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Long noncoding RNAs in human reproductive processes and diseases

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Abstract

Infertility has become a global disease burden. Although assisted reproductive technologies are widely used, the assisted reproduction birth rate is no more than 30% worldwide. Therefore, understanding the mechanisms of reproduction can provide new strategies to improve live birth rates and clinical outcomes of enhanced implantation. Long noncoding RNAs (lncRNAs) have been reported to exert regulatory roles in various biological processes and diseases in many species. In this review, we especially focus on the role of lncRNAs in human reproduction. We summarize the function and mechanisms of lncRNAs in processes vital to reproduction, such as spermatogenesis and maturation, sperm motility and morphology, follicle development and maturation, embryo development and implantation. Then, we highlight the importance and diverse potential of lncRNAs as good diagnostic molecular biomarkers and therapeutic targets for infertility treatment.

KEYWORDS

human reproduction, long noncoding RNAs, potential biomarkers, potential therapeutic targets, reproductive diseases

1 | INTRODUCTION

Infertility is defined as the inability to achieve pregnancy after 1 year of regular, unprotected sexual intercourse (Peipert et al., 2022; Zhu et al., 2022). It is estimated that the age-standardized prevalence rate of infertility increased by 0.291% per year for males and 0.370% per year for females in 195 countries and territories from 1990 to 2017 (Sun et al., 2019). Recent evidence has demonstrated that approximately 186 million people are affected by infertility, and 15% of reproductive-aged couples suffer from this common medical problem (Dongarwar et al., 2022). Given that infertility has become a global disease burden, assisted reproductive technologies (ARTs) have become widely used around the world (De Geyter, 2019) since the birth of the first "test tube baby" in 1978. ARTs involve ovarian stimulation, egg retrieval, in vitro fertilization, embryo culture, and embryo implantation (Chambers et al., 2017). Many new technologies have been introduced in ART in recent decades, including intracytoplasmic sperm injection, preimplantation genetic testing, and time-lapse monitoring (Giacobbe et al., 2022). However, the assisted reproduction birth rate is no more than 30% worldwide (Gao et al., 2023). Understanding the mechanism by which reproduction develops can provide new strategies to improve the clinical outcomes of enhanced implantation and live birth rates.

Long noncoding RNAs (lncRNAs) are noncoding transcripts with lengths no more than 200 nucleotides (Mattick et al., 2023). Since the first noncoding gene H19 was discovered in the late 1980s, the

Abbreviations: AM, adenomyosis; ART, assisted reproductive technology; EM, endometriosis; FSH, follicle-stimulating hormone; GC, granulosa cell; ICM, inner cell mass; lncRNA, long noncoding RNA; MA, maturation arrest; NOA, nonobstructive azoospermia; PCOS, polycystic ovary syndrome; RIF, recurrent implantation failure; scRNA-Seq, single-cell RNA sequencing.

Le Zhang and Hailong Sun contributed equally to this study.

investigation of lncRNAs has gradually become a focus in research (Pachnis et al., 1984). The identification and characterization of lncRNAs increased in the 2000s because global human genome sequencing revealed many noncoding transcripts (Jarroux et al., 2017). In central nervous system diseases, lncRNAs exert their regulatory roles at epigenetic, transcriptional, posttranscriptional, and structural levels to affect Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease (Policarpo et al., 2021). In hematopoiesis, lncRNAs, such as lncRNA FIRRE (Lewandowski et al., 2019), HOTTIP (Y. Qiu et al., 2021), and HOTAIRM1 (Zhang et al., 2009), are implicated in the regulation of the modulation of hematopoietic gene expression and differentiation in several hematopoietic and related lineages. Multiple lncRNAs, including lncDACH1 (Cai et al., 2020), lncRNA-Safe (Hao et al., 2019), and MALAT1 (Yan et al., 2020), were reported to be involved in cardiovascular diseases. Remarkably, the roles of lncRNAs in cancer are well established (Aprile et al., 2020). Given that lncRNAs are important regulators and potential mediators of physiological and pathological processes, they have attracted much attention.

Reproductive development is regulated by the interaction of multiple factors. LncRNAs have been identified as vital regulators of many of these factors, such as sex determination (Golicz et al., 2018), hormone responses (Sanbonmatsu, 2022), meiosis (Pondugala & Mishra, 2022), and nongenetic inheritance (Cheuquemán & Maldonado, 2021) in many species. However, mechanistic studies of human reproductive development are limited due to the scarcity of human samples and ethical constraints. In this review, we focus only on human studies, presenting evidence of lncRNAs in male and female fertility regulation, summarizing lncRNA dysregulation in pathological reproduction and discussing the potential application of lncRNAs in clinical reproduction.

