Advances of Long Noncoding RNAs-mediated Regulation in Reproduction

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Abstract

Objective: Advances in genomics and molecular biology have led to the discovery of a large group of uncharacterized long noncoding RNAs (lncRNAs). Emerging evidence indicated that many lncRNAs function in multiple biological processes and its dysregulation often causes diseases. Recent studies suggested that almost all regulatory lncRNAs interact with biological macromolecules such as DNA, RNA, and protein. LncRNAs regulate gene expression mainly on three levels, including epigenetic modification, transcription, and posttranscription, through DNA methylation, histone modification, and chromatin remodeling. LncRNAs can also affect the development of diseases and therefore be used to diagnose and treat diseases. With new sequencing and microarray techniques, hundreds of lncRNAs involved in reproductive disorders have been identified, but their functions in these disorders are undefined.

Data Sources: This review was based on articles published in PubMed databases up to July 10, 2017, with the following keywords: "long noncoding RNAs", "LncRNA", "placentation", and "reproductive diseases".

Study Selection: Original articles and reviews on the topics were selected.

Results: LncRNAs widely participate in various physiological and pathological processes as a new class of important regulatory factors. In spermatogenesis, spermatocytes divide and differentiate into mature spermatozoa. The whole process is elaborately regulated by the expression of phase-specific genes that involve many strains of lncRNAs. Literature showed that lncRNA in reproductive cumulus cells may contribute to the regulation of oocyte maturation, fertilization, and embryo development.

Conclusions: LncRNA has been found to play a role in the development of reproduction. Meanwhile, we reviewed the studies on how lncRNAs participate in reproductive disorders, which provides a basis for the study of lncRNA in reproduction regulation.

Key words: Cumulus Cell; Long Noncoding RNAs; Placentation; Reproductive Diseases

Introduction

Long noncoding RNAs (lncRNA), a class of nonprotein-coding RNA molecules, regulate gene imprinting and embryonic development. Although higher organisms transcribe lots of RNAs, the proteins or polypeptides encoded through this transcript only occupy 2% of the entire genomes. The remaining are noncoding RNAs (ncRNAs). NcRNAs, including small interfering RNA, micro-RNA (miRNA), piwi-interacting RNA (piRNA), and lncRNA, play an important role in spermatogenesis and female reproduction.[1] miRNAs, a class of endogenous noncoding single-stranded RNAs of about 21–25 nt, can degrade target messenger RNAs (mRNAs) or inhibit their translation and thus regulate the differentiation of target mRNAs.[2] piRNAs, a large class of small RNAs that are 24–32 nt in length, can interact with

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piwi proteins without dicer enzyme.[3] NcRNAs have been long thought as transcriptional noise because they lack biological functions.[4] LncRNAs regulate the expression of target genes at transcriptional and posttranscriptional levels.[5-7] LncRNAs are polyadenylated and catalyzed by RNA polymerase II and can perform various biological functions in nuclei and cytoplasm.[8,9] With the introduction of high-throughput sequencing, thousands of lncRNAs have been identified, characterized, and categorized.

According to their origins, lncRNAs can be classified into five categories:[10] (1) tandem duplicates in adjacent repeated units; (2) juxtaposed and restructured lncRNAs in untranscribed and separated gene sequence during chromosome recombination; (3) duplicates of nonencoding genes in reverse transcription; (4) lncRNAs produced by frame fracture of protein-coding genes; and (5) lncRNAs produced by transposable element insertion. According to its position with neighboring protein-coding genes, lncRNAs can be classified as (1) intergenic lncRNA; (2) intronic lncRNA; (3) sense lncRNA; and (4) antisense lncRNA.[11]

Functions of general lncRNAs participate in the proliferation, differentiation, and self-renewal of stem cells, including embryonic stem cells, induced pluripotent stem (iPS) cells, and spermatogonial stem cells (SSCs). Infertility has become a global concern. Due to environmental deterioration, food crisis, electromagnetic radiation, and even life stress, the incidence of human infertility is on the rise,[12,13] mainly in the developed countries.

