAs, most of which have not been functionally characterized. Recent RNA-seq profiling at different stages of spermatogenesis, however, highlight potential regulation of spermatogenesis by lncRNAs.

Stage-specific, differentially expressed lncRNAs have been found within 30 kb of coding-gene clusters by array-based profiling of lncRNAs and mRNAs during spermatogenesis. Positive and negative correlations between lncRNA expression and local mRNA expression were observed, depending on the gene cluster. The most pronounced changes in expression occurred after the onset of meiosis, with changes in lncRNA abundance correlating with expression of nearby mRNA clusters. A subset of these lncRNAs were characterized via cross-linking and immunoprecipitation (CLIP)-quantitative PCR (Bao et al., 2013); many were found to interact with EZH2 and KDM1A/ LSD1 in ways that potentially regulate nearby expression and methylation states. The coordinated change in expression of lncRNAs and corresponding gene clusters was also observed in an array-based profile (Liang et al., 2014). Such regulation is not surprising in the context of the promiscuous binding of PRC2 (Davidovich et al., 2015); the physiological relevance of these data, however, requires further characterization to clarify.

At birth, spermatogonia in mice possess a comparably low fraction of the total-testis lncRNA profile found in adults (Soumillon et al., 2013). *mhrl* is one interesting transcript detected at birth. This lncRNA resides in the nucleus, and has been shown suppress the WNT (wingless-type MMTV integration site family) signaling pathway in a spermatogonial cell line by regulating beta-catenin nuclear translocation (Arun et al.,2012). WNT signaling is a regulator of "stem cell-ness" and is implicated in maintaining a self-renewing population of spermatogonial stem cells (Golestaneh et al., 2009; Yeh et al., 2011). Although *mhrl*-mediated repression of WNT signaling suggests it influences spermatocyte differentiation, its specific function needs to be explored by in vivo manipulations of *mhrl* expression.

Upon induction of meiosis there is a considerable increase in lncRNA transcription in mouse spermatocytes (Soumillon et al., 2013). In pachytene spermatocytes, *Tsx* (testis-specific X-linked), a predominantly nuclear, testis-specific lncRNA, becomes highly expressed and escapes X-inactivation (Anguera et al., 2011). A *Tsx*-knockout produces viable and fertile offspring, although males have decreased testis size and exhibit increased apoptosis of pachytene spermatocytes. Interestingly, *Tsx*-knockout mice also showed deficiencies in learning and increased *Xist* expression. The nuclear localization and X-linked expression of *Tsx* therefore suggest a role in X-inactivation in pachytene spermatocytes that is far from understood.

The importance of RNA methyltransferases, such as IME4, was previously discussed in reference to gamete development. On the other hand, RNA demethylases, such as ALKBH5 (AlkB family member 5), are also vital during this time, specifically at the pachytene stage of spermatogenesis (Zheng et al., 2013a). *AIkbh5*-knockout mice exhibit decreased testis size, sterility, more m6A-modified mRNAs, altered RNA localization, and significant changes in gene expression. The increased half-life of demethylated RNAs at this stage (Batista et al., 2014) may contribute to the increased expression and overall abundance of lncRNAs in spermatocytes, which could potentially affect recruitment of other chromatin readers/writers such as PRC2 to specific loci. Alternatively, m6A may be regulating RNA-protein interactions or affinities via altered RNA base pairing (Liu et al., 2015a). m6A-seq has not yet been performed in developing testis.

TBCA13 (tubulin cofactor A chromosome isoform 13), a protein involved in tubulin assembly, increases in abundance from 14 to 25 days post partum in mouse testis. Transcription of *Tbca13* in a spermatocyte cell line is regulated by a pseudogene, *Tbca16*, which originated from a duplication of *Tbca13* with both sense and antisense transcription on chromosome 16. The antisense product of *Tbca16* appears to negatively regulate *Tbca13:* When *Tbca16* mRNA was depleted by short-hairpin RNA, *Tbca13* escaped silencing (Nolasco et al., 2012). The mechanism behind *Tbca16* silencing and the escape of *Tbca13* during spermatogenesis has not been elucidated, although a corollary might be found at the 3' actin pause site where antisense transcription and R-loop formation recruits AGO2 (Argonaute RNA-induced silencing complex catalytic component 2), EHMT2/G9A, and the repressive H3K9me2 mark to enhance mRNA termination (Skourti-Stathaki et al., 2014). The in vivo importance of such regulation and its involvement in spermatogenesis needs further exploration.

A majority of the transcriptome is depleted upon spermatozoa maturation. Most recently, the transcriptomes of the nucleus and periphery of mature spermatozoa were profiled, and revealed that the majority of spermatozoon RNA is localized to the cytoplasm while a minority (roughly 34%) localizes to the nucleus (Johnson et al., 2015). *MALAT1* highlights the potential for lncRNA-mediated chromatin organization in the male germ line: Despite the expulsion of most RNAs, it is enriched in the sperm nucleus. Yet *Malat1* knockouts do not exhibit defects in fertility, underlining the fact that its function at this stage is unclear (Zhang et al., 2012). Several RNAs are present in mature spermatozoa that are not present in unfertilized oocytes, but are delivered to the zygote upon fertilization (Johnson et al.,2015). It is currently not certain if spermatozoon- localized lncRNAs are vital for gamete formation or zygotic function after fertilization.

