Review Article

Long Noncoding RNA Mediated Regulation in Human Embryogenesis, Pluripotency, and Reproduction

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Long noncoding RNAs (lncRNAs), a class of noncoding RNAs with more than 200 bp in length, are produced by pervasive transcription in mammalian genomes and regulate gene expression through various action mechanisms. Accumulating data indicate that lncRNAs mediate essential biological functions in human development, including early embryogenesis, induction of pluripotency, and germ cell development. Comprehensive analysis of sequencing data highlights that lncRNAs are expressed in a stage-specific and human/primate-specific pattern during early human development. They contribute to cell fate determination through interacting with almost all classes of cellular biomolecules, including proteins, DNA, mRNAs, and microRNAs. Furthermore, the expression of a few of lncRNAs is highly associated with the pathogenesis and progression of many reproductive diseases, suggesting that they could serve as candidate biomarkers for diagnosis or novel targets for treatment. Here, we review research on lncRNAs and their roles in embryogenesis, pluripotency, and reproduction. We aim to identify the underlying molecular mechanisms essential for human development and provide novel insight into the causes and treatments of human reproductive diseases.

1. Introduction

Identification and functional characterization of noncoding RNAs (ncRNAs) have revolutionized our traditional view of RNA biology, as well as developmental biology [1]. Before discovering microRNAs (miRNAs) and small interfering RNAs, mRNAs that are transcribed from the coding region of the genome and translated as proteins are considered the primary regulators of the gene expression program in the cells [2]. The vast majority of the genome that is not translated into protein is junk DNA regions [3]. With the rapid development of microarray and high-throughput sequencing technology, a comprehensive annotation of the mammalian genome demonstrates that most mammalian genome is actively transcribed into RNAs, and thousands of ncRNAs have been identified [4, 5]. ncRNAs are divided into two main types according to the length of the transcripts: small noncoding RNAs (sncRNAs), which are composed of less than 200 nucleotides, and long noncoding RNAs (lncRNAs), which consist of more than 200 nucleotides [6]. In this review, we focused on the discussion of lncRNAs. There are five different sources of lncRNAs: (1) a protein-coding gene was mutated and transformed into a noncoding RNA sequence. (2) Following chromosome rearrangement, two separate nontranscribed sequence regions are juxtaposed together to produce expressed noncoding sequences. (3) lncRNAs without a protein-coding function are produced by duplicating noncoding genes by retrotransposition. (4) Local two tandem duplication produces adjacent repeat sequences, which increases the size of IncRNAs. (5) The insertion of transposable elements (TEs) can produce functional IncRNAs [7, 8].

It was questionable whether IncRNAs have putative functions in cells, as they are present in relatively low levels. It is estimated that total IncRNAs are present at two magnitudes less than total mRNAs. However, recent research suggests that IncRNAs may function at a very low level as a molecular scaffold or a catalytic molecule [9]. A growing
number of lncRNAs are found to play essential roles in regulating cell proliferation, survival, cell cycle, differentiation, and apoptosis [10]. They are also indicated as vital regulators in initiating and developing many diseases, including reproductive diseases [11]. X-inactive specific transcript (XIST), located on the X-chromosome of mammalian cells, is the first reported lncRNA. It has been proven to be a major regulator of the X-inactivation process [12]. Another well-established example of functional lncRNAs is H19, which is highly expressed in many tissues derived from endoderm and mesoderm. It regulates the network of imprinted genes that regulate fetal and postnatal growth [13], and it is differentially expressed in many disease tissues.

lncRNAs can be divided into five categories based on their genome localization and the direction of transcription relative to the protein-coding genes (pcGenes) in the genome: sense, antisense, bidirectional, intronic, and long intergenic (Figure 1) [14]. Sense lncRNAs are transcribed from the same strand and direction as pcGenes, and antisense lncRNAs are transcribed from the opposite strand of pcGenes. Sense and antisense lncRNAs are located within the regions of their surrounding pcGenes. Bidirectional lncRNA is located less than 1 kb from the surrounding pcGenes, sharing the same promoter as the protein-coding gene, but transcribed from the opposite direction [15]. Long intergenic noncoding RNAs (lincRNAs) are located within the intergenic regions of pcGenes, and they do not overlap with protein-coding regions.

lncRNAs could control transcription in cis or trans, regulate essential proteins or nucleic acid molecules, and are also involved in the organization of the nuclear domains [16]. The mechanisms of action vary depending on their structural conformations, biochemical properties, and specific subcellular localization [17, 18] (Figure 2). (1) They could function as signal molecules. In this case, lncRNAs respond to the environmental stimuli and then are transcribed at a specific time and space. This property makes them act as biomarkers for specific biological events. (2) They could act as decoy molecules by binding to the regulatory factors of transcription. For example, lncRNAs could bind to RNA-binding proteins, transcription factors, or chromatin modifiers to inhibit their biological activity. (3) They could function as guide molecules to direct the localization of regulatory factors. For example, lncRNAs can directly bind to protein molecules to form ribonucleoprotein complexes and mediate their precise localization to specific targets to regulate gene expression [19]. (4) lncRNAs could function as competing endogenous RNAs (ceRNAs) to sequester miRNAs, leading to the active transcription of their mRNA targets [20]. Several studies have shown that when TEs were embedded in lncRNAs, they may function in the processing, stability, and localization of lncRNAs. More importantly, TEs are often found to be the functional domains of lncRNAs [21]. For example, 73% of Linc-ROR sequences that have miRNA binding sites are derived from TE, and these sequences are essential for maintaining the pluripotency and self-renewal of embryonic stem cells [22]. Another example is XIST, which is important in early embryonic development and reproductive diseases [23]. XIST contains three functional repeat domains that are derived from TE. A-repeats that originated from ERVB5 TE are responsible for recruiting SPEN to silence the X chromosome; C-repeats, originating from ERVB4 TE, are required for the localization of XIST; and F-repeats, which are derived from a DNA transposon, are found to interact with JARID2 [24–28].