A complex disease can be defined when: first, it is related to two different genomes (oocyte and sperm qualities are two major factors determining reproductive success), it depends on endometrium receptivity.[14] The embryonic genesis, fertilization, and implantation are regulated by complex biological pathways involving many molecules (such as mRNAs, ncRNAs, and proteins), which make the disease more complicated. In female gametogenesis, oocyte competence develops through complex processes beginning with embryonic formation and ending with metaphase II oocyte ovulation.[15] During ovulation, the oocyte is enclosed into a lineage of ovarian somatic cells and pregranulosa cells and then grows into a primordial follicle.[16] The primordial follicle pool, an embryonic product of the most mammal species including human, represents the female's ovarian reserve.[17] Hence, the embryo quality is mainly decided by the competence of the oocyte selected for fertilization. This competence is also affected by the oocyte's follicular environment.[18] However, these lncRNAs have a series of functions and participate in the development of many diseases,[19-21] including cervical cancers and neurodegenerative diseases. Recently, some lncRNAs have been found associated with preeclampsia.[22-24]

In 2014, global transcriptome profiles of the samples compact cumulus cells (CCs) were obtained using state-of-the-art RNA sequencing techniques. Yerushalmi et al.[25] identified 1746 differently expressed genes of compact and expanded CCs. Most of these genes were involved in cellular growth and proliferation, movement, cycles. Out of the differentially expressed (DE) genes, Yerushalmi et al.[25] found 89 lncRNAs, 12 of which are encoded within introns of genes involved in granulosa cell processes. Analysis of these genes helps identify genes and ncRNAs potentially involved in cumulus-oocyte complexes maturation and cumulus expansion.

Long Noncoding RNA Databases

Biological characteristics of lncRNAs (e.g., gene organization characteristics, sequence conservation, expression profiles, molecular interactions, epigenetic modifications, and functional annotation) have become much clearer. Some investigators have established the databases about the basic information of lncRNAs (e.g., primary sequence and genome seat). DeepBase database identifies lncRNAs based on RNA-Seq datasets. LncRNA expression profiles from 478 data sets of 14 species, their functions, and evolutionary conservation can be understood.[26] DIANA-LncBase database is a collection of experimental evidence and miRNA-lncRNA target relationships predicted by the DIANA-microT algorithm.[27] ChIPBase database provides information on how transcription factors regulate lncRNAs and miRNAs.[28] LncRNA database (LncRNAdb) is a professional database including comprehensive annotation of lncRNAs in eukaryotic organisms.[29] LncRNA DISEASE is a Chinese database of lncRNAs and human diseases, containing multiple lncRNAs and their relevance to human diseases.[30]

LNCipedia provides the primary sequence and secondary structure of human lncRNAs and evaluates the protein-coding potential of lncRNA with bioinformatic tools and ribosome sequencing data.[31] LncRNA single-nucleotide polymorphism (SNP) includes information on SNPs in human and mouse lncRNAs, data from the genome-wide association study, and their impact on lncRNA structure and lncRNA-miRNA combination.[32] LncRNome is developed by the Indian Institution of Council of Scientific and Industrial Research Genome and Integrative Biology, which provides stable annotations, cross-references, and biological significance of lncRNAs.[33]

NONCODE organizes the information of lncRNAs in 16 species, including the location, sequence, expression profile, evolutionary conservation, functional annotation, and relevant diseases.[34] An miRNA target database, supported by high-throughput experimental data (CLIP-Seq, aka, PAR-CLIP, and iCLIP) and mRNA degradome sequencing data, describes the regulatory interaction between miRNA and mRNA, miRNA and lncRNA, miRNA and circular RNA, miRNA and competing endogenous RNA, and RNA and protein. This database integrates the data from popular target prediction platforms.[35]

LncRNAtor collects data from TCGA, GEO, ENCODE, and modENCODE and compiles lncRNA expression profiles for cancer samples, as well as provides

protein-coding gene coexpression analysis and gene ontology enrichment analysis of coexpressed genes.[36-39] It provides information on the differential expression of lncRNAs, identifies tissue or cellular expression with specific microarray, and confirms the results by quantitative polymerase chain reaction (qPCR). The interference and overexpression of RNA can be used to study specific lncRNA functions. The characteristics of lncRNA databases are listed in Table 1.

