The role of lncRNAs in the development of endometrial carcinoma (Review)

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Abstract. Endometrial carcinoma (EC) is one of the most common types of gynecological cancer. Long noncoding RNAs (lncRNAs) are associated with the carcinogenesis and progression of EC. In the following review, the emerging role of lncRNAs in EC initiation and progression is considered. The profile of lncRNAs is becoming higher as the contribution of lncRNAs to carcinogenesis through diverse mechanisms is being increasingly recognized, including in EC. A number of lncRNA-profiling studies have identified aberrantly expressed lncRNAs in EC tissue, and the regulatory network associated with these lncRNAs may be critical in EC progression. Additionally, certain lncRNAs may have diagnostic and/or prognostic significance. The potential function of lncRNAs as prospective therapeutic and prognostic targets in EC will be evaluated.

Contents

1. Introduction

Endometrial carcinoma (EC). EC is one of most common types of gynecological cancer, including worldwide and in China (1-4). Despite advances in a variety of types of treatment, the incidence of EC appears to be gradually increasing. The estimated number of new cases of uterine corpus was 63,230 in 2018, and 61,380 in 2017 (5). For patients with disease metastasis or recurrence, regardless of the grade or stage, the prognosis is poor; the patients are at a significantly higher risk of mortality and typically experience a poor quality of life, with a median overall survival time of <16 weeks (6). The poor prognosis is contributed to by the substantial rate of adjuvant therapy failure following tumor debulking by surgery, including chemotherapy, radiotherapy and hormone therapy. It remains unclear how genetic regulatory networks direct EC initiation. Although certain improvements have been made, including classifying patients by estrogen receptor status, it remains difficult to establish a prognosis for patients with EC (7-9).

lncRNAs. A relatively small proportion of the human genome encodes protein (~2%); the majority of the genome is not translated into proteins, and may instead code a range of non-coding RNA (ncRNA) types (>90% of the genome). A group of ncRNAs designated as long-non coding RNAs (lncRNAs) have been identified and characterized during recent decades; the group is so-named as, in contrast to other classes of ncRNA, lncRNAs range from 200 nt to 200 kb in length (10). The majority of lncRNAs are likely to be typically located in the nucleus, where they may serve critical roles in epigenetic regulation, including via chromatin modification. However, a growing number of studies have identified the presence of lncRNAs in the cytoplasm, suggesting that lncRNAs also function in the translational and post-translational-level regulation of gene expression (11-13). lncRNA transcription is highly regulated (14,15). lncRNAs may also contain various types of binding domains, allowing effector and repressor molecules to be bound, and bringing protein complexes together into larger functional units (16,17).

Function of lncRNAs. Based on biological function, the majority of lncRNAs can be classified as follows:

i) Signaling lncRNAs. These lncRNAs function in the regulation of RNA splicing, and gene activation or expression. lncRNAs may interact with the promoter or enhancer sequence of a specific gene to activate its expression. Other lncRNAs regulate mRNA processing by interacting

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with complementary transcripts to induce the abnormal splicing of mRNAs. Additionally, lncRNAs may regulate a protein's function, or control cellular localization via the formation of nuclear acid-protein complexes (18). Huarte *et al* (19) reported that lincRNA-p21, a lncRNA upstream of the cyclin dependent kinase inhibitor (CDKN) 1A gene, may serve an important regulatory role in the p53 transcriptional pathway. p53 is a critical tumor suppressor gene; its downregulation is associated with cancer progression (20,21).

ii) Decoy lncRNAs. lncRNAs of this type inhibit target microRNAs (miRNAs) or prevent interactions with a target protein. Decoy lncRNAs may mimic the gene sequence of specific miRNAs or contain miRNA-binding sequences, competing with miRNAs for target mRNAs (18). The pseudogene PTENP1 is an example of a decoy lncRNA; it may act to reinstate the level of tumor suppressor gene PTEN by binding to PTEN-regulatory miRNAs (22).

iii) Scaffold lncRNAs. lncRNAs may function in the epigenetic regulation of gene expression via regulating chromosome rearrangement, histone modification or alterations to RNA polymerase II activity. CDKN2B antisense RNA 1 (ANRIL) is an lncRNA from the CDKN2A/B locus that functions as a molecular scaffold; ANRIL may associate with PRCs (polycomb repressive complex) 1 and 2 to cause the transcriptional silencing of CDKN2A/B (23,24). Another lncRNA with a similar function is HOX transcript antisense RNA (HOTAIR). HOTAIR is a 2.2 kb transcript from the mammalian HOXC locus which may recruit the PRC2 complex to specific target genes genome-wide, inducing histone H3 K27 trimethylation and the epigenetic silencing of genes, including those associated with the suppression of metastasis (25). lncRNAs may also serve roles in other types of chromatin modification, X chromosome inactivation, and genomic imprinting (26).

iv) Precursor lncRNAs. A further category of lncRNAs may be cleaved to produce small RNAs, including miRNA or piwi-interacting RNA (27,28).