Oogenesis—The developing mammalian oocyte exists in a complex where in a network of cumulus cells surrounds the oocyte and remains in intimate communication with the oocyte through gap junctions. Early during oogenesis, cumulus cells form a compact layer around immature oocytes, which are arrested at prophasel. Surgesoffollicle-stimulating hormone and luteinizing hormone at ovulation cause the cumulus-oocyte complex to expand and detach from the follicle wall, coincident with the oocyte resuming meiosis (Yokoo and Sato, 2004). Although the transcriptional change in cumulus cells is considerable during expansion of the cumulus-oocyte complex, a small number of lncRNAs were detected as differentially expressed by RNA-seq (Yerushalmi et al., 2014). Ninety-six non-coding RNAs, 45 anti-sense, and 44 long-intergenic noncoding RNAs, were identified as differentially expressed between compact and expanded cumulus cells. While not evaluated functionally, the presence of antisense transcripts during this interval suggests a regulatory role for them. Another study investigated lncRNAs in “high-quality” versus “poor-quality” human cumulus cells by microarray (Xu et al., 2014). The samples were derived from in vitro fertilization, and quality was defined by their morphology. Of the 20,000 lncRNAs examined, 633 were identified as being differentially expressed between high-quality and poor-quality cumulus cells.

These cumulus-cell lncRNA profiles are especially important because of the evidence that the cytoplasm and its contents are shared in a limited way between cumulus cells and the oocyte. In mammals, cumulus cells that have been independently transfected with a GFP (green fluorescent protein) reporter allowed *GFP* mRNA to move into the oocytes, resulting in GFP-expressing oocytes that lack the reporter plasmid(Macaulay et al.,2014). In Drosophila, nurse cells transfer RNA and other cytoplasmic components to oocytes (Cha et al., 2001; Nicolas et al., 2009); similar phenomena are seen in hydra (Alexandrova et al., 2005) and in mouse (Cossetti et al., 2014), the latter of which might be an exosome-mediated process (Gezer et al., 2014; Pefanis et al., 2015). Such communication by cytoplasmic sharing is a perfect medium by which regulatory lncRNAs may be moved from a somatic cell type into the developing germ line.

In a single-cell RNA-seq profile of metaphase-II (MII) oocytes and preimplantation embryos, 8,700 maternal lncRNAs were identified in the preimplantation embryo (Yan et al., 2013). Six hundred sixty differentially expressed lncRNAs were identified between MII oocytes and zygotes, which are hypothesized to affect gene activation during the maternal-

to-zygotic transition. Many lncRNAs with possible functional relevance in the transition from MII oocytes to 2-cell embryos have also been identified (Hamazaki et al., 2015). In an impressive screen using strand-specific RNA-seq, more than 1,000 potentially functional lncRNA/mRNA pairs have been identified, with a subset acting as promoter-associated noncoding RNAs in zygotes. A subsequent screen of these identified pairs may help elucidate their functions. Similarly, extensive antisense transcription was found near promoters in Drosophila oocytes (Brown et al., 2014b).

Several lncRNAs have been characterized in oogenesis in non-mammalian systems. Much like the previously mentioned *SRA* and *SRY* gene products, Drosophila *oskar* is a good example of an RNA with coding and noncoding functions. Loss of the oskar protein causes defects in oocyte polarity, embryonic germ line specification, and abdominal development; the loss of the *oskar* RNA, however, caused early arrest in oogenesis (Jenny et al., 2006). This lncRNA is only translated when localized to the posterior pole, where its 3'UTR is necessary to recruitment other factors involved in the establishment of cell polarity (Kugler and Lasko, 2009). The independent activity of *oskar* 3'UTR was further supported when it was identified years later in a genome-wide profile of 3'UTR-associated RNAs (Mercer et al., 2011). A similar RNA scaffolding function is found in Xenopus, in which two RNAs are required for proper cytoskeletal organization and oocyte polarity (Kloc et al., 2005). *XIsirt* is a lncRNA composed of short tandem repeats that are suspected to form stem-loop structures for its correct localization (Allen et al., 2003). *VegT* (vegetal T-box protein) mRNA, another dual-purpose transcript, is necessary for cytokeratin network assembly whereas the VegT protein is a transcription factor required for mesoderm and endoderm differentiation (Kofron et al., 1999; Xanthos et al., 2001). Mammals do not have the same asymmetric distribution of molecules associated with oocyte development as either Drosophila or Xenopus, so the structural functions described above are not likely applicable in these animals—but this does not preclude similar lncRNA function in mammalian oocytes.

Studies in plants are revealing additional lncRNA-based mechanisms essential for gamete formation. An RNA-seq screen for lncRNAs expressed in reproductive tissues of rice identified a number of transcripts. *One,XLOC_057324*, was expressed exclusively in young panicles and pistils. Strains with a transfer-DNA insertion in *XLOC_057324* flowered prematurely and set fewer seeds (Zhang et al., 2014b). In another study, rice hybrids exhibiting long-day-specific male sterility were shown to carry a mutation in the lncRNA *LDMAR* (long-day-specific male-fertility-associated RNA). A point mutation in *LDMAR* increased DNA methylation of the locus, reduced *LDMAR* expression under long daylight conditions, and caused premature apoptosis of developing anthers (Ding et al., 2012). The mechanisms underlying these effects are not known.