2 | THE CLASSIFICATION AND FUNCTION OF LNCRNAS

LncRNAs can be classified into five categories according to the location of lncRNAs with respect to protein-coding genes: intergenic lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs, and sense lncRNAs (Yousefi et al., 2020). Based on their structure, lncRNAs are classified into linear lncRNAs and circular lncRNAs (Dahariya et al., 2019). In addition, other classifications of lncRNAs have been proposed depending on their characteristics, such as length, transcript properties, and function (Jarroux et al., 2017).

With a plethora of studies on the functional characterization of lncRNAs, it is worth noting that lncRNAs play crucial roles in cellular functions through various mechanisms. In the nucleus, lncRNAs modulate chromatin architecture, chromatin remodeling, and transcriptional regulation (Yao et al., 2019). For example, lncRNA Xist recruits the X chromosome to the nuclear lamina, and lamina recruitment changes the 3D structure of DNA, enabling Xist and its silencing proteins to spread across the X chromosome to silence transcription (Chen et al., 2016). LncRNAs, such as lncRNA KHPS1, TARID, and APOLO, hybridize with DNA to regulate chromatin accessibility (Statello et al., 2021). lncTCF7 and lncRNA AGAP2-AS1 modulate transcription through cis and trans regulation, respectively, while lncRNA GAS5 directly functions as a transcription factor to regulate transcription (Gao et al., 2020). In the cytoplasm, lncRNAs regulate mRNA turnover, translation, and posttranslational modifications. For instance, lncRNAs can influence alternative splicing (lncRNAs DGCR5 [Duan et al., 2021] and PLANE [Teng et al., 2021]), stability and degradation of mRNA (lncRNA Sros1 [Xu et al., 2019] and MACC1-AS1 [Zhao et al., 2018]). For translation and posttranslational modifications, lncRNAs regulate translational factors (LincRNA-p21 [Yoon et al., 2012] and SNHG4 [Hu et al., 2013]) and posttranslationally modified proteins (lnc-DC [Wang et al., 2014] and MALAT1 [Zhang et al., 2019]).

3 | THE ROLES OF LNCRNAS IN MALE REPRODUCTION

3.1 | The influence of lncRNAs on physiology

Spermatogenesis is a continuous process to produce mature spermatozoa. First, spermatogonia divide mitotically to form primary spermatocytes that contain 46 pairs of sister chromatids, called tetraploids (Babatunde et al., 2017). Then, primary spermatocytes undergo meiotic division I to form secondary spermatocytes, of which genetic material is halved. Subsequently, secondary spermatocytes generate haploid spermatids through meiotic division II (Babatunde et al., 2017). Finally, spermatids transform into mature spermatozoa by undergoing the process in which they lose most cytoplasm, highly condense genetic material, and form a flagellated tail (Lehti & Sironen, 2017). In the process of spermatogenesis, lncRNAs are ubiquitously expressed. Jan et al. selected six specific germ cell subtypes (A_{pale} and A_{dark} spermatogonia, leptotene/zygotene, early pachytene and late pachytene spermatocytes and round spermatids) to explore differentially expressed (DE) lncRNAs during spermatogenesis. They discovered that 137 of the 2736 lncRNAs exhibited germ cell subtype-specific expression patterns (Jan et al., 2017). RNA sequencing was employed to reveal the transcriptome of human spermatogenesis by using spermatogonial, spermatocyte, and spermatid samples. A total of 157 of the 1800 DE lncRNAs were found during human spermatogenesis. Due to the expression patterns of these ncRNAs, they might be important for meiosis, spermiogenesis, and premeiotic development (Zhu et al., 2016). A study reported by Corral-Vazquez et al. employed 12 semen samples from fertile donors to reveal RNA-seq profiling of human sperm mRNAs and lncRNAs through high-throughput transcriptome analyses (Corral-Vazquez et al., 2021). There were 7521 expressed lncRNAs (transcripts with a mean population expression of FPKM ≥ 0.5) in these semen samples, among which 4254 lncRNAs were highly expressed (transcripts with a mean population expression of FPKM ≥ 10) and 116 lncRNAs were ubiquitously expressed (transcripts with a minimum expression of

FPKM ≥ 0.5) (Corral-Vazquez et al., 2021). Predicted target genes of expressed lncRNAs in healthy human sperm were mostly enriched in the regulation of signaling and embryo development pathways (Corral-Vazquez et al., 2021).