In mammals, development starts from the fusion of mature germ cells, sperms, and eggs, generating a totipotent zygote. Then, the zygote differentiates to form pluripotent stem cells that have the potential to give rise to an entire organism, including germ cells [29]. Thus, germ cells are the most remarkable cell type capable of reestablishing totipotency and transmitting heritable genetic and epigenetic information between generations [30]. Understanding the unique cell fate change from totipotent embryos to
pluripotent stem cells and germ cells will enable us to develop novel strategies for disease treatments, particularly in regenerative medicine [31]. Although substantial progress has been made to dissect the molecular mechanism underpinning this cell fate change, the role of lncRNAs remains largely unknown. In this article, we have reviewed the recent progress of lncRNAs studies in embryogenesis, pluripotency, and reproduction, aiming to shed light on future research to probe the genetic program that drives the multistep developmental processes.

2. lncRNAs in Early Human Embryonic Development

lncRNAs are present from the beginning of human embryo development. After embryonic gene activation (EGA), lncRNAs become the main category of transcripts [14]. RNA-seq and hierarchical clustering analysis demonstrated that lncRNAs show distinct developmental stage-specific expression patterns [32]. Furthermore, the epigenetic signatures of lncRNAs are similar to those of protein-coding genes, including methylation distribution at the transcription start site (TSS), methylation dynamics, and negative correlation between gene expression and promoter methylation level. Collectively, these data suggest that lncRNAs may play essential roles in early human embryonic development by regulating gene expression [33].

Human endogenous retroviruses (HERV) are remnants from ancient germline infections by exogenous retroviruses and account for 8% of the human genome [34]. HERV-derived lncRNAs are found to express at specific stages and function in human-specific or even individual-specific aspects of early human embryo development [35]. HERVK is activated by the master transcription regulator of pluripotency, OCT4, from embryonic genome activation at the eight-cell stage to human embryonic stem cell derivation. It is involved in the immunoprotective process of human embryos against exogenous viral infection [36]. Another species of HERV, HERVH, is considered the most successful endogenous retrovirus in the human genome. It is expressed during human preimplantation embryogenesis and regulates human pluripotency by providing alternative binding sites for key transcription factors, functioning as a long-range enhancer, and producing pluripotency-specific lncRNAs [37].

Human pluripotency-associated transcripts 2, 3, and 5 (HPAT2, HPAT3, and HPAT5) are derived from transposable elements (TEs) and are essential for preimplantation embryo development by modulating the acquisition of pluripotency and the formation of the inner cell mass [38].

In addition, the activity of the X chromosome is regulated by the antagonistic action of lncRNAs XIST and XACT in the early development of human embryogenesis [39].

3. lncRNAs in Pluripotent Stem Cells

Pluripotent stem cells (PSCs) cultured in vitro provide a unique model for studying the molecular mechanisms of human embryogenesis [40] and are considered the seed cells to differentiate into functional cells for cellular therapeutics [41]. The core regulatory network for self-renewal and pluripotency involves transcription factors, chromatin modifiers, and lncRNAs [42, 43](Figure 3). PSCs express a characteristic set of lncRNAs that interact with the other members of the core regulatory transcription factor network (OCT4, NANOG, SOX2, and SALL4) to regulate the gene expression profiles and safeguard pluripotency [22, 38, 44, 45]. Mechanically, Linc-RoR works as a competing endogenous RNA to connect the network of miRNAs

Figure 2: Schematic diagram of lncRNA mechanisms of action. Mechanisms of action: (a) signaling, (b) decoy, (c) guides, (d) scaffold, and (e) miRNA sponge.
with core transcription factors in PSCs. Linc-ROR prevents the core transcription factors from miRNA-mediated suppression in PSCs, thus regulating the self-renewal and pluripotency of PSCs [22]. HPAT5 acts as a miRNA sponge to modulate the balance between pluripotency and differentiation by counteracting the activity of let-7 [38].

Another group of lncRNAs, such as LincU, FAST, and GAS5, maintains the pluripotency of PSCs by modulating signaling pathways that are essential for PSCs [45–47]. Mechanistically, LincU binds to DUSP9 protein, an ERK-specific phosphatase, and stabilizes its expression, thereby inhibiting the MAPK/ERK signal pathway and maintaining the naive state of ESCs [46].

Examples of lncRNAs that modulate the epigenetic status of PSCs include ES1-3 and IncRESS1. They are shown to function as molecular scaffolds that bridge different chromatin modifiers to maintain the epigenetic signatures of PSCs. ES1-3 are highly expressed in undifferentiated hESCs. As a modular scaffold, they recruit the suppressive PRC2 component SUZ12 to silence the SOX2 neural targets in PSCs, thus maintaining pluripotency [48–50].

lncRNAs are also involved in the differentiation of PSCs into three germ layers. RMST and TUNA (Tcl1 upstream neuron-associated lincRNA) promote neuronal differentiation of human PSCs [48, 49], while DEANR1, GATA6-AS1, and LINC00458 promote endodermal lineage specification [51–53]. For example, RMST interacts with SOX2 and binds to the promoter regions of neurogenic target genes to promote neuronal differentiation [48, 49]. DEANR1, an endoderm-specific lncRNA, interacts with SMAD2/3 to activate the expression of FOXA2, thus enabling the differentiation towards endoderm [51]. In addition, HBL1, BANCR, and YylncT are identified as critical regulators for mesoderm development [54–56].

lncRNAs are also involved in reprogramming. LincROR, as a negative regulator of p53, directly binds to heterogeneous nuclear ribonucleoprotein I (hnRNP I) to inhibit the expression of p53, thereby inhibiting p53-mediated cell cycle arrest and apoptosis and promoting cell reprogramming [57]. HERVH is significantly upregulated in the reprogramming process of fibroblasts to induce pluripotent stem cells (iPSCs). By recruiting P300 and OCT4 to the HERVH LTR7 region, HERVH regulates the expression of neighboring genes, as well as pluripotency-associated transcripts. It is suggested that HERVH plays an essential role in the acquisition of somatic pluripotency [44], lincRNA-p21 (P53-induced large intergenic noncoding RNA p21) interacts with the H3K9 methyltransferase SETDB1 and the DNA methyltransferase DNMT1 through the RNA-binding protein HNRNPK to maintain high levels of H3K9me3 modification and/or CpG methylation at the pluripotency gene promoter, thus hindering somatic cell reprogramming [58].
Knockdown of HPAT5 impairs reprogramming, indicating that it contributes directly to reprogramming and acquisition of pluripotency [38].