Long Noncoding RNA Expression in Male Reproduction

SSCs differentiate into sperms through spermatogenesis that involves genes such as B-cell CLL/lymphoma 6/member B, Ets-variant 5, kit ligand, and epithelial cell adhesion molecule. Nuclear paraspeckle assembly transcript 1 (Neat1),

a 3.2 kb lncRNA, forms paraspeckles and, along with other RNA complexes, modifies the transcript of coding genes.[40] In 2012, Nakagawa *et al.*[41] found that metastasis-associated lung adenocarcinoma transcript (MALAT1; a type of lncRNA) was embedded in the subnuclei of mouse embryonic fibroblasts. Pre-mRNA regulated many biological processes, such as the growth of synapses and change of cellular cycles.[41,42] In 2014, Hu *et al.*[43] found that Neat1 was expressed in rat testicular tissues and GC-l cell lines. After the injection of lentiviruses, testicular indexes (testicular weight/experimental weight × 100%) in the experimental group rose, but not significantly. At the same time, the proportion of seminiferous tubules harboring sperms dropped to 86%, indicating that Neat1 regulated rat spermatogenesis.

With a length of 2.4 kb, miotic recombination hot spot locus (Mrhl) is a type of single-axon lncRNA encoded by

Table 1: Characteristics of lncRNAs databases

Databases	Characteristics	Linking
ENCODE-LncBae[39]	The ENCODE project helped map over 8800 small RNAs and 9600 lncRNAs and is still widely cited as a central database of known ncRNAs	http://www.nature.com/authors/editorial_policies/license.html#terms
LNCipedia 2.0[31]	In addition to basic transcript information and structure, several statistics are calculated for each entry in the database (such as secondary structure information, protein-coding potential, and miRNA binding sites)	http://www.ncipedia.org/
lncRNAdb[29]	lncRNAdb containing a comprehensive list of lncRNAs that have been shown to have, or to be associated with, biological functions in eukaryotes, as well as messenger RNAs that have regulatory roles	http://www.Lncrnadb.org/
lncRNA Disease[30]	This website provides both experimentally supported and predicted lncRNA-human disease relationships, based on hundreds of publications	http://www.Cuilab.cn/lncrnadisease
lncRNASNP[32]	This website identified SNPs in lncRNAs and analyzed their potential impacts on lncRNA structure and function	http://bioinfo.Life.hust.edu.cn/lnc RNASNP/
lncRNAtor[36]	Gene expression data of 208 RNA-Seq studies, collected from GEO, ENCODE, modENCODE, and TCGA databases, were used to provide expression profiles in various tissues, diseases, and developmental stages	http://lncrnator.ewha.ac.kr/index.Htm
lncRNome[33]	The resource hosts information on over 17000 lncRNAs in human and provides information on the types, chromosomal locations, description on the biological functions and disease associations of lncRNAs	http://genome.igib.res.in/lncRNome
lncRNome NONCODE[34]	NONCODE is an integrated knowledge database dedicated to ncRNAs (excluding tRNAs and rRNAs). Now, there are 16 species in NONCODE	http://www.noncode.org/
lncstarBase[35]	StarBase v2.0 has been updated to provide the most comprehensive ChIP-Seq experimentally supported miRNA-mRNA and miRNA-lncRNA interaction networks to date	http://starbase.sysu.edu.cn/
ChIPBase[28]	The chip base have developed to facilitate the comprehensive annotation and discovery of transcription factor binding maps and transcriptional regulatory relationships of lncRNAs and miRNAs from ChIP-Seq data	http://deepbase.sysu.edu.cn/chipbase/index.php
DeepBase[26]	DeepBase is a platform, to decode evolution, expression patterns and functions of diverse ncRNAs across 19 species	http://biocenter.sysu.eu.cn/deepBase/index.Php
DIANA-LncBase[27]	The experimental module contains detailed information for >5000 interactions, ranging from miRNA and lncRNA related facts to information specific to their interaction, the experimental validation methodologies and their outcomes	http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=lncBase/index