The morbidity and mortality associated with gynecological cancer is increasing (5). The expression profiles of lncRNAs in tumor tissue may be associated with tumor progression and metastasis (29). A number of lncRNAs may exhibit potential as biomarkers for the diagnosis and prognosis of EC. lncRNAs may also be a molecular target for the treatment of EC. The lncRNAs involved in the development of EC are included in Table I.

2. Aberrant expression of lncRNAs in EC

As will be described in the subsequent text, lncRNAs are associated with a range of biological processes in EC, including cell proliferation, differentiation, apoptosis and metastasis. The expression profile of lncRNAs may aid improvements to the classification of poorly differentiated cancer cells. However, the contribution of lncRNAs to the initiation and development of EC remains unclear.

Upregulated lncRNAs in EC. Microarray analysis and genome-wide sequencing have revealed the aberrant expression of lncRNAs in various types of cancer, including EC, although the majority of studies focused on a single, specific lncRNA. Zhai *et al* (30) recently performed the first comprehensive characterization analysis of the lncRNA subtype classification in EC. A total of 53 differently expressed lncRNAs were identified between cancer and normal endometrial tissue; these were associated with multiple signal pathways, biological processes, cellular components and molecular functions. Small nucleolar RNA host gene 12 (ASLNC04080) was the most significantly upregulated lncRNA identified in the study; it may contribute to the progression of EC by co-regulating with protein-coding genes. The downregulation of ASLNC04080 in HEC-1-B endometrial adenocarcinoma cells induced the repression of cell proliferation, and increased apoptosis and G1 phase arrest (30).

Genomic imprinting is the preferential silencing of one parental allele due to epigenetic modifications. H19, one of first lncRNAs identified (31), is downstream of insulin-like growth factor (IGF)-2 and functions in genomic imprinting during cell growth. The imprinted and developmentally regulated H19 has been implicated in the pathogenesis of a number of types of human cancer (31); however, the underlying mechanisms are not well characterized. Doucrasy *et al* (31) identified that H19 was upregulated in EC and associated with EC progression; the level of H19 in the myometrium and stroma was associated with the rate of cell proliferation. Additionally, studies by Lottin *et al* (32) identified that H19 expression in the tumor tissue and epithelial cells of endometrial hyperplasia could serve as a histopathological and prognostic marker. Yan *et al* (33) demonstrated that H19 promoted the invasive and migratory abilities of cancer cells via the downregulation of let-7, a tumor-suppressive miRNA that may post-transcriptionally inhibit the expression of oncogenes associated with the regulation of cell growth and motility in EC, including high mobility group AT-hook 2, c-Myc and IGF-2 binding protein 3. In *in vivo* experiments, a H19-let-7 axis-independent pathway was identified for the co-expression of H19 and certain oncogenes in EC and ovarian cancer. Furthermore, the study demonstrated that the anti-diabetic drug metformin could inhibit the motility of cancer cells, partially due to the downregulation of H19 through DNA methylation. The results revealed a mechanism for H19-mediated metastasis and may explain why, in certain cases, increases in the expression of let-7, a tumor suppressor, were unexpectedly associated with a poor prognosis (34).

Yang *et al* (35) identified the role of lncRNAs in the development of EC by comparing the expression of lncRNAs in EC with adjacent normal tissues. The abnormal expression of lncRNAs from HOX loci emerged as a characteristic of the cancer tissue, which was similar to a previous report that described the transcription of a large amount of lncRNAs in human HOX clusters (35). Compared with normal tissues, 4,010 lncRNAs were upregulated and 3,350 were downregulated. To confirm the microarray data, 7 lncRNAs were quantified with reverse transcription-quantitative polymerase chain reaction. Pathway analysis of these lncRNAs revealed that 24 pathways were associated with the upregulated transcripts, whereas 27 pathways were associated with the downregulated transcripts. The study demonstrated that the expression of a large amount of lncRNAs was altered in EC compared with normal tissue, suggesting that lncRNAs may have potential as diagnostic biomarkers in EC (35).