3.2 | The influence of lncRNAs on pathology

In addition to physiological conditions, the expression of lncRNAs in pathology has also been extensively studied. By using lncRNA microarrays to detect lncRNA profiles in the testes of infertile men with maturation arrest (MA) ($n = 3$) or hypospermatogenesis (Hypo) ($n = 2$) compared with three control subjects, 757 downregulated and 475 upregulated lncRNAs were identified in MA, while 2370 downregulated and 163 upregulated lncRNAs were identified in Hypo (Lü et al., 2015). In asthenozoospermia, research revealed that 29,038 lncRNAs were testis/sperm-specifically expressed, among which 1566 were annotated lncRNAs and 27,472 were predicted novel lncRNAs with semen samples from asthenozoospermic patients ($n = 36$) and normal sperm samples ($n = 48$) (Zhang et al., 2019). Another study also discovered 995 known DE lncRNAs and 11,706 novel DE lncRNAs from seminal plasma exosomes between the asthenozoospermia ($n = 25$) and normal groups ($n = 25$) (Lu et al., 2020). By using seminal plasma extracellular vesicles from normozoospermia ($n = 6$) and azoospermia ($n = 5$), 33,489 extracellular vesicle lncRNAs (exlncRNAs) were identified (Xie et al., 2020). With inclusion ($p < 0.05$ and $|\text{Log2FC}| \geq 2.0$) and exclusion (|FPKM| in every sample <1) criteria, 88 lncRNAs were filtered, including 26 upregulated and 62 downregulated lncRNAs (Xie et al., 2020).

Functional studies have also revealed many regulatory roles of lncRNAs (Figure 1). Two similar studies uncovered the correlation between sperm motility and lncRNAs. In asthenozoospermia, three sperm/testis-specific/enriched lncRNAs, lnc32058, lnc09522, and lnc98487, were negatively associated with the sperm progressive motility rate ($p < 0.05$; lnc3208, $r = -0.1533$; lnc09522, $r = -0.2412$; lnc98487, $r = -0.1824$) (Zhang et al., 2019). In addition, Lu and his colleagues constructed a lncRNA–miRNA–mRNA regulatory network consisting of 11 lncRNAs, 35 miRNAs, and 59 mRNAs and discovered 254,981 positively correlated lncRNA–mRNA pairs, including 7 cis-regulated correlation pairs, which provided clues regarding candidate lncRNAs involved in sperm motility with asthenozoospermia (Lu et al., 2020). LncRNA NLC1-C (narcolepsy candidate-region 1 gene) accumulated in the nucleus of spermatogonia and primary spermatocytes in the testes of patients with MA by binding to nucleolin and repressing miR-320a and miR-383 transcripts (Lü et al., 2015). This led to hyperactive proliferation of germ cells and correlated with male infertility (Lü et al., 2015). In asthenozoospermia or oligoasthenozoospermia patients, HOTAIR expression levels were positively associated with sperm quality, including sperm progressive motility

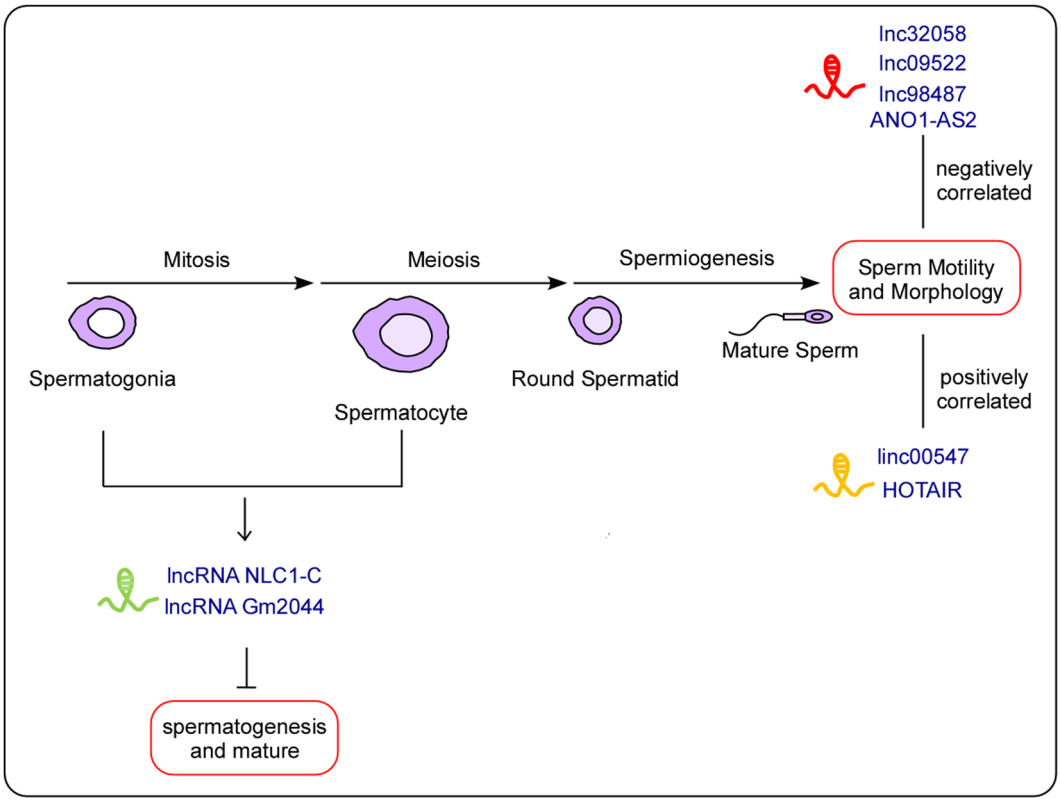

FIGURE 1 lncRNAs are involved in the regulation of male reproduction, including spermatogenesis, maturation, sperm motility, and morphology.