Placentation

Initial data, though limited, are consistent with a role for lncRNAs in placenta formation and function, with some of the strongest results coming from studies of *H19*. *H19* is a source for miR-675, a miRNA that directly down-regulates NOMO1 (Nodal modulator 1) and inhibit its ability to stimulate proliferation of a human trophoblast cell line (Gao et al., 2012; Keniry et al., 2012). In normal placentae, *H19* and its miR-675 repress NOMO1-mediated

proliferation, but in preeclamptic placentas, *H19* and the miRNA are repressed, allowing NOMO1 mis-regulation to cause placental overgrowth.

The lncRNA *SPRY4-IT1* (Sprouty homolog 4, intronic transcript 1), which is expressed in placenta, was overexpressed in preeclamptic placentae. siRNA knockdown of *SPRY4-IT1* in a transformed human trophoblast line increased cell migration and reduced apoptosis, whereas overexpressing *SPRY4-IT1* had the opposite effects (Zou et al., 2013). Additional lncRNAs were reported to exhibit differential expression in preeclamptic versus control placentae, although the functional relevance has not be tested (He et al., 2013). In vivo manipulations are necessary to assess directly the importance of these lncRNAs in placenta function.

A disease-associated locus was mapped to an intergenic region harboring a lncRNA that is expressed in several trophoblast subtypes in human placentae in studies of HELLP syndrome—a maternal condition of hemolysis, elevated liver enzymes, and low platelets (hence its abbreviation) that has its origins in placental insufficiency. When knocked down in extravillous trophoblast cells, gene expression changes were associated with increased G1/S and cell death functions, as well as decreased G2/M, cell survival, and migration. Accumulation of the *HELLP* lncRNA had the opposite effects, specifically decreasing cell invasion (van Dijk et al., 2012). The mechanisms by which the *HELLP* lncRNA exerts these effects are unknown.

Intrauterine growth restriction (IUGR) is associated with a fourfold enrichment in *NEAT1* (nuclear paraspeckle assembly transcript 1) lncRNA compared to control placentae at term pregnancies (Gremlich et al.,2014). This lncRNA is present in nuclear paraspeckles, and is essential for their assembly (Clemson et al., 2009). Unfortunately, it is not clear if increased *NEAT1* contributes to, or is a consequence of, IUGR.

Unique lncRNA-mediated control of some previously mentioned imprinted loci occurs in the placenta as well. For example, *Airn* controls imprinted expression of *IGF2R* globally, and controls the placenta-specific imprinted expression of two additional adjacent genes, *SLC22A2* and *SLC22A3* (Zwart et al., 2001; Nagano et al., 2008). The lncRNA *Kcnq1ot1* similarly regulates imprinting of four nearby genes in all tissues, but controls four additional, more distantly located genes in placental tissue (Pandey et al., 2008). Both *Airn* and *Kcnq1ot1* directly interact with chromatin-modifying machinery in a lineage-specific way, suggesting that other lncRNAs might work similarly. These imprinting mechanisms are probably more tightly regulated in the placenta due to the tissue's direct role in embryonic growth.

Inheritance

While DNA is responsible for genetic inheritance, non-genetic transmission of traits through meiosis—a phenomenon referred to as trans-generational epigenetic inheritance (TEI)—has been observed (Rakyan and Whitelaw, 2003). Mechanisms underlying TEI are mediated by his-tone modifications, DNA methylation, prions, and RNA species. The first evidence for the involvement of RNA in TEI came from studies of paramutation, a form of TEI involving the *b1* locus in maize. Two alleles of *b1* exist, *B-I* and *B'*, which are genetically identical.

B', however, is silent and harbors DNA methylation in a repeat region necessary for paramutation, whereas *B-I* is active and lacks methylation in the region (Haring et al., 2010). When present in the same plant, *B'* converts *B-I* to its own state; this conversion is stable through meiosis for several generations. The role of RNA in paramutation was demonstrated when a 6-kb tandem repeat 100 kb upstream of the locus that has enhancer activity was shown to be transcribed and processed into small RNAs—a process that requires the RNA-dependent RNA polymerase MOP1 (modifier of paramutation 1) (Dorweiler et al., 2000; Stam et al., 2002; Alleman et al., 2006; Arteaga-Vazquez et al., 2010).

Animal systems display similar RNA-mediated paramutation inheritance. Studies of murine Kit^{+} (Rassoulzadegan et al., 2006), *Sox9* (SRY box 9) (Grandjean et al., 2009), *Cdk9* (cyclin-dependent kinase 9) (Wagner et al., 2008), *Rasgrf1* (Herman et al., 2003), and work in stressed mice (Gapp et al., 2014) revealed paramutation-like effects that are consistent with RNA-mediated mechanisms. Some of these early studies sought to prove the sufficiency of small RNAs to recapitulate a phenotype-of-interest by injecting miRNA species into wild-type zygotes. While making a strong argument for sufficiency, these studies do not answer all of the questions. For instance, elimination of the miRNA pathway by *Drosha* knockout or the piRNA pathway by *Mov10I1* knockout increased the penetrance of the *Kit* phenotype, suggesting that miRNAs and piRNAs act as suppressors rather than activators of paramutation (Yuan et al., 2015). The mechanisms controlling TEI in mammals are unknown, but one would be in error to rule out either the importance of indirect lncRNA control via small RNA regulation or of direct lncRNA transmission upon fertilization. Indeed, RNA modifications appear to play a role, as the *Kit* and *Sox9* phenotypes are dependent on the RNA methyltransferase DNMT2 (transfer RNA aspartic acid methyltransferase 1) (Kiani et al., 2013), although the universality of the effect must be studied further.