4. IncRNAs in Human Germ Cell Development

Germ cell development is a complex differentiation process essential for the generation of gametes, which pass on the genetic information between generations [59]. Disruption of germ cell development or misregulation of gene expression in germine-related cells leads to infertility or reproductive diseases [60]. This dynamic developmental process is precisely regulated by a tissue- or cell-specific gene network [61]. As a new regulator in gene expression networks, cell type-specific IncRNAs have recently been discovered and suggested to be involved in many cellular processes during human germ cell development [62]. Several IncRNAs show differential expression or regulatory roles in the development of human primordial germ cells (hPGCs), the first progenitor cells of the germ line [63]. For example, HIPSTR (heterogeneously expressed from the Intronic Plus Strand of the TFAP2A-locus RNA) has been identified as a novel IncRNA transcribed from the TFAP2A locus and shows differential expression in human primordial germ cells [64]. In addition, XACT and XIST are expressed to regulate X-chromosome dosage in hPGCs before meiosis [65]. RNA-seq analysis of human testicular cells has identified thousands of syntenic IncRNAs associated with spermatogenesis [66–71]. The narcolepsy candidate-region 1 gene (NLC1-C), a lncRNA expressed in the cytoplasm of spermatogonia and early spermatocytes, is found to be associated with male infertility and promotes testicular embryonal carcinoma cell proliferation [71]. Single-cell RNA-seq profiling of metaphase II oocytes also found 8,700 maternal IncRNAs expressed in the preimplantation embryos [32]. Note that a large number of RNA-binding proteins are found to be critical for germ cell development across species, including VASA (DDX4) and DAZL (Deleted in Azoospermia Like) [72]. These proteins might function by influencing IncRNA action to reinforce germ cell fate.

5. IncRNAs in Reproductive Diseases

Besides the roles in development, differential expression of many IncRNAs has been identified using microarray or RNA-seq between control and reproductive disease samples [73], indicating potential roles in pathogenesis. Although most of their functions and mechanisms of action need to be further annotated and characterized, these IncRNAs could serve as potential targets for the diagnosis and treatment [74] (Table 1).

5.1. IncRNAs Associated with Male Infertility. Spermatogenesis is a complex developmental process that is essential for male fertility [75]. The process is classified into three major phases: (1) mitotic proliferation of spermatogonia, (2) the meiosis of spermatocytes, and (3) spermiogenesis and maturation of spermatocytes to spermatozoa [76]. Each phase is strictly regulated by transcriptional factors, hormones, epigenetic regulators, and IncRNAs. Disruption of any steps of spermatogenesis, referred to as maturation arrest (MA), causes male infertility [77]. Nonobstructive azoospermia (NOA) is considered the most severe case of male infertility, and it is characterized as no sperm in the ejaculate due to failure of spermatogenesis [78]. Several IncRNAs have been indicated to play roles in the process of spermatogenesis and NOA.

The narcolepsy candidate-region 1 gene (NLC1-C, also known as LINCO0162) is expressed in spermatogonia and primary spermatocytes. Compared with fertile controls, its expression is significantly downregulated in the cytoplasm and accumulated in the nucleus in the testis of infertile MA patients. NLC1-C forms a regulatory feedback loop with miR-320a and miR-383 to control the survival and proliferation of the germ cells in the process of spermatogenesis. In the cytoplasm, NLC1-C is the target of miR-320a and miR-383; while accumulated in the nucleus of spermatogonia and primary spermatocytes, it is suggested to repress the expression of miR-320a and miR-383 by direct binding to nucleolin, resulting in the hyperactive proliferation of germ cells, which leads to male infertility [71].

Gm2044 is indicated to play an essential role in NOA and specific in reproductive diseases. It is the miR-202 host gene, and its expression is significantly increased with its host gene miR202 in NOA of spermatognial arrest. IncRNA Gm2044 inhibits the proliferation of the human testicular embryonic carcinoma cell NCCIT through the miR-202-Rbfox2 molecular signal pathway [79].

The expression of Hox transcript antisense intergenic RNA (HOTAIR) is decreased in asthenozoospermic and oligoasthenozoospermic patients [80]. The low expression of HOTAIR was also observed to be associated with specific sperm function parameters, including motility and vitality. It is found that low HOTAIR leads to downregulation of nuclear factor erythroid 2-related factor 2 (NRF2), a gene related to the expression of antioxidant genes and the quality of spermatozoa [81]. This eventually results in reactive oxygen species- (ROS-) related defects in sperm function.

IncRNA growth-arrested DNA damage-inducible gene 7 (Gadd7) is indicated in the regulation of the oxidative stress response and specific in reproductive diseases. Its expression is upregulated in patients with varicocele compared with fertile controls. Further functional analysis in mouse cell lines indicates that overexpression of gadd7 inhibits cell growth and promotes apoptosis by upregulating the proapoptotic regulator Bax and downregulating the antiapoptotic regulator Bcl2, resulting in male infertility [82].