($p < 0.01$, $R = 0.71$), normal sperm morphology ($p < 0.01$, $R = 0.53$), and vitality ($p < 0.01$, $R = 0.65$), in 90 semen samples (Zhang et al., 2015). Downregulation of HOTAIR inhibited the expression of Nrf2 by decreasing histone H4 acetylation in the Nrf2 promoter, and the reduction in sperm HOTAIR expression level was positively associated with SOD activity (Zhang et al., 2015). It has been reported that Nrf2 is correlated with sperm quality and that SOD prevents a decrease in sperm motility by scavenging ROS in spermatozoa (Chen et al., 2012; Cocchia et al., 2011; Dandekar et al., 2002). In mice, HOTAIR facilitates proliferation and inhibits apoptosis of mouse spermatogonium GC-1 cells by acting as a sponge of miR-761 to regulate NANOS2 expression (Kong et al., 2022). In asthenozoospermia and teratoasthenozoospermia, two lncRNAs have been well studied and revealed. According to docking analysis, lncRNA ANO1-AS2 might bind to the ANO1 gene promoter, and it was negatively associated with the ANO1 gene. ANO1-AS2 had an inverse association with sperm motility and morphology ($p < 0.05$) (Saberiyan et al., 2020). Linc00574 was positively associated with TCTE3 ($p < 0.05$), while TCTE3 had a significant positive relationship with sperm motility and morphology ($p < 0.05$). TCTE3 is one of the light chains in the outer dynein arm that is an important component of the flagellum (Saberiyan et al., 2021). In nonobstructive azoospermia (NOA), LINC00467 in the DE lncRNA-mediated ceRNA network (integrating E-TABM-1214, E-TABM-234, and GSE45885 datasets) regulates the expression of LRGUK and TDRD6, which are closely involved in NOA (Bo et al., 2020). lncRNA Gm2044 was upregulated in testicular tissue from NOA with spermatogonial arrest. Moreover, Gm2044 was weakly expressed in spermatogonia and highly expressed in healthy spermatocytes (Liang et al., 2019). Increased expression of lncRNA Gm2044 functions as a miR-202 host gene to suppress male germ cell development in NOA (Liang et al., 2019). In mice, Gm2044 was enriched in spermatocytes and suppressed the proliferation of mouse spermatogonia GC-1 cells and spermatocyte GC-2 cells by inhibiting translation of the spermatogenesis-related gene Utf1 (Hu et al., 2018). In mouse spermatocyte-derived GC-2spd (ts) cells, A-MYB-mediated transcriptionally activated Gm2044 modulated the expression of Sycp1 by sponging miR-335-3p (Liang et al., 2020). A-MYB deficiency in mice resulted in the arrest of spermatogenesis, and Sycp1 was an important regulator of meiosis during spermatogenesis (Sage et al., 1999; Toscani et al., 1997). This study provided new insight into the mechanistic roles of lncRNA Gm2044/miR-335-3p in the regulation of spermatocyte function by transcription factor A-MYB (Liang et al., 2020). Importantly, using the transgenic mouse model of lncRNA-Gm2044, researchers found that the upregulation of lncRNA-Gm2044 did not affect testicular morphology and fertility but partially impaired spermatogenesis in transgenic mice (Hu et al., 2022).

Although many studies have investigated the expression and function of lncRNAs in human spermatogenesis, there are still several limitations. Existing evidence comes from the analysis of a limited number of human samples, and common patterns of lncRNAs need to be explored based on a large sample size. Most studies have investigated the association between lncRNAs and disease, and further functions and mechanisms remain to be elucidated. Few studies have verified the role of lncRNAs in vivo, such as employing animal models to simulate and reconstruct the process of spermatogenesis.

4 | THE ROLES OF LNCRNAS IN FEMALE REPRODUCTION

4.1 | The influence of lncRNAs on physiology

Folliculogenesis is a dynamic process starting with primordial follicles, then primary follicles, and then secondary/preantral follicles with proliferation of granulosa cells (GCs) (Georges et al., 2014). Subsequently, upon follicle-stimulating hormone (FSH) stimulation, antral follicles become preovulatory follicles, in which the antrum is formed and GCs are de facto divided into cumulus and mural GCs (Georges et al., 2014). During this stage, most follicles undergo atresia, and only one or a limited number of follicles can grow to the preovulatory stage. Finally, ovulation is triggered by luteinizing hormone (LH) and FSH. In ARTs, ovarian stimulation and egg retrieval are performed by doctors. In vitro fertilization replaces natural fertilization in the laboratory. Preimplantation embryo development involves oocyte fertilization along with pronuclear formation. The first cell of the embryo divides into two cells, then into four, then into eight, and so forth. Subsequently, 16-32 cells compact into a morula, and then the morula differentiate into the inner cell mass (ICM) and the trophectoderm to form blastocysts (Yamanaka et al., 2006). High-quality embryos are chosen for transfer to the uterus.