MiRNAs: Micro-RNAs; NcRNAs: Noncoding RNAs; LncRNAs: Long noncoding RNAs; SNPs: Single-nucleotide polymorphisms; ChIP-seq: Chromatin immnoprecipitation-sequencing.

the nuclear genome and expressed in testes.[44] In 2008, the studies found that Mrhl regulated spermatogenesis through two molecular mechanisms. First, Mrhl is divided by Drosha into a midbody of 80 nt. These RNAs are located in the nuclei of GC1 spermatogonial lines, probably interacting with chromatin.[45] Second, Wnt is critical to mammalian spermatogenesis.[46] Cooperating with p68, Mrhl showed its negative regulation in Wnt signal. Knockdown of Mrhl expression in GC-1 SPg cell line could disrupt the expression of genes that are responsible for cell signal transduction and development. Most of these genes are members of the Wnt-signaling pathway promoting cell differentiation and inhibiting cell growth. Therefore, Mrhl is crucial for spermatogonial division and differentiation.[47] Further studies are needed in gene-knocked-out mice to define the regulation of Mrhl in spermatogenesis.

Male infertility is often caused by maturation arrest (MA). *HongrES2* is a 1588-nt-long lncRNA co-transcribed by rats' chromosome 5 and 9 and expressed in testes; its expression in rates increases at the end of the first phase of spermatogenesis and reached a plateau at around day 450. Space-time specificity of this expression is manifested in the spermatogenesis. HongrES2 is a 1.6 kb mRNA-like precursor that gives rise to a new microRNA such as HongrES2 (*Mil-HongrES2*). *Mil-HongrES2*, the spliced *HongrES2*, can downregulate the expression of *CES7*, the products of which affects capacitation.[48] Nuclei weakly express mil-HongrES2 but strongly express HongrES2, indicating a splicing mechanism exists. Therefore, HongrES2 can regulate the maturation of sperms. Besides, the overexpression of mil-HongrES2 can weaken spermatic capacitation, indicating lowly expressed endogenic HongrES2 promotes spermatic development.[48] Narcolepsy candidate-region 1 gene (NLC1-C) is a cytoplasmic lncRNA expressed in spermatogonia and early-stage spermatocytes. NLC1-C overexpression promotes cell growth, whereas its low expression inhibits cell growth and accelerates apoptosis. Microarray analysis found that NLC1-C expression in MA patients was lower than normal persons. NLC1-C was also bound to the RNA-binding domain of nucleolin, which inhibited the transcription of miR-320a and miR-383 and induced the proliferation of spermatogonia and early-stage spermatocytes in MA patients.[49] Results from a study of Liu *et al*.[50] provided a catalog of chicken testis lncRNAs. In total, 2597 lncRNAs were identified in the chicken testis, including 1267 lincRNAs, 975 anti-sense lncRNAs, and 355 intronic lncRNAs. They shared similar features with previous studies. Of these lncRNAs, 124 were DE. Among 17,690 mRNAs detected in this study, 544 were DE, including a bunch of genes affecting sperm motility. Integrating analysis of lncRNA and mRNA and lncRNA expression in spermatogenesis are listed in Table 2 and Figure 1.