5.2. IncRNAs Associated with Prostate Tumors. Prostate cancer is the most common cancer among men, and the androgen receptor (AR) plays a central role in its progression by regulating the expression of genes associated with the identity and behavior of prostate cancer cells [83]. A number of IncRNAs are identified as potential regulators for disease progression and may be applied as novel therapeutic targets. PRNCR1 and PCGEM1 are highly expressed in aggressive prostate cancer and bind to AR successively. They enhance the activation of ligand-dependent and ligand-
| Diseases                          | IncRNA                  | Full name                          | Expression level | Assessed cell line               | Signaling pathways and molecules | Functions                                                                                                                                         | In other diseases                                      | References   |
|----------------------------------|-------------------------|------------------------------------|------------------|-----------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|--------------|
| Nonobstructive azoospermia (NOA) | NLC1-C                  | Narcolepsy candidate-region 1 gene | Downregulated    | NCCIT, NTERA-2 (NT2), HEK293 T    | Sponge for miR-320a and miR-383 transcripts by binding to nucleolin, resulting in a hyperactive proliferation of germ cells             | Inhibits the proliferation of the human testicular embryonic carcinoma cell NCCIT                                                       | Testicular embryonal carcinoma                         | [71]         |
|                                  | GM2044                  | —                                  | Upregulated      | NCCIT                             | miR-202-Rbfox2 pathway          | Polarity inverted for the miR-202-Rbfox2 pathway                                                                                             | —                                                      | [79]         |
|                                  | HOTAIR                  | Hox transcript antisense intergenic RNA | Downregulated    | —                                 | NRF2                            | Relates to defects in sperm function                                                                                                          | Breast cancer, lung cancer, and pancreatic cancer      | [80, 81, 123]|
|                                  | Gadd7                   | IncRNA growth-arrested DNA damage-inducible gene 7 | Upregulated      | GC-1, GC-2                       | Bax, Bcl2                       | Inhibits cell growth and promotes apoptosis by upregulating the proapoptotic regulator Bax and downregulating the antiapoptotic regulator Bcl2 | —                                                      | [82]         |
|                                  | PRNCR1/PCGEM1           | Prostate cancer-associated noncoding RNA 1/PCGEM1 prostate-specific transcript | Upregulated      | LNCaP, LNCaP-cds1, LNCaP-cds2, CWR22Rv1 | AR                              | Promotes the proliferation of prostate cancer cells                                                                                           | Breast cancer and lung cancer                          | [84, 124]    |
|                                  | NEAT1                   | Nuclear-rich transcriptase 1        | Upregulated      | LNCaP and PC3, RWPE1, VCaP and DU145 | Estrogen receptor alpha (ERα)    | Promotes the development of prostate cancer                                                                                                   | Non-small-cell lung cancer, breast cancer, and hepatocellular carcinoma | [85, 125]    |
| Prostate tumors                  | PCAT-1                  | Prostate cancer-associated transcript-1 | Upregulated      | LNCaP                             | PRC2, cMyc                       | Promotes the proliferation of prostate cancer cells                                                                                            | Colorectal cancer, hepatocellular cancer, and gastric cancer | [86, 126]    |
|                                  | MALAT-1                 | Metastasis-associated lung adenocarcinoma transcript 1 | Upregulated      | LNCaP-AI, 22Rv1                   | ZEB1, ZEB2, Skil                 | Is associated with the increase in the Gleason score, prostate-specific antigen (PSA), and tumor stage and promotes the invasion and growth of prostate cancer | Glioma, hepatocellular carcinoma, and multiple myeloma | [87, 127]    |
|                                  | SChLAP1                 | Second chromosome locus associated with prostate-1 | Upregulated      | —                                 | —                               | Relates to poor prognosis and could be used as an important biomarker to identify patients with a high risk of lethal prostate cancer | Triple negative breast cancer and bladder cancer        | [88, 128, 129]|
| Diseases          | IncRNA     | Full name                          | Expression level | Assessed cell line | Signaling pathways and molecules | Functions                                                                 | In other diseases                                                                 | References         |
|------------------|------------|------------------------------------|------------------|--------------------|----------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------|
|                  | GAS5       | Growth arrest specific 5           | Downregulated    | PC3, DU145, and PNT2C2 | E2F1, P27kip1                    | Induces a cell cycle arrest in the G0–G1 phase and acts as a tumor suppressor | Colorectal cancer,   | [89] [89, 130] |
|                  |            |                                    |                  |                    |                                  |                                                                           | gastric cancer,       |                    |
| XIST             | Inactive X chromosome-specific transcripts | Downregulated    | ALST, CAOV3, OVCA3, OVCA420, OVCA429, OVCA432, OVCA433, OVCA633, OVCA680, OVCA702, OVCA810, SKOV3, ES-2, TOV21G | XIAP                  | Downregulation of Xist may increase the expression of linked inhibitors of apoptosis protein and lead to the phenotype of drug | Non-small-cell lung cancer, breast cancer, and primary hepatocellular carcinoma | [91, 131, 132]    |
|                  |            |                                    |                  |                    |                                  |                                                                           |                               |                    |
|                  | H19        | Imprinted maternally expressed transcript | Upregulated      | SKOV3, OV90, TOV112D, ES2 | Caspase-3, caspase-9, Bax, Bcl-2, cyclin B1/Cdc2 | Promotes ovarian cancer cell proliferation                                | Head and neck cancer, pancreatic cancer, and osteosarcoma                   | [92, 93, 133]     |
|                  | MALAT1     | Metastasis-associated lung adenocarcinoma transcript 1 | Upregulated      | SKOV3, SKOV3.ip1, 293T | —                                | Promotes cell proliferation and metastasis and inhibits cell apoptosis    | Glioma, hepatocellular carcinoma, and multiple myeloma                      | [94–96, 127]      |
| Ovarian cancer   | LINC00565  | Long intergenic nonprotein coding RNA 565 | Upregulated      | OVCAR3, SKOV3, HO8910, A2780, and HEY | GAS6, cyclinE1, cyclinD1, CDK4 P16, P21 | Relates to the FIGO (International Federation of Gynecology and Obstetrics) stage, cell cycle, and size of tumor cells and promotes cell proliferation, invasion, and migration | Gastric cancer and colorectal cancer                                        | [97, 134, 135]    |
|                  | DARS-AS1   | DARS1 antisense RNA 1              | Upregulated      | A2780, SKOV3, and OVCAR-3 | Sponge for miR-532-3p            | Promotes the proliferation, migration, and invasion of ovarian cancer cells | Thyroid cancer, clear cell renal cell carcinoma, and non-small-cell lung cancer | [98, 136, 137]    |
|                  | FEZF1-AS1  | FEZF1 antisense RNA 1              | Upregulated      | SKOV-3, HO8910, HO8910PM, ES2, and HG-SOC | JAK-STAT3 pathway               | Relates to poor prognosis, promotes cell proliferation, and inhibits cell apoptosis | Colorectal cancer, gastric neoplasia, and hepatocellular carcinoma          | [99, 138]         |
|                  | LEF1-AS1   | LEF1 antisense RNA 1               | Upregulated      | SKOV3, OVCAR3         | miR-1285-3p                      | The absence of LEF1-AS1 results in inhibiting proliferation, migration, and invasion of ovarian cancer cells | Glioblastoma, colorectal cancer, and retinoblastoma                        | [100, 139–141]    |
|                  | H19        |                                    | Upregulated      | —                   | —                                | —                                                                         | —                                                                           | [102, 133]         |