4.1.1 | Ovarian function

Existing evidence has shown that lncRNAs play vital roles in the whole folliculogenesis process (Figure 2a). Ernst et al. isolated primordial, primary follicles, and small antral follicles from ovarian tissue donated by three women to perform transcriptome sequencing (Ernst et al., 2018). They found that the lncRNAs XIST, NEAT1, MALAT1, and GAS5 were expressed during follicle development. Of note, the presence and dynamics of lncRNAs and paraspeckle proteins indicated that they may be involved in functions in the cyclic recruitment and differentiation of human follicles by regulating gene expression control, scaffold formation, and epigenetic control (Ernst et al., 2018). During the preovulatory follicle stage, cumulus and mural GCs are formed, which are important for successful folliculogenesis and oocyte maturation. Three independent studies revealed the roles of cumulus lncRNAs in follicular maturation and embryo development. Yerushalmi et al. discovered 89 DE lncRNAs between cumulus cells from a single GV oocyte and M2 oocyte, of which 12 lncRNAs are located within the introns of genes that closely participate in GC physiology. This study gained our knowledge of potential regulatory lncRNAs involved in final follicular maturation and ovulation (Yerushalmi et al., 2014). Li and

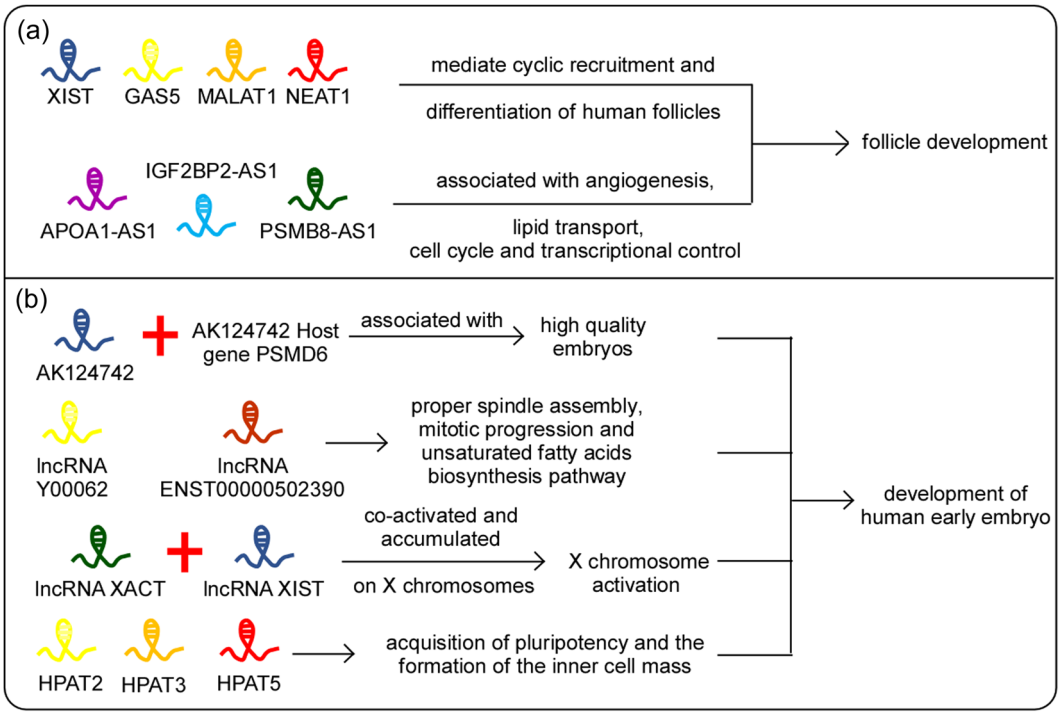

FIGURE 2 Influence of lncRNAs on the physiology of female reproduction. (a) Regulatory roles of lncRNAs in ovarian function. (b) Regulatory roles of lncRNAs in embryonic growth.