Table I. lncRNAs associated with endometrial carcinoma.

lncRNA	Full name	Expression	Cellular function	(Refs.)
ASLNC04080	Small nucleolar RNA host gene 12	Upregulated	Cooperates with other genes to repress cell proliferation, increase cell apoptosis and induce cell cycle arrest in G1.	(30)
H19		Upregulated	Promotes tumor cell migration and invasion.	(31-34)
OVAL	Ovarian adenocarcinoma amplified lncRNA	Upregulated	Undergoes somatic copy-number amplification.	(36)
CASC2	Cancer susceptibility candidate 2	Downregulated	Inhibits cellular growth in a nchorage-independent growth assays.	(48,49)
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1	Downregulated	Novel Wnt pathway regulatory element.	(50-53)
HOTAIR	HOX transcript antisense RNA	Downregulated	Inhibits cell proliferation, migration and invasion, and induces cell cycle arrest at G0/1.	(25,37-45)
SRA	Steroid receptor RNA activator	Upregulated	Promotes cellular proliferation and differentiation; inhibits ras-induced tumorigenesis.	(47)
Linc-RoR	Large intergenic non-coding ribonucleic acids-regulator of reprogramming	Upregulated	An microRNA-145 'sponge' to inhibit the differentiation of endometrial cancer stem cells.	(54)

The ovarian adenocarcinoma amplified lncRNA (OVAL), which is located in the AXI region between the acyl-CoA binding domain containing 6 and xenotrophic and polytropic retrovirus receptor 1 protein-coding genes, may affect the extent of tumor aggressiveness in EC (36). By detecting regions of copy-number alterations that lack protein-coding targets, Akrami *et al* (36) identified that OVAL exhibited narrow focal genomic amplification in certain types of cancer tissue. Similar genomic amplification patterns were identified in serous EC and sixteen other types of cancer. OVAL may also be a suitable biomarker for distinguishing type I and II EC (36).

HOTAIR was the first identified example of an lncRNA that could affect the transcription of genes on another chromosome, as it occurs in the HOXC locus on chromosome 12 and can repress the transcription of HOXD genes on chromosome 2 (37). HOTAIR is upregulated in breast cancer (25), hepatocellular carcinoma (38), pancreatic cancer (39) and laryngeal squamous cell carcinoma (40). Furthermore, the high expression of HOTAIR has been demonstrated to negatively regulate metastasis-suppressing genes to promote tumor malignancy (41). Its expression in EC cells and tissues is significantly higher than in normal endometrial tissues, and its expression is associated with the clinical stage and the myometrial invasion and lymph node metastasis status (42). In a previous study, knockdown of HOTAIR induced a suppression of cell proliferation, migration and invasion, and inhibited EC tumorigenesis *in vivo* (43). He *et al* (43) analyzed the correlations between HOTAIR expression and the clinicopathological characteristics of patients. The results demonstrated that the expression of HOTAIR in EC was increased compared with normal tissue. The authors also identified that higher levels of HOTAIR expression were associated with lymphovascular space invasion. Patients with higher expression of HOTAIR exhibited reduced overall survival time compared with the patients with lower expression. These results demonstrated that HOTAIR was associated with the progression of EC, and therefore may be suitable as a biomarker for poor prognosis (44) or as a target for EC therapy (45).

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is ~8,000 nt. The overexpression of MALAT1 has been identified in endometrial hyperplasia and low-grade EC (46). However, MALAT1 was significantly downregulated in high-grade EC, including clear cell carcinoma, serous papillary carcinoma and metastatic EC. MALAT1 transcription was regulated by Wnt/β-catenin signaling via T-cell factor promoter binding; protocadherin 10 (PCDH10), a tumor suppressor protein associated with a variety of types of malignancy, decreased MALAT1 expression by modulating this pathway (46).

In vitro, steroid receptor RNA activator (SRA) is an lncRNA that co-activates steroid hormone receptor-mediated transcription. The expression of SRA was significantly upregulated in many types of cancer, including uterine, breast and ovarian cancer, indicating its role in steroid-dependent types of tumor (47). SRA-transgenic mice in the research conducted by Lanz *et al* (47) did not develop any tumors. However, SRA upregulation in tumor tissue decelerated the increased proliferation of tumor cells. Furthermore, they demonstrated that SRA-transgenic mice counteracted the raised mitotic activity and increased apoptosis rate. Therefore, SRA may be suitable as a predictive diagnostic marker.

As EC cell lines and tumor tissues exhibit the increased expression of these lncRNAs, they may contribute to oncogenesis in EC development and progression.

Downregulated lncRNAs in EC. Though the majority of identified lncRNAs associated with EC exhibit tumorigenic

activity, there are also lncRNAs that are downregulated in EC. The ectopic expression of these lncRNAs in cancer cells leads to the inhibition of cell proliferation and motility.