| Diseases                      | IncRNA                        | Full name                                      | Expression level | Assessed cell line | Signaling pathways and molecules | Functions                                                                 | In other diseases                                      | References |
|------------------------------|-------------------------------|------------------------------------------------|------------------|--------------------|----------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------|------------|
| Endometrial carcinoma (EC)   | CCAT1                         | Colon cancer-associated transcript 1           | Upregulated      | HEC-1-A, KLE, Ishikawa | Sponge for miR-181a-5p           | Regulates migration and invasion of the tumor cells                      | Head and neck cancer, pancreatic cancer, and osteosarcoma | [103, 142] |
|                              | MIR22HG                       | MIR22 host gene                                | Downregulated    | HEC-1 A, KLE       | Sponge for miR-141-3p            | Promotes the proliferation and migration of endometrial cancer cells     | Breast cancer and multiple myeloma                        | [104, 143] |
|                              | MEG3                          | Maternal expression gene 3                     | Downregulated    | Ishikawa, HEC-1B   | PI3K/mTOR pathway, BclxL, VEGFA  | Inhibits the proliferation and migration and promotes the apoptosis of cancer cells | Esophageal cancer, lung cancer, and hepatocellular carcinoma | [105, 144] |
|                              | AC002454.1                    | —                                               | Upregulated      | —                  | CDK6                             | Promotes the migration, invasion, and proliferation of cells and regulates the cell cycle | Bladder cancer                                         | [107, 145] |
|                              | MALAT1                        | Metastasis-associated lung adenocarcinoma transcript 1 | Upregulated      | —                  | NF-κB/iNOS pathway, MMP-9, caspase-3 | Promotes the proliferation and migration of endometrial cells             | Glioma, hepatocellular carcinoma, and multiple myeloma    | [108, 127] |
|                              | AFAP1-AS1                     | Actin filament-associated protein 1 Antisense RNA1 | Upregulated      | Ishikawa           | ZEB1                             | Promotes the EMT process of endometriosis                                | Esophageal cancer, pancreatic ductal adenocarcinoma      | [109, 146] |
|                              | CCDC144NL-AS1                 | CCDC144NL antisense RNA 1                       | Upregulated      | hEM15A             | MMP-9, F-actin, vimentin          | Affects the cytoskeleton structure and promotes cell invasion and migration | Osteosarcoma, gastric cancer, non-small-cell lung cancer, and hepatocellular carcinoma | [110, 147-150] |
|                              | TC0101441                     | —                                               | Upregulated      | ECSCs              | TCF8/ ZEB1, slug, snail, and N-cadherin | EV shuttling of TC0101441 promotes invasion and migration of endometriosis | Gastric cancer                                          | [151, 152] |
| Diseases | IncRNA | Full name | Expression level | Assessed cell line | Signaling pathways and molecules | Functions | In other diseases | References |
|----------|--------|-----------|-----------------|-------------------|-------------------------------|-----------|-----------------|------------|
| **UCA1** | Urothelial carcinoma-associated-1 | Downregulated | — | — | Is involved in the pathogenesis of endometriosis and can be used as a biomarker for diagnosis and prognosis | Urothelial carcinoma-associated 1 gastric cancer and colorectal cancer | [153, 154] |
| **H19** | Imprinted maternally expressed transcript | Downregulated | 293T, HESCs | H19/Let-7/IGF1R, H19/miR-216a-5p/ACTA2 pathway | Regulates endometrial stromal cell proliferation, invasion, and migration | Head and neck cancer, pancreatic cancer, and osteosarcoma | [133, 155, 156] |
| **aHIF** | Antisense hypoxia-inducible factor | Upregulated | ECSCs, HUVECs | (VEGF)-A, VEGF-D | Facilitates endometriosis angiogenesis and is used as a potential biomarker and therapeutic target for endometriosis | Gastric cancer, glioblastoma multiforme, and paraganglioma | [157–159] |
| **MALAT1** | Metastasis-associated lung adenocarcinoma transcript 1 | Upregulated | HeLa, CaSki | VEGF, MMP-9, E-cadherin, β-catenin, vimentin, snail, twist | Promotes the proliferation and invasion of cervical cancer cells and reduces apoptosis | Glioma, hepatocellular carcinoma, and multiple myeloma | [112, 127] |
| **HOTAIR** | Hox transcript antisense intergenic RNA | Upregulated | SiHa, HeLa, CaSki | VEGF, MMP-9, E-cadherin, β-catenin, vimentin, snail, twist | Promotes metastasis and invasion of tumor cells | Breast cancer, lung cancer, and pancreatic cancer | [113, 123] |
| **Cervical cancer** | RP11-480H12.5 | Upregulated | PCS-480-011, SiHa (HTB-35), HeLa229 (CCL-2.1), and MS751 | Wnt/β-catenin pathway | Induces EMT through the Wnt/β-catenin pathway and promotes migration, invasion, and proliferation of cervical cancer cell lines | Breast cancer | [114, 160, 161] |
| **RP1-93H18.6** | — | Upregulated | SiHa, HeLa, CaSki, and C-33A | PEK/Akt/mTOR pathway | Promotes growth and metastasis of tumor cells and reduces apoptosis | — | [115] |
| **DSCAM-AS1** | DSCAM antisense RNA 1 | Upregulated | SiHa, HeLa, C-33A, and CaSki | Sponge for miR-361-5p | Enhances the ability of cells to migrate, invade, and proliferate and promotes the development of cervical cancer | Non-small-cell lung cancer, colorectal cancer, and osteosarcoma | [116, 162] |
| **GASS-AS1** | GASS antisense RNA 1 | Downregulated | Caski, SiHa, C33A, and HeLa | GAS5 | Relates to the FLGO stage, lymphatic metastasis, distant | Glioma, non-small-cell lung | [117, 153, 163, 164] |
| Diseases                        | IncRNA | Full name                                      | Expression level | Assessed cell line     | Signaling pathways and molecules | Functions                                                                 | In other diseases                                | References          |
|--------------------------------|--------|-----------------------------------------------|------------------|------------------------|---------------------------------|---------------------------------------------------------------------------|-----------------------------------------------|---------------------|
|                                |        |                                               |                  |                        |                                 | metastasis, and poor prognosis and promotes proliferation, migration, and invasion | cancer, and hepatocellular carcinoma          | [118, 165]         |
|                                |        |                                               |                  |                        |                                 | Promotes the proliferation and metastasis of cervical cancer              | Clear cell renal cell carcinoma and thyroid cancer | [120, 133]         |
|                                |        |                                               |                  |                        |                                 | May be a key factor in endocrine and metabolic diseases in patients with PCOS | Head and neck cancer, pancreatic cancer, and osteosarcoma                 | [165, 166]         |
|                                |        |                                               |                  |                        |                                 | Regulates the apoptosis and the proliferation of ovarian granulosa cells | Clear cell renal cell carcinoma and thyroid cancer | [167, 168]         |
| Polycystic ovary syndrome (PCOS)|        |                                               |                  |                        |                                 | Wnt/β-catenin and Notch pathways, TIMP2                                    | Hepatocellular carcinoma, colorectal cancer, and squamous cell lung carcinoma tissues | [169, 170]         |
|                                |        |                                               |                  |                        |                                 | Serve as a potential target to treat PCOS                                  | Lung cancer, breast cancer, and colorectal cancer | [125, 171]         |
|                                |        |                                               |                  |                        |                                 | Promotes cell proliferation and represses cell apoptosis                   | Non-small-cell lung cancer, breast cancer, and hepatocellular carcinoma | [172, 173]         |
|                                |        |                                               |                  |                        |                                 | LINC00477/miR-128 axis may represent a potential method for the treatment of PCOS | Gastric cancer |
independent AR-mediated genes and promote the proliferation of prostate cancer cells [84].