her colleagues found that the expression levels of lncRNA AK124742 and its host gene PSMD6 were higher in the high-quality embryo/pregnancy group than in the poor-quality embryo/nonpregnancy group ($p < 0.01$), which might prove the potential of the AK124742-PSMD6 gene pair as a biomarker to aid embryo selection (Li et al., 2015). A microarray analysis from a study by Xu revealed 633 DE lncRNAs (fold change ≥ 2.0) between 3 pairs of cumulus cells from mature oocytes resulting in high-quality embryos and those from oocytes resulting in poor-quality embryos (Xu et al., 2015). DE lncRNAs, such as lncRNA Y00062 and lncRNA ENST00000502390, might facilitate the development of oocytes and early embryos by regulating proper spindle assembly, mitotic progression and the unsaturated fatty acid biosynthesis pathway (Xu et al., 2015). In addition, differential lncRNA expression profiles in human cumulus and oocyte cells were also assessed. By analyzing publicly available RNA-sequencing data, Bouckenheimer et al. reported that 2021 and 6236 lncRNAs were upregulated in MII oocytes and cumulus granulosa samples, of which 149 and 470 lncRNAs showed a fold change ≥100 in MII oocytes and cumulus GCs, respectively (Bouckenheimer et al., 2018). By quantitative PCR, they validated the expression of lncRNAs specifically expressed in MII oocytes (BCAR4, TUNAR, CASC8, C3orf56, LINC01118, and OOEP-AS1) and in cumulus cells (ANXA2P2, IL6STP1, and MALAT1) in an independent cohort. Cumulus lncRNAs were coexpressed with genes involved in apoptosis and extracellular matrix-related functions, while MII oocyte lncRNAs might participate in cell pluripotency, chromatin remodeling, and early embryonic development (Bouckenheimer et al., 2018). Furthermore, they discovered that lncRNAs APOA1-AS, IGF2BP2-AS1, and PSMB8-AS1 with age-related decreased expression might participate in oocyte maturation and follicle development. This study provided a new direction for studying aging oocytes and identified potential biomarkers to evaluate IVF feasibility in aged couples [35].

4.1.2 | Embryonic growth

In human early embryonic development, lncRNAs are also hot topics attracting much attention (Figure 2b). Single-cell RNA sequencing (scRNA-Seq) was employed to detect human preimplantation embryos (zygote (2PN), two-cell, four-cell, eight-cell, morula, and late blastocyst stages) and embryonic stem cells. They found a stage-specific expression pattern of lncRNAs, such as variable changes in maternally inherited lncRNAs in developmental stages and apparent decreases after the four-cell stage (Yan et al., 2013). In addition, they also revealed relatively abundant lncRNAs in individual cells. Heterogeneity of lncRNA expression indicated their potential function in human embryos because they have variable expression in cells of the same embryo and appearance in different embryos of the same stage (Yan et al., 2013). A total of 1197 out of 2733 novel lncRNAs were expressed variably across all embryo development stages (Yan et al., 2013). Bouckenheimer et al. revealed that some lncRNAs (OOSP1, BCAR4, C3orf56, TUBB8P7, LINC01118, etc.) were stable during the first early cleavage stages and dramatically decreased at the time of maternal genome

degradation and embryonic genome activation (four-cell and eight-cell stages), which indicated that they might have potential regulatory roles in these processes (Bouckenheimer et al., 2018). Through scRNA-Seq, lncRNA editing sites were found to have much more occurrence on RNA splicing sites than mRNAs (lncRNA: odds ratio = 2.19, $P = 1.37 \times 10^{-8}$; mRNA: odds ratio = 0.22, $P = 8.38 \times 10^{-46}$), and RNA editing might regulate lncRNA alternative splicing during embryo development due to a higher correlation coefficient with the percentage spliced index (PSI) of lncRNA exons ($R = 0.75$, $P = 4.90 \times 10^{-16}$) (J. Qiu et al., 2021). RNA editing-regulated lncRNAs were found to be closely involved in the regulation of transcript expression, signal transduction, and the transmembrane transport of mitochondrial calcium ions, which engaged in distinct key events during human early embryo development (J. Qiu et al., 2021). Despite the analysis of scRNA-Seq data, there is also experimental evidence. Vallot et al. demonstrated that lncRNAs XACT and XIST were coactivated and accumulated in the early stages of human development, and XACT antagonized XIST activity of X chromosome silencing, which provided new insight into the contribution of lncRNAs in human-specific developmental mechanisms (Vallot et al., 2017). In cloned mice, knockout or knockdown of XIST increased the cloning efficiency of mouse embryos (Dong et al., 2022). Durruthy and colleagues provided the first evidence supporting the vital roles of lncRNAs in human embryogenesis (Durruthy-Durruthy et al., 2016). They found that lncRNAs HPAT2, HPAT3, and HPAT5 contributed to the formation of the ICM and the acquisition of pluripotency, thus exerting their functions in human preimplantation development and nuclear reprogramming (Durruthy-Durruthy et al., 2016).