Development

lncRNAs associated with preimplantation development have been characterized by RNA-seq of zygotes and other preimplantation stages of development (Paranjpe et al., 2013; Yan et al., 2013; Caballero et al., 2014; Zhang et al., 2014a; Hamazaki et al., 2015). By comparing lncRNA profiles of the zygotes with those of its parental gametes, it is possible to identify lncRNAs arising immediately after zygote activation. Evaluating the importance of these lncRNAs for early embryonic events will require their experimental manipulation (Sauvageau et al., 2013).

Some of the most-extensive findings related to preim-plantation embryos come from studies of embryonic stem cells. Cultured embryonic stem cells express at least 226 lncRNAs, 137 of which have been shown to affect gene expression and 26 of which are necessary to repress differentiation and to maintain pluripotency (Guttman et al., 2011). These lncRNAs contribute to many activities. For instance, *Meg3* (maternally expressed gene 3) interacts with JARID2 (Jumonji, AT-rich interactive domain 2) to specifically recruit PRC2, and its repressive activity, to embryonic development genes in *trans* (Kaneko et al., 2014). On the other hand, six lncRNAs were shown to interact with WDR5 (WD repeat domain 5), a protein that actively recruits KMT2A/MLL and its H3K4me3 activity (Wang et al., 2011;

Yang et al., 2014). By a distinct approach, the lncRNA *RoR* (regulator of reprogramming) does not control chromatin remodelers, instead maintaining expression of the core pluripotency factors by acting as a sponge to titrate out repressive miRNAs that would down-regulate their translation (Wang et al., 2013). Through a variety of mechanisms, the central role for lncRNAs at this stage of development is to maintain self-renewal characteristics (reviewed in Flynn and Chang, 2014).

Many critical steps in post-implantation somatic development are regulated by lncRNAs (see Table 3). The reader is referred to recent reviews addressing this issue, including stem cell maintenance and differentiation (Batista and Chang, 2013; Ghosal et al., 2013; Fatica and Bozzoni, 2014; Flynn and Chang, 2014; Yao and Jin, 2014).

REPRODUCTIVE DISEASE

Beyond placental insufficiencies that are associated with perturbations in lncRNA regulatory mechanisms, several lines of evidence document additional roles for lncRNAs in various reproductive pathologies. A study of nineteen men with idiopathic infertility and histologically confirmed meiotic arrest revealed copy-number variants of three genes, including the lncRNA *LOC100507205*, that are unique to the meiotic-arrest patients as compared to 95 fertile controls (Eggers et al., 2015). Similarly, a screen in women for lncRNAs associated with premature rupture of the placental membranes (PPROM) identified thirteen lncRNAs that were differentially expressed in PPROM versus full-term placentae. These lncRNAs appear to play roles in the inflammatory response, smooth muscle contraction, and ligand-receptor interactions (Luo et al., 2013, 2015). In a third study, women suffering from polycystic ovary syndrome—characterized by high serum androgens, absence or irregular menstruation, and infertility—the lncRNAs *SRAP/SRA1* and *CTBP1-AS1* (carboxy-terminal binding protein 1, antisense transcript 1) were overexpressed compared to healthy controls (Liu et al., 2014,2015b).

Many studies have focused on the role of lncRNAs in various reproductive cancers. For example, *SRA*, already discussed as a regulator of nuclear hormone responses, is elevated in estrogen-responsive ovarian and breast cancer (Leygue et al., 1999; Murphy et al., 2000; Hussein-Fikret and Fuller, 2005). *PCGEM1* and *PCNR1* lncRNAs were first identified in aggressive prostate adenocarcinomas due to their overexpression (Yang et al., 2013), while *NEAT1* was implicated in the progression of androgen-insensitive prostate tumors (Chakravarty et al., 2014).

Extensive phenotypes are also linked to *H19* expression. Two related genital malformation syndromes are associated with epigenetic alterations at *H19*, which is methylated on the paternal allele and thereby silenced. In addition to silencing the paternal copy of *H19*, methylation is required for expression of the paternal copy of *IGF2*, to which *H19* is linked. Silver-Russell syndrome is clinically and genetically heterogeneous, with some patients exhibiting hypomethylation of *H19*. The most-severely hypomethylated females show congenital aplasia of the uterus and upper vagina, and severely hypomethylated males exhibit cryptorchidism and testicular agenesis (Bliek et al., 2006; Bruce et al., 2009). *H19* hypomethylation is also associated with some Müllerian aplasia patients, whose congenital

abnormalities of the female genital tract produce vaginal and uterine malformations that limit reproduction to methods involving surrogacy (Sandbacka et al., 2011). Because paternal silencing of *H19* and paternal expression of *IGF2R are* coupled, it is not clear whether aberrant expression of either or both loci is responsible for the reproductive phenotypes of these patients.

Evidence beyond associations are required to demonstrate the importance of candidate lncRNAs, identified from human clinical studies, in reproductive processes, and further investigation is necessary to reveal their mechanisms of action. Animal studies will be important in this regard, such as those demonstrating that mice deficient for the lncRNA *NEAT1* have impaired corpus luteum formation and failure to maintain pregnancy (Nakagawa et al., 2014).