*Nuclear-rich transcriptase 1 (NEAT1)*, a potential target of estrogen receptor alpha (ERα), is significantly overexpressed in prostate cancer. NEAT1 is shown to regulate the expression of prostate cancer genes and promotes the development of prostate cancer by changing the epigenetic landscape of the target gene promoter [85].

*PCAT-1* is upregulated in prostate cancer and promotes the proliferation of prostate cancer cells through PRC2 and cMyc proteins [86].

**MALAT-1** is upregulated in prostate cancer and is associated with the increase in the Gleason score, prostate-specific antigen (PSA), and tumor stage. Downregulating the expression of MALAT-1 inhibits the migration, invasion, and growth of prostate cancer cells, increases the rate of apoptosis, and blocks the cell cycle [87].

*SChLAP1* is highly expressed in prostate cancer and is associated with a poor prognosis. Thus, it could be used as an essential biomarker to identify patients with a high risk of lethal prostate cancer [88].

**GAS5** is downregulated in prostate cancer cells compared with prostate epithelial cells. GAS5 inhibits prostate cancer cell proliferation. It can bind directly to E2F1 and activate the P27Kip1 which is a regulator of the cell cycle. Thus, GAS5 induces a cell cycle arrest in the G0–G1 phase and acts as a tumor suppressor [89].

5.3. *IncRNAs* Associated with Ovarian Cancer. Ovarian cancer is one of the most common gynecological cancers that affect women’s health worldwide. As there has been no effective method to detect ovarian cancer at an early stage, most patients are diagnosed in an advanced stage, which has developed resistance to multiple treatment modalities [90]. Despite the revolutionary role of surgery and chemotherapy in curing ovarian cancer, the overall prognosis of ovarian cancer is poor. Thus, improving our understanding of the pathogenesis of ovarian cancer is essential for developing more effective treatments.

**XIST** encodes a specific spliced IncRNA, and it is a vital regulator of X chromosome inactivation. It is identified to be the most differentially expressed gene and downregulated in recurrent ovarian tumors. Downregulation of Xist may increase the expression of linked inhibitors of apoptosis protein (X-linked Inhibitor of Apoptosis Protein (XIAP)) and lead to the phenotype of drug resistance [91].

**H19** is significantly increased in ovarian cancer cells and ovarian cancer tissues. Ectopic expression of H19 promotes cell proliferation while silencing the expression of H19 by RNA interference inhibits the growth of ovarian cancer cells and induces cell cycle arrest and apoptosis [92]. Moreover, overexpression of H19 enhances the ability of tumor cells to invade in *vitro* and metastasize in *vivo* [93].

**Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)** is one of the earliest cancer-related IncRNAs identified to be related to ovarian cancer [94]. The expression level of MALAT1 is associated with ovarian cancer cells with different metastatic potentials. MALAT1 may play a role in the metastasis of epithelial ovarian cancer cells, but its mechanism needs to be further studied [95]. Knockdown of MALAT1 in ovarian cancer cells changes the expression of many genes related to cell proliferation, metastasis, and apoptosis, and inhibition of MALAT1 can significantly inhibit the tumorigenicity of SKOV3 cells [96].

**LINC00565** is highly expressed in ovarian cancer tissues, and its expression level was negatively correlated with the prognosis of patients with ovarian cancer. It has been found that the expression level of LINC00565 is related to the FIGO (International Federation of Gynecology and Obstetrics) stage and the size of tumor cells. Knockdown of LINC00565 in ovarian cancer cells inhibits the proliferation, invasion, and migration of the cells and induces cell cycle arrest. In *vivo* studies have shown that downregulating the expression of LINC00565 has an inhibitory effect on the growth of ovarian cancer cells by mediating the expression of cell cycle-related genes [97].