4.2 | The influence of lncRNAs on pathology

LncRNAs play a fundamental role not only in reproductive physiology but also in the pathology of female reproduction. Several studies have revealed the functional role of lncRNAs in embryo implantation (Figure 3a). Li et al. discovered that three lncRNAs (ENST00000448179, ENST00000433673, and ENST00000414116) had higher expression in uterine endometrial tissues from normal people than in those from patients with adenomyosis (AMs), endometriosis (EMs), and recurrent implantation failure (RIF) by reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) detection (Li et al., 2019). Bioinformatics analysis revealed an interaction between ENST00000433673 and its target mRNA ITGAL and its interacting mRNA ICAM1. RT-qPCR analysis found that ITGAL and ICAM1 were downregulated in AMs, EMs, and RIF, consistent with ENST00000433673 expression. ICAM1 is a transmembrane glycoprotein that is best known for influencing cell adhesion (Wang et al., 2023). They speculated that the ENST00000433673/ITGAL/ICAM1 axis might regulate embryo adhesion (Li et al., 2019). Wang and colleagues revealed that lncRNA TUNAR was significantly more highly expressed in RIF patients and that enforced expression of TUNAR destroyed spheroid attachment to endometrial epithelial cells (EECs) as well as repressed decidualization of endometrial stromal

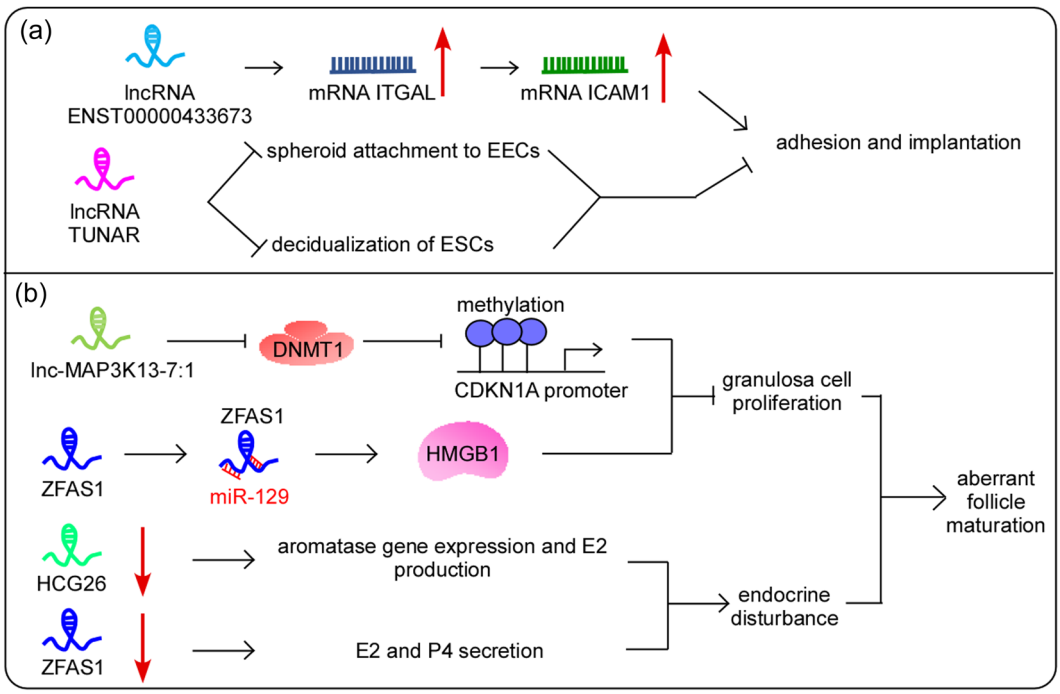

FIGURE 3 The influence of lncRNAs on the pathology of female reproduction. (a) The lncRNAs participating in adhesion and implantation. (b) The lncRNAs involved in aberrant follicle maturation. E2, estradiol; EEC, endometrial epithelial cell; ESC, endometrial stromal cell; P4, progesterone.

cells (ESCs) (Wang et al., 2020). These findings uncovered the function of TUNAR in embryo implantation by modulating endometrial receptivity. Huang et al. found seven DE lncRNAs (PART1, LINC00173, H19, SCARNA9, SNHG11, C1orf229, and MIR17HG) from the GSE111974 data set (consisting of samples from RIF and normal women) and constructed a lncRNA-related competing endogenous RNA network (Huang et al., 2021). They identified five hub genes (TRPM6, MAP2K6, TET2, LRRC1, and GJA1) coexpressed with these lncRNAs and DE in the RIF endometrium, enriched in cell adhesion, regulation of cell motility, and so forth, which might be new targets of RIF for early diagnosis and treatment (Huang et al., 2021). GC proliferation was identified as a vital regulator of aberrant follicle maturation (Khristi et al., 2018). It was reported that lncRNA HCG26, lnc-MAP3K13-7:1 and lncRNA ZFAS1 had increased expression in polycystic ovary syndrome (PCOS) and inhibited GC proliferation (Figure 3b). Mechanistically, lnc-MAP3K13-7:1 decreased DNMT1 expression, resulting in CDKN1A promoter hypomethylation to suppress GC proliferation (Geng et al., 2021). LncRNA ZFAS1 functions as a sponge of miR-129 to facilitate HMGB1 expression, leading to inhibition of GC proliferation (Zhu et al., 2020). In addition, lncRNA HCG26 and ZFAS1 could influence endocrine disturbance to contribute to PCOS. Silencing HCG26 increased aromatase gene expression and E2 production, and lncRNA ZFAS1 knockdown promoted E2 and P4 secretion (Liu et al., 2017; Zhu et al., 2020).