CONCLUSION

While lncRNAs are recognized as important mediators of cellular fate and function, their roles in the reproductive processes are only now being elucidated. Descriptive, hypothesis-generating studies that characterize lncRNAs associated with reproduction represent the low-hanging fruit in the field. These studies are heavily concentrated in specific reproductive events, but remain sparse in others, and have been applied to a limited number of organisms. The more challenging studies entail identifying which of the discovered lncRNAs influence reproductive processes and how they do so. Detailed mechanistic studies will require manipulating lncRNA expression and evaluating reproductive phenotypes; characterizing lncRNA structures, ideally in vivo; identifying proteins and other factors interacting with lncRNAs; cataloging the chemical modifications present on lncRNAs and their interacting partners; and assessing the importance of those modifications for structure and function. Expanding such analyses across many species and a diversity of individuals within human populations will help reveal the evolutionary conservation of those lncRNA-mediated mechanisms that affect reproduction and the genetic variants that are important for reproductive health. Given the vast array of lncRNAs transcribed from complex genomes and their range of activities, such studies will rival the complexity and importance of functional genomic analyses of the coding genome.

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Abbreviations

Airn	antisense of IGF2R non protein-coding RNA
BOLL/BOULE	Boule-like RNA-binding protein
DAZ[L]	deleted In azoospermia [-like]
EHMT2/G9A	euchromatic histone-lysine N-methyltransferase 2
EZH2	enhancer of Zeste 2 polycomb repressive comlpex 2 subunit

H3H#me1/2/3	histone H3 lysine & methylation mono-/ di-/ or tri-methylation
HOX	homeobox
HOTAIR	HOX transcript antisense RNA
IGF2R	insulin-like growth factor 2 receptor
IME	inducer of meiosis
Kcnq1ot1	voltage-gated KQT-like potassium channel, subfamily Q member 1 KCNQ1 opposite strand/antisense transcript 1
KDM1A/LSD1	lysine-specific demethylase 1A
KMT2A/MLL	lysine-specific methyltransferase 2A/mixed-lineage leukemia
lncRNA	long noncoding RNA
m6A	N6-methyladenine
MALAT1	metastasis-associated lung adenocarcinoma transcript 1
miRNA	micro RNA
MOV1OL	Mov10 RNA-induced silencing complex RNA helicase-like 1
NEAT1	nuclear paraspeckle assembly transcript 1
PCGEM1	prostate-specific transcript
PGC	primordial germ cell
piRNA	piwi-interacting RNA
Poly(A)	polyadenylation
PRC2	polycomb repressive complex 2
Rasgrfl	Ras protein-specific guanine nucleotide-releasing factor 1
RNA-seq	RNA sequencing
siRNA	small-interfering RNA
SLC22A	solute-carrierfamily 22 member
SRA [SRAP/SRA1]	steroid receptor RNA activator [protein]
SRY	sex-determining region Y
UTR	untranslated region
Xist	X-chromosome inactive-specific transcript

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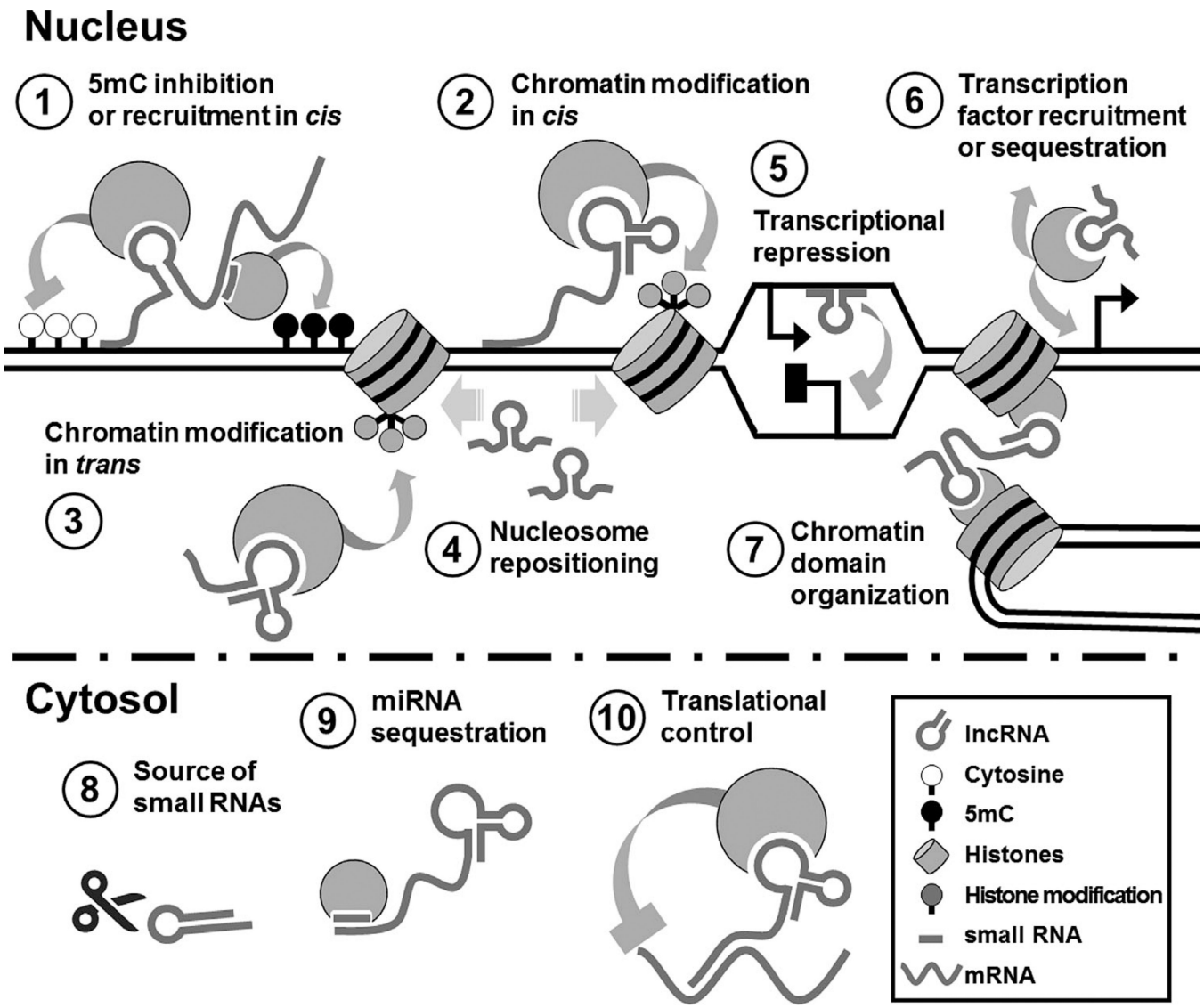