**DARS-AS1** is expressed higher in ovarian cancer tissues than in adjacent normal tissues. It promotes the migration and invasion of ovarian cancer cells. MicroRNA-532-3p (miR-532-3p) is identified as the direct target of DARS-AS1 in ovarian cancer, and DARS-AS1 via sponging miR-532-3p promotes the proliferation, migration, and invasion of ovarian cancer cells [98].

**FEZF1-AS1** is identified as a carcinogenic gene in ovarian cancer, as it is highly expressed in ovarian cancer tissues compared with adjacent normal tissues. Its expression is associated with a poor prognosis. After knocking down FEZF1-AS1, the proliferation of ovarian cancer cells was inhibited, and apoptosis was promoted. The mechanistic analysis found that FEZF1-AS1 regulated the JAK-STAT3 signal pathway by regulating the phosphorylation of STAT3 [99].

**LEF1-AS1** is upregulated in ovarian cancer and is related to poor prognosis. The absence of LEF1-AS1 results in the inhibition of proliferation, migration, and invasion of ovarian cancer cells. LEF1-AS1 interacts with miR-1285-3p, a tumor suppressor in ovarian cancer, to inhibit the expression of miR-1285-3p and promote the growth and metastasis of ovarian cancer cells [100].

5.4. *IncRNAs* Associated with Endometrial Carcinoma (EC). Endometrial carcinoma is the most common cancer in the uterus. It is formed by the outgrowth of the cells that develop the glands in the endometrium. Although it tends to have a favorable prognosis if an early sign of abnormal uterine bleeding is presented, once it develops into metastasis or recurrence, the patients are at a significantly higher risk of mortality, with a median overall survival time of <16 weeks [101]. The genetic factors that cause endometrial carcinoma remain unclear, and a growing number of studies have associated IncRNAs with its initiation and progression. **H19** is expressed higher in EC and tumor tissues than in the normal endometrial epithelium, and it regulates migration and invasion of the tumor cells [102].

**Colon cancer-associated transcript 1 (CCAT1)** is expressed significantly higher in EC and tumor tissues than in normal endometrial tissue. Downregulation of CCAT1 expression leads to the inhibition of tumor cell growth and
metastasis. In addition, it was found that CCAT1 was the direct target of miR181a-5p in endometrial carcinoma cells. It promotes the proliferation and migration of endometrial cancer cells by negatively regulating the expression of miR-181a-5p [103].

MIR22HG has been identified as a tumor repressor in EC. Its expression is significantly downregulated in endometrial carcinoma tissue. Functional tests in vitro showed that increased expression of MIR22HG could inhibit the proliferation and promote the apoptosis of cancer cells. In addition, the study proposed that MIR22HG inhibits the proliferation and migration of cancer cells by regulating the miR-141-3p/DAPK1 axis [104].

Maternal expression gene 3 (MEG3) is a tumor suppressor gene, and its expression level in EC tissue is significantly lower than that in normal endometrial tissue. High expression of MEG3 inhibits the migration, invasion, and proliferation of EC cells and increases apoptosis, probably through the PI3K/mTOR signal transduction pathway [105].

5.5. IncRNAs Associated with Endometriosis. Endometriosis is a benign gynecological disorder characterized by the presence of endometrial cells from the lining of the uterus outside of the uterine cavity. Although research efforts have been devoted to uncovering the underlying cause of endometriosis, the pathophysiological mechanisms causing this disease remained obscure. Recent studies, especially the results from high-throughput RNA sequencing [106], have shown differential expression of lncRNAs in endometriosis-related tissues and indicate the contribution of lncRNAs to the pathogenesis of endometriosis.

AC002454.1 is upregulated with cyclin-dependent kinase-6 (CDK6) in patients with endometriosis, and there was a significant positive correlation between them. After downregulating the expression of AC002454.1 and CDK6, the ability of cells to migrate, invade, and proliferate decreased, the proportion of cells in the S phase decreased, and the proportion of cells in the G0/G1 phase increased. Therefore, AC002454.1 and CDK6 have a synergistic effect on the biological behavior of endometrial cells [107].

MALAT1 plays a vital role in endometriosis. Compared with normal tissues, the expression of MALAT1 in endometriosis is upregulated. Knockdown of MALAT1 inhibits the proliferation and migration of endometrial cells, enhances the activity of caspase-3, and induces apoptosis by inhibiting the NF-kB/INOS signal pathway [108].

AFAP1-AS1 is significantly upregulated in ectopic endometrial tissues and is positively correlated with epithelial-mesenchymal transition (EMT). Knocking down AFAP1-AS1 can inhibit the activity of the EMT-related transcription factor ZEB1, thus inhibiting the EMT process of endometriosis [109].

CCDC144NL-AS1 is a newly identified lncRNA whose expression is upregulated in ectopic endometrium tissues. Downregulation of CCDC144NL-AS1 inhibited the migration and invasion of EC cell lines. Mechanism studies have shown that the knockdown of CCDC144NL-AS1 leads to changes in the distribution of filamentous actin (F-actin) stress fibers in the cytoskeleton and affects the cytoskeleton structure. In addition, the expression of the CCDC144NL-AS1 gene promotes the protein expression of vimentin filament and matrix metalloproteinase-9 (MMP-9), which promotes cell invasion and migration [110].

5.6. IncRNAs Associated with Cervical Cancer. Cervical cancer is one of the most frequently diagnosed gynecological cancers that endanger women’s health and lives [111]. Increasing data have shown the regulatory roles of lncRNAs in the pathogenesis of cervical cancer, with the prospective clinical application in the diagnosis and treatment of cervical cancers.

In cervical cancer, the expression of IGF2 was significantly increased, and the expression of H19 was decreased considerably. However, the mechanism of this disorder is not precise, and further research is needed [102].

MALAT1 is identified as an essential regulatory factor involved in the occurrence of cervical cancer. Its expression in cervical cancer tissues is significantly higher than that in normal tissues. When endogenous MALAT1 is knocked out, it reduces the proliferation and invasion of cervical cancer cells and promotes apoptosis [112].

The expression of HOTAIR in cervical cancer is higher than that in normal tissues. HOTAIR has indicated a role in metastasis and invasion of tumor cells by regulating the expression of vascular endothelial growth factor, matrix metalloprotein-9, and epithelial-to-mesenchymal transformation (EMT)-related genes [113].