5 | POTENTIAL CLINICAL APPLICATION OF LNCRNAS IN HUMAN REPRODUCTION

Regarding the potential biomarker utility of sperm lncRNAs, a panel of extracellular vesicle lncRNAs (LINC00301, LINC00343, LOC101929088, LOC100505685, LOC101929088, LOC440934, GABRG3-AS1, CCDC37-DT, and SPATA42) in seminal plasma was verified for predicting testicular spermatozoa in NOA patients (auv = 0.986, $p < 0.001$) (Xie et al., 2020). Sun and colleagues employed sequencing data from 12 human normozoospermic and oligozoospermic samples and revealed that DE lncRNAs induce oxidative stress and spermatogenesis by regulating endoplasmic reticulum genes and pathways (Sun et al., 2021). LncRNAs were also reported to be potential biomarkers for PCOS. lncRNA CTBP1-AS, a regulator of androgen receptor (AR) activity, had higher expression in peripheral blood leukocytes from women with PCOS than in controls (Liu et al., 2015). Expression of CTBP1-AS was recognized as an independent risk factor for PCOS. Aberrant expression of lncRNAs in cumulus cells could be used to discriminate the cumulus cells of PCOS patients from those of normal patients (Huang et al., 2016). LncRNA AK124742 and its host gene PSMD6 were positively correlated with high-quality embryos ($p < 0.01$) and pregnancy outcome ($p < 0.01$), which might indicate the clinical role of lncRNAs as biomarkers for evaluating the viability of an embryo (Li et al., 2015). Given the promising and potential clinical application of lncRNAs in human reproduction, it is important to explore the function and mechanism of lncRNAs in reproduction, driving the translation of basic research to clinical research that verifies their utility.

6 | CONCLUSION AND FUTURE PERSPECTIVES

Existing evidence has revealed that lncRNAs are closely involved in reproductive processes and reproductive diseases. Using RNA sequencing, many studies have compared healthy controls and samples with reproductive diseases to distinguish the DE lncRNAs, which indicated the potential regulatory roles of these lncRNAs in reproduction. Furthermore, functional analysis revealed that lncRNA NLC1-C and Gm2044 participate in human spermatogenesis and maturation (Liang et al., 2019; Lü et al., 2015). Five lncRNAs (lnc32058, lnc09522, lnc98487, HOTAIR, ANO1-AS2, and Linc00574) were identified as regulators of sperm motility and morphology (Saberiyan et al., 2020; Saberiyan et al., 2021; Zhang et al., 2015, 2019). Research on particular lncRNAs revealed their biological function in follicle development (lncRNAs XIST, NEAT1, MALAT1, GAS5, APOA1-AS, IGF2BP2-AS1, and PSMB8-AS1) (Bouckenheimer et al., 2018; Ernst et al., 2018), follicle maturation (lncRNA HCG26, lnc-MAP3K13-7:1 and LncRNA ZFAS1) (Geng et al., 2021; Liu et al., 2017; Zhu et al., 2020), embryo development (lncRNA AK124742, Y00062, ENST00000502390, XACT, XIST, HPAT2, HPAT3, and HPAT5) (Durruthy-Durruthy et al., 2016; Li et al., 2015; Vallot et al., 2017; Xu et al., 2015), and embryo implantation (lncRNA ENST00000433673 and TUNAR) (Li et al., 2019; Wang et al., 2020).

In reproductive pathology, lncRNAs have been proposed as good diagnostic molecular biomarkers and therapeutic targets for infertility treatment. A panel of lncRNAs was verified for distinguishing NOA and oligozoospermic individuals from healthy controls (Sun et al., 2021; Xie et al., 2020). lncRNA CTBP1-AS has high diagnostic potential to discriminate the cumulus cells of PCOS patients from those of normal patients (Huang et al., 2016). LncRNA Gm2044 functions as a ceRNA of miR-138-5p to facilitate 17β-estradiol synthesis, which might be a potential target for the treatment of PCOS (He et al., 2021).

Due to the scarcity of human samples and ethical constraints, research on human reproduction has mainly focused on in vitro and disease-related cell line levels. Therefore, the function of lncRNAs in human reproduction is in its infancy and has tremendous possibilities. With advances in related technologies in reproduction, such as relevant in vivo model establishment and single-cell resolution functional annotation, investigation of lncRNA-mediated mechanisms in reproduction will provide new strategies for the diagnosis and treatment of infertility.

AUTHOR CONTRIBUTIONS

Le Zhang: Conceptualization; writing—original draft; funding acquisition; writing—review and editing. **Hailong Sun**: Methodology; resources; writing—original draft. **Xiujuan Chen**: Conceptualization; writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

ETHICS STATEMENT

Not applicable.

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