LONG NONCODING RNAs EXPRESSION IN FEMALE REPRODUCTION

Long noncoding RNA Gtl2

Recent studies revealed that lncRNAs (including Gtl2) from Dlk1-Dio3 region were positively correlated with the pluripotency of iPS cells. To uncover the spatiotemporal expression patterns and changes of lncRNA Gtl2, Wei *et al*.[51] analyzed the mechanism of Gtl2 epigenetic regulation. No changes of IG-DMR and Gtl2-DMR expression were found before and after lncRNA Gtl2 expression, which suggested that its activation was not regulated by two DMRs' DNA methylation. Hence, Wei *et al*.[51] checked the histone modifications in the promoter regions. They chose H3k9me3, H3K27me3, H3K4me3, and H3ac to perform the micro-ChIP assay with a micro-ChIP method published on nature protocols and found that lncRNA

Table 2: LncRNAs expression in reproductive diseases

LncRNA	Length	Chromosomal location	Functions
Neat1	3.2 kb	11q13.1	Corpus luteum formation and pregnancy maintenance[51]
Mrhl	2.4 kb	Chromosome 8	Wnt signaling regulation in spermatogonial cells; spermatogonial division and differentiation[46]
Mil-HongrES2	1.6 kb	Chromosome 5 and 9	Space-time specificity in spermatogenesis; sperm maturation[48]
RNAsGtl2	1.6 kb	14q32.2	Human early-stage embryonic development; oocyte maturation; zygotic genome activation[51]
Neat AK124742	6078 bp	3p14	Oocyte maturation and embryo development[38]
LncRNA274	–	–	Cytoskeletal organization and oocyte polarity in Xenopus[52]
XIST	19,296 nt	Xq13.2	X-chromosome inactivation[53]
H19	2322 nt	11p15.5	Upregulation in most ovarian cancer tissues compared with adjacent nontumor samples with a significantly positive correlation between its expression and tumor stages and tumor size[54-56]
MALAT1	8708 nt	11q13.1	Tumor pathogenesis,[57] high levels of MALAT1 in endometrioid endometrial cancer[58]
HOTAIR	2377 nt	12q13.13	Tumorigenic factor and biomarker in various cancer types; the most investigated lncRNA in cervical cancer[59-61]

NEAT1: Nuclear paraspeckle assembly transcript 1; Mrhl: Miotic recombination hot spot locus; XIST: X-chromosome inactive-specific transcript; H19: Imprinted maternally expressed transcript; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; HOTAIR: HOX transcript antisense RNA; Mil-HongrES2: Micro RNA-like HongrES; –: Not retrieved; LncRNAs: Long noncoding RNAs.
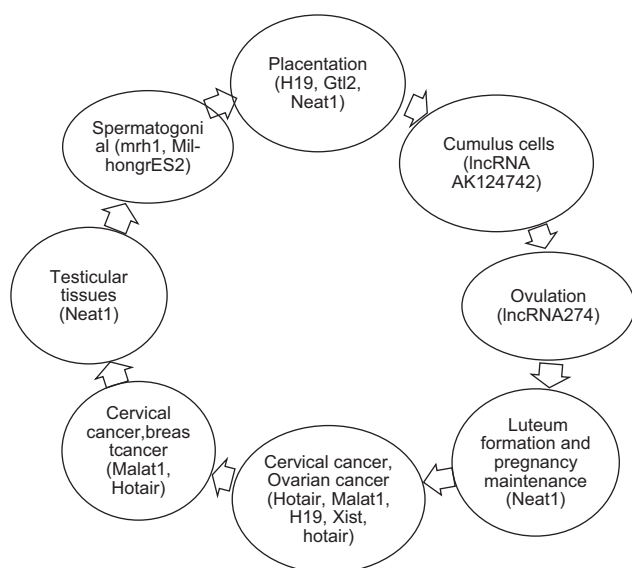
Figure 1: Different expressions of *lncRNA* build up a regulatory system in reproductive diseases. NEAT1: Nuclear paraspeckle assembly transcript 1; Mrhl: Miotic recombination hot spot locus; XIST: X-chromosome inactive-specific transcript; H19: Imprinted maternally expressed transcript; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; HOTAIR: HOX transcript antisense RNA; Mil-HongrES2: microRNA-like HongrES2.

expression rose as H3K4me3 increased and developed from 8-cell stage to blastocyst.