Figure 1.

Processes controlled by lncRNAs. In the nucleus (top), lncRNAs can either recruit or inhibit placement of a variety of chromatin modifications including DNA methylation (1) and histone modifications, either in *cis* (2) or in *trans* (3). They also control the positions of nucleosomes on the DNA by recruiting chromatin remodelers (4). While the simple act of antisense transcription (head-to-head orientation between a lncRNA and the gene it regulates) can directly inhibit gene expression (5), lncRNAs can also affect transcription by recruiting or sequestering transcription factors (6). The three-dimensional organization of the nucleus can be regulated by lncRNAs through chromatin looping (7), a phenomenon that brings distant regions of the DNA together. In the cytosol (bottom), lncRNAs can act as a source of miRNAs (8) or sponges to sequester them, inhibiting repression of translation by miRNAs (9). Additional small RNAs, including siRNAs and piRNAs, are also processed from lncRNAs outside the nucleus (8). Furthermore, lncRNAs can regulate protein accumulation either by inhibiting mRNA translation by the ribosome (10) or by changing

the stability of target mRNAs. Specific examples of all these mechanisms can be found in Table 1.

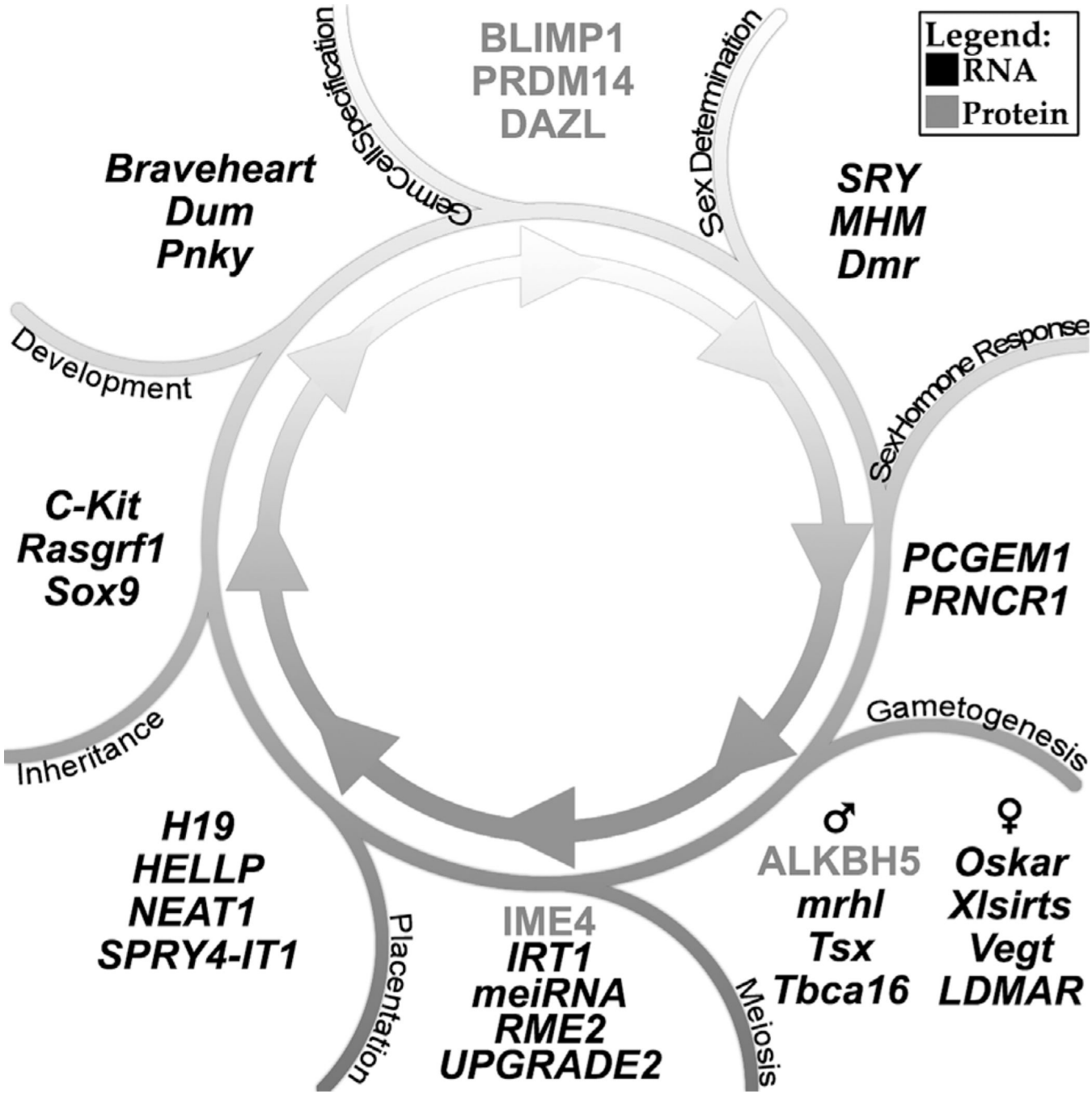

Figure 2.

Key steps in reproduction regulated by lncRNAs and lncRNA regulatory factors. lncRNAs denoted with italics; proteins denoted in upper case letters with no italics.

TABLE 1

Processes Controlled by lncRNAs

	Examples	References
Nuclear processes		
DNA methylation inhibition in *cis*	Extra-coding RNA, CpG island R-loop RNAs	Ginno et al. (2012); Di Ruscio et al. (2013)
DNA methylation recruitment in *cis*	Ribosomal DNA, promoter-associated non-coding RNA, piRNA-targeted RNA	Schmitz et al. (2010); Watanabe et al. (2011); Hamazaki et al. (2015)
Histone modification recruitment in *cis*	*Xist, Airn, HOTTIP*	Sleutels et al. (2002); Nagano et al. (2008); Zhao et al. (2008); Wang et al. (2011)