The expression level of RP11-480112.5 in the cervical carcinoma cell line is higher than that in normal tissue. RP11-480112.5 induces EMT through the Wnt/β-catenin pathway and promotes cervical cancer cell lines’ migration, invasion, and proliferation [114].

IncRNARP1-93H16.6 is expressed higher in paracancerous tissues in cervical cancer and specific in cervical cancer. Overexpression of RP1-93H16.6 promotes growth and metastasis of tumor cells and reduces apoptosis. Knocking down the expression of IncRNARP1-93H18.6 promotes apoptosis and inhibits the development of cervical carcinoma cells by blocking the PI3K/Akt/mTOR pathway [115].

DSCAM-AS1 is related to the occurrence and development of various tumors, and its role in cervical cancer has recently been studied. The expression of DSCAM-AS1 in cervical carcinoma is increased. DSCAM-AS1 enhances the ability of cells to migrate, invade, and proliferate and promotes the development of cervical cancer through regulating the miR-877-5p/ATXN7L3 axis [116].

GAS5 is a tumor suppressor factor that inhibits proliferation, EMT, invasion, and metastasis of tumor cells. GAS5-AS1 is the antisense RNA of GAS5, located on chromosome 1q25.1. Compared with normal tissues adjacent to cancer, the expression of GAS5-AS1 in cervical cancer is downregulated, and its expression is related to the FLG0 stage, lymphatic metastasis, distant metastasis, and poor prognosis in patients with cervical cancer. Mechanistically, GAS5-AS1 regulates the tumor suppressor GAS5 in an ALKBH5-m6A-YTHDF2-dependent manner. Specifically, GAS5-AS1 reduced the level of GAS5-methyladenosine (m6A) modification and improved the stability of GAS5 through the
interaction of RNA demethylase and ALKBH5. In addition, YTHDF2 specifically recognizes and binds to the RNA containing M6A and degrades M6A-modified transcript [117].

Plasmacytoma variant translocation-1 (PVT1) promotes the proliferation and metastasis of cervical cancer. The expression of PVT1 is upregulated in cervical cancer cells, and PVT1 binds directly to miR-140-5p, which promotes the expression of Smad3 and then promotes the development of cervical cancer [118].

5.7. lncRNAs Associated with Polycystic Ovary Syndrome (PCOS). Polycystic ovary syndrome (PCOS) is one of the most common metabolic and reproductive disorders that has been estimated to affect approximately 5 to 20% of reproductive-aged women worldwide [119]. Although the etiology of PCOS remains unclear, most researchers believe that the causes are multifactorial, and lncRNAs have recently been suggested to play pivotal roles in its pathogenesis and prognosis.

H19 is suggested to be involved in the occurrence and development of PCOS. In patients with PCOS, the expression of H19 is increased. The expression level of fasting plasma glucose (FPG), a sensitive indicator in the early stage of metabolic disease, is positively correlated with H19 in PCOS patients. These results suggest that the expression of H19 may be a critical factor in endocrine and metabolic disorders in patients with PCOS [120].

Taken together, many lncRNAs, including H19, NEAT1, MALAT1, HOTAIR, and PVT1, are upregulated in the progression of many reproductive diseases. Interestingly, the expression of several lncRNAs, which is highly expressed in embryonic development, is reactivated in the development of reproductive cancer. For example, H19 is highly expressed in embryonic stem cells and essential for early human embryonic development. While its expression is downregulated after birth, the expression of H19 is significantly upregulated in endometrial carcinoma and ovarian cancer [121]. Recently, the reemergence of fetal-associated features in the tumor ecosystem is getting much attention and is referred to as oncofetal reprogramming [122]. Upregulation of specific lncRNAs in reproductive cancer development could be one of the features reminiscent of fetal development and serves as one of the potential targets for therapeutic interventions.

6. Conclusion and Future Perspectives

With the advances in sequencing technology, especially at the single-cell level, more and more lncRNAs have been identified at specific stages or within a particular type of cells, during human embryo and reproductive development. While expanding the repositories of lncRNAs, we notice that a unique subset of lncRNAs is expressed during human development. Dissection of the function of human-specific lncRNAs may be of preeminent importance for understanding the unique specifics of human development.

As a newly discovered role in gene regulatory networks, lncRNAs provide an additional layer of complexity for transcriptional and posttranscriptional regulation of gene expression programs. In addition, an increasing number of lncRNAs are differentially expressed within the disease tissues. They were found to regulate the initiation and progression of reproductive diseases through mediating the gene expression program. However, most of the functional results are based on the analysis in vivo on disease-related cell lines. Rigorous investigations in vitro or in organoids that resemble the physiological environment of development or diseases are necessary to reveal the biological and physiological functions of lncRNAs.

lncRNAs are proposed as therapeutic or diagnostic targets for disease treatment, as many of their expression are restricted to a specific tissue/or cell type within a specific cellular stage, which renders superior specificity. Furthermore, the diversity of strategies to target lncRNAs offers a wide range of therapeutic options. At the transcription level, we can inhibit the expression of lncRNAs by genome editing techniques or upregulate their expression by knockdown of the corresponding natural antisense transcripts (NATs). At the posttranslational level, lncRNAs can be degraded by nucleic acid-based approaches, including siRNAs, antisense oligonucleotides (ASO), and morpholinos.

Although immense enthusiasm is aroused in the field of lncRNA-based therapy, especially nucleic acid-based approaches, several challenges must be addressed before the progression to large-scale clinical applications. First, we need to have a thorough understanding of the molecular function of lncRNAs to identify disease-determining lncRNAs. Second, robust and physiologically relevant preclinical models need to be established. As we mentioned above, a few lncRNAs associated with diseases are human/primate-specific or even patient-specific. So patient-derived xenograft models or 3D organoids have gained much interest in preclinical research. Third, for nucleic acid-based therapies, a lack of an efficient delivery system to cross the cellular plasma membrane, the risk of the overactivating innate immune response, and the possibility of the off-target effect are the main issues that need to be solved.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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