Wei *et al.*[51] also studied the functions of lncRNA Gtl2 in preimplantation development. They knocked down lncRNA Gtl2 by shRNA lentiviral particle microinjection. Although about 60% of *Gtl2* was knocked down, the blastocyst formation rate did not change compared to the control group. However, interference of *Gtl2* compromised the outgrowth of both trophoblast cell (trophectoderm) and inner cell mass and downregulated the adjacent genes from *Dlk1-Dio3* imprinted region and some stem cell pluripotency factors. Expression profile analysis revealed that lncRNAs expression was changed in different stages of human embryos and different time of mouse embryos. Weighted gene coexpression network analysis suggested that lncRNAs involved in human early-stage embryonic development were associated with oocyte maturation, zygotic genome activation, and mitochondrial functions. Results from a study of Qiu *et al.*[38] showed that the network of lncRNAs involved in zygotic genome activation was highly preserved in human and mouse embryos, whereas in other stages, no strong correlation was observed.

Nuclear paraspeckle assembly transcript 1

Neat1 is a nonprotein-coding RNA. Nakagawa *et al.*[52] found that Neat1-knocked-out mice with normal ovulation were stochastically infertile and unilateral transplantation of wild-type ovaries or progesterone changed the phenotype, suggesting that corpus luteum dysfunction and low-level progesterone were the primary causes of decreased fertility.

Despite faint expression in most adult tissues, Neat1 was highly expressed in corpus luteum. However, luteal tissues were severely impaired in nearly half Neat1-knocked-out mice. These observations suggested that Neat1 is essential for corpus luteum formation and the pregnancy under a suboptimal condition.

AK124742 and long noncoding RNA274

Another study found that *AK124742* and PSMD6 expression levels in CCs of high-quality embryo group were significantly higher than those in poor-quality group, which might affect oocyte maturation and embryonic development. The expression of m*RNA PSMD6* was positively correlated with that of lncRNA *AK124742* in CCs, indicating that *AK124742* may regulate the expression of PSMD6. Therefore, the expression levels of *AK124742* and *PSMD6* in human CCs may be biomarkers to predict pregnancy outcome.[62]

Ovary is a major female reproductive organ and has functions in two ways: first, it produces oocytes and provides them a base to develop and mature; second, it secretes ovarian steroid hormones to regulate follicular development and reproductive cycle. Ovary development is regulated by multiple factors, such as gonadotropins, cytokines, and small nucleic acids. A study of Li[63] found that nine lncRNAs were relatively highly expressed in multiple mouse tissues by qPCR, and lncRNA647, lncR147, and lncRNA274 were specifically highly expressed in ovary at 8 weeks and metestrus. The expression of lncRNA274 and genes for follicular development were elevated and the number of ovulation increased after *in vivo* transfection. Transgenic mice with *lncRNA274* as target gene were established. According the phenotype analysis, the number of offsprings significantly increased. These experimental results demonstrated that *lncRNA274* could promote ovulation. Rosalia *et al.*[64] found that 41 lncRNAs could interact with oocyte miRNAs and may regulate folliculogenesis. These findings are important in both basic reproductive research and clinical application.

H19

A study analyzed the overexpression of H19 in human trophoblasts and detected the cell proliferation with CCK-8 technology. Then, the invasive ability of H19 in human trophoblasts was examined with matrix reagent through transwell method. Reverse transcription PCR showed *lncRNA-H19* was highly expressed in human villous tissues from early spontaneous abortion patients and in human villous tissues from induced-abortion patients. Further, upregulation of *lncRNA-H19* inhibited the cell proliferation in HTR8/SV neo-trophoblasts overexpression of *lncRNA-H19* showed decreased motility in HTR8/SVneo trophoblasts. LncRNA-H19 inhibited early placenta growth and early vegetative layer cells, which could lead to early spontaneous abortion.[53,65] LncRNAs expression in female reproductive diseases is shown in Table 2 and Figure 1.