Histone modification recruitment in *trans*	*HOTAIR*	Rinn et al. (2007)
Histone modification state maintenance	*Firre*	Yang et al. (2015)
Nucleosome positioning	*SCHLAP1, MHRT, enhancer RNAs*	Mousavi et al. (2013); Prensner et al. (2013); Han et al. (2014)
Transcription interference	*Airn*	Latos et al. (2012)
Transcription factor sequestration	*Gas5, PANDA*	Kino et al. (2010); Hung et al. (2011)
Transcription factor recruitment	*BCAR4*	Xing et al. (2014)
Organize chromatin domains and *nuclear* bodies	*HOTTIP, Firre, MALAT1*	Tripathi et al. (2010); Wang et al. (2011); Yang et al. (2015)
Enhancer control	*ncRNA-a3,4,5,7,* enhancer RNAs *LED LUNAR*	Oram et al. (2010); Lam et al. (2013); Trimarchi et al. (2014); Leveille et al. (2015)
Histone variant recruitment	centromeric lncRNA	Quenet and Dalai (2014)
Splicing control	*MALAT1, FGF2R* antisense lncRNA	Tripathi et al. (2010); Gonzalez et al. (2015)
Cytoplasmic processes		
Source of mi RNAs	*H19*	Gao et al. (2012); Keniry et al. (2012)
miRNA sequestration	competing endogenous RNAs: *HULC, linc-MD1, HncRNA-RoR, H19 circular RNAs*	Franco-Zorrilla et al. (2007); Wang et al. (2010, 2013); Cesana et al. (2011); Hansen et al. (2013); Kallen et al. (2013)
Translation control RNA stability control	*Uchl1* antisense lncRNA, *HncRNA-p21 TINCR*	Carrieri et al. (2012); Yoon et al. (2012) Kretz et al. (2013)
Source of siRNAs and piRNAs	piRNA-targeted RNA, centromeric transcripts	Hall et al. (2002); Volpe et al. (2002); Watanabe et al. (2011)

BCAR4, breast cancer anti-estrogen resistance 4; *FGF2R*, fibroblast growth factor receptor 2; *Firre*, Firre Intergenic Repeating RNA Element; *HOTTIP, HOXA* distal transcript antisense RNA; *MHRT, Myheart;* myosin heavy chain-associated RNA transcript; *PANDA*, promoter of CDKN1A antisense DNA damage activated; RoR, regulator of reprogramming; *TINCR*, tissue differentiation-inducing non-protein coding RNA; *Uchl1*, ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase).