The cancer susceptibility candidate 2 (CASC2) gene has been identified at this locus. CASC2a, one of three alternative transcript forms, may also encode a protein of 102 amino acids with no similarity to any other identified gene product. CASC2a was demonstrated to be mutated at a low frequency, with a decreased level of expression in EC and colorectal cancer (48). Enforced expression of CASC2a in AN3CA undifferentiated EC cells suppressed cell growth in anchorage-independent growth assays. The infrequent mutations may have reduced the function of the gene, which may act as a tumor suppressor gene; epigenetic and genetic modifications were identified that were concordant with gene inactivation (48). Similar results were also reported in the study by Baldinu *et al* (49).

3. Mechanisms for the differential expression and function of lncRNAs in EC

The aberrant expression of lncRNAs in human cancer may be caused by a range of mechanisms, including epigenetics, genomic abnormalities, DNA mutations, transcriptional regulation and polymorphisms. The development of EC is a complicated biological process including cell proliferation, differentiation, invasion, metastasis and angiogenesis. As in other types of cancer, lncRNAs can act as oncogenes or tumor suppressors, and the aberrant expression of lncRNAs may be an important contributor to cancer cell transformation and the subsequent progression. The available information on the function of specific lncRNAs in EC will be summarized in this section.

Tumor suppressor genes may be silenced following the hypermethylation of their promoter regions. lncRNAs may also be epigenetically modified. For example, it has been identified that PCDH10 may be downregulated by promoter hypermethylation in various types of tumor, although the functional role for PCDH10 as a tumor suppressor gene is not well established (50-53). PCDH10 was identified as a potential Wnt pathway regulatory element in endometrial endometrioid carcinoma (EEC). PCDH10 was downregulated in EEC cancer cells following aberrant promoter methylation (53). The downregulation of MALAT1 expression can be induced by PCDH10 in EEC cells (53).

Large intergenic non-coding ribonucleic acids-regulator of reprogramming (linc-ROR) may regulate the expression of the core stem cell transcription factors. Linc-ROR is overexpressed in EC cell lines and tumor tissues (54). However, the mechanism by which this lncRNA affects EC has yet to be determined. The effects of miR-145 were eradicated following the upregulation of linc-RoR. Linc-RoR acted as an miR-145 'sponge' to suppress the differentiation of EC stem cells. This result suggested that linc-RoR has an important role in endometrial carcinogenesis (54).

As previously described, H19 also acted as a sponge to bind let-7, an miRNA associated with the inhibition of IGF-1 receptor (R) mRNA to induce a decrease in IGF-1R protein. The expression of IGF-1R is essential for the proliferation of the endometrial stroma (34).

4. lncRNA as diagnostic and prognostic tools, or therapeutic targets, in EC

MALAT1 has been demonstrated as a biomarker for lung cancer, uterine endometrial stromal sarcoma, cervical cancer and hepatocellular carcinoma screening due to its association with cancer cell metastasis (55). Furthermore, MALAT1 is a potential target for anti-metastatic therapy in non-small cell lung carcinoma (55). The PCDH10-Wnt/β-catenin-MALAT1 regulatory axis may contribute to EEC development. The exact mechanism for the effect of this axis in various physiological and pathological conditions has yet to be fully characterized in EC (56), but MALAT1 is nonetheless under consideration as a potential biomarker and therapeutic target for EC.

As previously described, HOTAIR expression was associated with myometrial invasion and lymph node metastasis in EC. RNA interference against HOTAIR is a promising therapeutic strategy against EC (57). The major advantage of lncRNA-based therapy is that a single lncRNA can contribute to multiple aspects of cancer cell physiology, and the function of several pathways can be altered by the inhibition of a single lncRNA.

The diagnosis of early stage EC may be difficult due to its asymptomatic characteristics. In aggressive type II EC, including serous adenocarcinoma, there is a lack of sensitive and specific biomarkers for prognosis; transcriptomics and proteomics have yet to yield accurate biomarkers (58). lncRNA expression profiles may be a promising alternative, because the expression profile can offer more predictive information for cancer diagnosis than profiling hundreds and thousands of targeting mRNAs or proteins (16). The role of lncRNAs as prognostic markers and therapeutic targets in EC is not well established, and the role of lncRNAs in drug resistance should also be further explored.

In conclusion, EC-associated lncRNAs with an experimentally confirmed function may be suitable candidates for therapeutic strategies against EC. However, the study of lncRNAs in EC is a relatively new area. Further efforts will be required to clarify the function of EC-associated lncRNAs *in vivo* (59).

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BL collated the references and wrote this review. XW reviewed and edited the manuscript.

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Consent for publication

Not applicable.

Competing interests

The author's declare that they have no competing interests.

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