Long Noncoding RNAs Expression in Female Reproductive Tumors

For their roles in cell proliferation, differentiation, and apoptosis, lncRNAs are focused in the research on genesis of cancers or cancer subtypes. Furthermore, their differential expressions show difference in different tumor stages.[54,66]

Long noncoding RNA X-chromosome inactive specific transcript

Engreitz *et al*.[55] found that mouse lncRNA inactive specific transcript (XIST) inactivating X-chromosome was transferred from its transcription site to distant region on the X-chromosome. XIST, initially in the periphery of active genes on the X-chromosome, gradually spreads across the genes with its a-repeat domain, to be bound with inactive X-chromosome in differentiated female cells. XIST encodes a spliced lncRNA with a unique characteristic from an inactive X-chromosome. A study compared the total RNA expression profiles of primary and recurrent ovarian tumors from the same patient. The results showed that XIST was the most DE gene and downregulated in the recurrent tumor. In addition, *in vitro* studies showed that the expression of XIST was correlated with Taxol sensitivity. The loss of inactive X-chromosome led to the loss of XIST transcripts in ovarian cancer cell lines. The downregulation of XIST caused the upregulation of X-linked apoptotic inhibitor, a mechanism that prevented drug-induced apoptosis and brought resistant phenotypes of cancer cells.[55]

H19

A recent *in vivo* study has shown the coexpression between oncogenes and H19 in both primary human ovarian and endometrial cancers, confirming the existence of H19/let-7-dependent regulation. The antidiabetic drug, metformin, can suppress the tumor cell migration and invasion, partly by epigenetic downregulation of H19.[57] The loss of *H19* imprinting has been detected in malignant serous cystadenocarcinomas. H19 is also upregulated in most ovarian cancer tissues compared with adjacent nontumor samples, which indicates a significantly positive correlation between its expression and tumor development. Cooperated with histone H1.3 overexpression, *H19* knockdown inhibits the growth and clonogenicity of epithelial ovarian cancer cells.[67] Literature has revealed that the silencing of *H19* induces cell apoptosis and cell cycle arrest at the G2/M phase. *H19* RNA has been detected in a majority of patients with ovarian cancer ascites fluid.[68] H19 was overexpressed in ovarian carcinomas, a result of expressed prometastatic genes.[69] In ovarian cancer cells, H19 overexpression enhanced their migration and invasion.[70] In addition, H19 sequestering of let-7 was required for H19 to function in epithelial-mesenchymal-transition (EMT) processes such as cell invasion and migration in ovarian cancer and uterine serous carcinoma cell lines.[71] The levels of H19 expression increased throughout endometrial epithelium tumorigenesis. Level of H19 expression was low in normal endometrial epithelium but high in hyperplastic endometrium, especially in endometrial carcinoma and tumor tissue-dedifferentiated tumor tissues. Furthermore, in cervical cancer, markedly increased levels of IGF2 expression and decreased levels of H19 expression were reported. However, the mechanism promoting this dysregulation is still unclear and needs to be further investigated.[59]

Metastasis-associated lung adenocarcinoma transcript 1

As one of the first identified cancer-associated lncRNAs, MALAT1 acts in the pathogenesis of different tumors, including hepatocellular carcinoma, cervical cancer, breast cancer, and colorectal cancer.[60] MALAT1 knockdown could suppress the proliferation, invasion, and metastasis of human osteosarcoma cells. MALAT1 was mediated through PI3K/AKT signaling pathway. In addition, the expression of MALAT1 increased in primary metastatic bladder tumors but not in nonmetastasized tumors. Its silencing could result in a decrease in the EMT-associated zinc finger E-box binding 1 and 2 and Slug levels, as well as an increase in the E-cadherin levels in bladder cancer cells. MALAT1 in EMT enhancement activated the Wnt signaling.[61] Although its mechanism in ovarian cancer is unclear, it is differently expressed in cells of metastatic ovarian cancers.[66] It was found that lowering the expression of MALAT1 in Hela cells could effectively reduce cell proliferation and migration.[72]