TABLE 2

lncRNAs With Identified Functions in Reproduction

Reproductive process	lncRNAs involved	Mechanisms	References
Gonadogenesis	*Sxl* promoter proximal RNAs	Activates *Sxl* (sex-lethal) and recruits chromatin modifiers like Polycomb and Trithorax.	Mulvey et al. (2014)
Sex determination	*SRY*	Acts as a miRNA sponge that competitively binds miR-138 to potentially influence sex determination.	Hansen et al. (2013)
	Dmr	Regulates splicing of *DMRT1* (Doublesex and Mab-3 related transcription factor 1).	Zhang et al. (2010)
Sex hormone responses	enhancer RNAs from ESR-bound enhancers	Controls estrogen receptor-regulated enhancer activity.	Li et al. (2013)
	PCGEM1	Binds androgen receptor and lncRNA *PRNCR1* (prostate cancer- associated non-coding RNA 1); alters chromatin topology affecting androgen responses.	Yang et al. (2013)
	PRNCR1	Binds androgen receptor and methyltransferase DOT1L (DOT1-like histone H3K79 methyltransferase); alters AR modification state and chromatin topology affecting androgen responses.	Yang et al. (2013)
	enhancer RNAs from the *KLK3* enhancer cluster	Recruits mediator and androgen receptor to *KLK3* and *KLK2* (Kallikrein-related peptidases 3 and 2).	Hsieh et al. (2014)
	SRA	Binds to and modulates activity of androgen receptor, estrogen receptor, and progesterone receptor; binds additional transcriptional regulators.	Lanz et al. (1999); Shi et al. (2001); Watanabe et al. (2001); Lanz et al. (2002); Hatchell et al. (2006)
Meiosis	*UPGRADE2*	Expressed specifically in Boechera species capable of asexual reproduction.	Mau et al. (2013)
	IRT1	Increases nucleosome occupancy and repressive modifications to silence the meiotic regulator *IME1*.	van Werven et al. (2012)
	RME2	Silences the oppositely transcribed meiotic regulator *IME4*, possibly by transcriptional interference.	Gelfand et al. (2011); Hongay et al. (2006); van Werven et al. (2012)
	meiRNA	Regulates nuclear import of the meiosis regulator Mei2 and formation of nuclear dots that are used to sequester Mmi1, which is capable of degrading meiosis regulating transcripts.	Yamashita et al. (1998); Harigaya et al. (2006); Shichino et al. (2014)
Spermatogenesis	*mhrl*	Regulates Wnt signaling in spermatogonia! cells.	Arun et al. (2012)
	Tsx	Suppresses apoptosis of pachytene spermatocytes.	Anguera et al. (2011)
	LDMAR	Required for anther development in rice.	Ding et al. (2012)
Oogenesis	*oskar*	Non-coding functions of *oskar* mRNA required for early establishment of oocyte polarity.	Jenny et al. (2006)
	Xlsirt and *VegT*	Required for cytoskeletal organization and oocyte polarity in Xenopus.	Kloc et al. (2005)
	XLOC_057324	Regulates flowering time and seed setting in rice.	Zhang et al. (2014)
Placentation	*H19*	Controls placental growth regulated by NOM01 (NODAL modulator 1) by encoding miR-675 that controls *NOM01* translation.	Gao et al. (2012); Keniry et al. (2012)
	HELLP	Controls cell survival and migration of trophoblast cells.	van Dijk et al. (2012)
	SPRY4-IT1	Controls cell survival and migration of trophoblast cells.	Zou et al. (2013)
	Airn	Regulates imprinted expression of *Igf2r*, *Slc22a2*, and *Slc22a3*, which influence placental growth.	Nagano et al. (2008); Zwart et al. (2001)
	Kcnq1ot1	Regulates imprinted expression of eight linked genes that influence placental growth.	Pandey et al. (2008)

Reproductive process	lncRNAs involved	Mechanisms	References
Reproductive disease	*NEAT1*	Required for corpus luteum formation and pregnancy maintenance	Nakagawa et al. (2014)

TABLE 3

lncRNAs With Identified Functions in Development

Tissue	lncRNA	Function	References
Cardiovascular	*Fendrr*	Regulates cardiac development	Grote and Herrmann (2013); Grote et al. (2013)
	Braveheart	Regulates cardiovascular development	Klattenhoff et al. (2013)
	tie 1AS	Regulates TIE1 (tyrosine kinase with immunoglobulin-like and EGF-like domains 1) and vascular development	Li et al. (2010)
Hematopoietic	*H19*	Maintains hematopoietic stem cell quiescence	Venkatraman et al. (2013)
	lncRNA-αGT	Necessary for embryonic to adult alpha-globin switching	Arriaga-Canon et al. (2014)
	7 species	Controls terminal erythroid differentiation	Paralkar et al. (2014)
Musculoskeletal	*SRA*	Enhances myogenic differentiation and myogenic conversion of non-muscle cells	Hube et al. (2011)
	lincMD1	Enhances myoblast differentiation	Cesana et al. (2011)
	Dum	Regulates myoblast differentiation	Wang et al. (2015)
	MUNC	Induces myoblast differentiation	Mueller et al. (2015)
Neural	*Six3OS*	Regulates SIX3 (SIX homeobox 3) and retinal development	Rapicavoli et al. (2011)
	TUNAR	Regulates pluripotency and neural differentiation	Lin et al. (2014)
	Evf2	Represses DLX5 (distal-less homeobox 5) and controlling GABA circuitry	Berghoffet al. (2013)
	Pnky	Regulates neurogenesis from neural stem cells	Ramos et al. (2015)
Mammary	*Pinc1*	Regulates alveolar development	Shore et al. (2012)
	Zfas1	Regulates alveolar development	Askarian-Amiri et al. (2011)
Endoderm	*DEANR1/LINC00261*	Regulates endoderm differentiation	Jiang et al. (2015)
Adipose	*HOTAIR*	Regulates preadipocyte differentiation	Divoux et al. (2014)
	10 species	Regulates preadipocyte differentiation	Sun et al. (2013)