MALAT1 was also overexpressed in SKOV3ip, an ovarian cancer cell line derived from SKOV3 with a more metastatic phenotype.[66] Furthermore, MALAT1 inhibition markedly suppressed tumorigenicity in SKOV3 ovarian cancer cells and changed the expression of several genes that were involved in cell proliferation, metastasis, and apoptosis. However, the mechanism in this situation is still unclear and requires more detailed evaluation.[73] In addition, high levels of MALAT1 have been reported in endometrioid endometrial cancer,[58] in relation with aberrant activation of the Wnt/beta-catenin pathway where the Wnt-effector transcription factor TCF4 interacts with the MALAT1 promoter region. This Wnt/beta-catenin aberrant activation was caused by the expression loss of the tumor suppressor PCDH10 which repressed Wnt/beta-catenin activation.[74] In addition, higher levels of MALAT1 were found in cervical cancer tissues and associated with a poor prognosis. MALAT1 was overexpressed in the cervical cancer CaSki cell line, which promoted the cell growth and invasion and decreased its apoptosis.[75,76]

Hox transcript antisense RNA

Hox transcript antisense RNA (*HOTAIR*), a long intervening ncRNA (lincRNA) transcribed from HOXC, is involved in epigenetic regulation, cooperative with polycomb repressive complex 2 and required for histone H3 lysine-27 trimethylation of the HOXD. The expression of *HOTAIR* was associated with cancer cell invasion and metastasis.[77] Furthermore, its expression was higher in ovarian cancer stem cells (CSCs) than non-CSCs.[78] Hazard ratios (*HRs*) of lncRNAs in cervical cancer patients showed that *HOTAIR*

generated the highest *HR* of 5.28. *HOTAIR* increased in a variety of human cancers.[77] Meanwhile, *HOTAIR* was a tumorigenic factor and could be adopted as a diagnosing or predictive biomarker in various cancer types.[79,80] *HOTAIR* is the most investigated lncRNA in cervical cancer. Hopefully, it can be used as a new biomarker in diagnosing and treating cervical cancer.

Moreover, in several ovarian cancer cell lines, the expression of HOTAIR caused resistance to cisplatin through Wnt/β-catenin pathway activation.[81] In cervical cancer, vascular endothelial growth factor and matrix metalloproteinase-9 expression were upregulated by HOTAIR. These two factors increased the migration and invasion of the tumor. HOTAIR was also correlated with recurrence of cervical cancer.[82,83] LncRNAs expressed female reproductive tumor disease [Table 2 and Figure 1].

Conclusion and Future Perspectives

More and more lncRNAs have been proved to be involved in reproductive diseases. Compared with miRNAs, lncRNAs are less conservative with overlapped functional domains. They act differently as decoy molecules, guide molecules, and scaffold molecules are all engaged in expression.

As a form of epigenetic regulation, lncRNAs may function in female reproductive processes through histone modification and chromatin reconstruction. Different expression of lncRNA124742, lncRNA Gtl2, lncRNA-H19 and lncRNA ENST00000502521, Neat1, Mrhl, and HongrES2 builds up a regulatory system in reproductive diseases, providing us a new way into the reproductive disorders.

LncRNA expression profiling should be assessed in each cancer type as the most altered lncRNAs are different in cancers. In addition, they may facilitate differentiation between different cancer histologic subtypes due to difference in expression pattern among different subtypes.

Further studies are needed to understand the roles of lncRNAs in reproductive diseases. With new technologies and searchable databases, such as bioinformatics tools and ontology databases, lncRNAs may serve as biomarkers and/or targets to diagnose and/or treat reproductive disorders.

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