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Review

Long Noncoding RNAs in Ovarian Cancer—Functions and Clinical Applications

Lili Zhong[1], Xin Li[1], Yicun Wang[1], Bin Liu[2], Xiangfu Ding[3,*,†], Yinlong Zhao[4,*,†]

[1] Department of Research Center, Jilin Provincial Key Laboratory on Molecular and Chemical Genetics, The Second Hospital of Jilin University, 130041 Changchun, Jilin, China
[2]Department of Breast Surgery, The Second Hospital of Jilin University, 130041 Changchun, Jilin, China
[3]Department of Thyroid Surgery, The Second Hospital of Jilin University, 130041 Changchun, Jilin, China
[4]Department of Nuclear Medicine, The Second Hospital of Jilin University, 130041 Changchun, Jilin, China
*Correspondence: jdeyjzxwkdxf@163.com (Xiangfu Ding); yinlong@jlu.edu.cn (Yinlong Zhao)
[†]These authors contributed equally.
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Abstract

Long noncoding RNAs (lncRNAs) are RNA molecules with a length of more than 200 nt that have been discovered in recent years. LncRNAs can participate in regulating gene expression and various biological activities through multiple pathways, such as at the epigenetic level, transcriptional level, and posttranscriptional level. In recent years, with the increasing understanding of lncRNAs, a large number of studies have shown that lncRNAs are closely related to ovarian cancer and participate in its occurrence and development, providing a new method to investigate ovarian cancer. In this review, we analyzed and summarized the relationship between various lncRNAs and ovarian cancer in terms of occurrence, development, and clinical significance, in order to provide a theoretical basis for basic research and clinical application of ovarian cancer.

Keywords: long noncoding RNAs; ovarian cancer; expression disorder; diagnosis; therapy; prognosis

1. Introduction

Long noncoding RNAs (lncRNAs), which have a length of more than 200 nt, are mainly located in the nucleus or cytoplasm and are transcribed by RNA polymerase. They are a kind of noncoding RNA molecules with high tissue and organ specificity [1–3]. The mechanisms and types of lncRNAs action are complex: (a) they can inhibit translation and degradation through complementary binding with mRNA bases; (b) as competing endogenous RNAs (ceRNAs), they can competitively bind to microRNAs to regulate the expression of target genes; (c) they recruit chromatin remodeling proteins to specific genomic sites to regulate chromatin status, participate in chromatin modification, and regulate gene expression at the epigenetic level; (d) they can promote the cyclization of enhancers and activate gene expression, with enhancer activity; (e) they can act as transcriptional regulatory factors and play a role in transcriptional regulation; and (f) they can conduct post-transcriptional regulation through splicing and translation control [4–6]. Ovarian cancer (OC) is one of the most common malignancies of the female reproductive system, and its incidence and mortality rates have remained high for many years. OC seriously endangers the health of women worldwide; statistically, there are nearly 240,000 new OC patients worldwide every year, and approximately 140,000 women die of OC every year [7,8]. In recent years, some specific lncRNAs have been found to be abnormally expressed in OC cells and tissues, and closely related to the occurrence and development of OC. These findings have brought new enlightenment to the study of OC [9–15]. In this review, we summarized and analyzed the relevant studies and reports on the relationship between lncRNAs and OC in recent years to provide a reliable theory for basic research, clinical diagnosis, therapy, and efficacy monitoring of OC.

2. The Relationship between LncRNAs and Ovarian Cancer

2.1 Some LncRNAs can Promote the Occurrence and Development of Ovarian Cancer

In recent years, a variety of lncRNAs have been found to be abnormally expressed in OC, which can promote the occurrence and development of OC [16–20]. The *lncRNAs ROR*, *SRA*, *H19*, *UCA1* and *PTAR* have been reported to promote the occurrence and development of OC by regulating epithelial-mesenchymal transformation (EMT) [21–25]. Wang *et al*. [26] detected the expression of *lncRNA RHPN1-AS1 i*n tissues samples of 86 epithelial ovarian cancer (EOC) patients and 9 EOC cell lines by quantitative real-time polymerase chain reaction (qRT-PCR). The results showed that the expression of *lncRNA RHPN1-AS1* was significantly higher in EOC cancer tissues and cell lines than in control samples. Further mechanistic studies demonstrated that *lncRNA RHPN1-AS1* binds to the target gene *miR-596*,

resulting in the upregulation of leucine zipper EF-hand domain transmembrane protein 1 (LETM1) and activation of the FAK/PI3K/AKT signaling pathway, which promote the proliferation, invasion, and migration of EOC cells. The *lncRNA RHPN1-AS1* accelerates the progression of OC. Pei *et al*. [27] found that *lncRNA DANCR* expression level in OC tissues was significantly higher than that in control samples, and *lncRNA DANCR* overexpression could promote proliferation, migration and invasion of OC cells. Mechanistic experiments showed that *DANCR* overexpression resulted in significant downregulation of *UPF1*, and the expression level of *UPF1* was negatively correlated with the expression of *DANCR*. *LncRNA DANCR* could enhance the proliferation, migration, and invasion of OC cells by downregulating *UPF1* and promoting the progression of OC. Cao *et al*. [28] found that the *lncRNA LBX2-AS1* expression level was higher in OC samples and was related to tumor growth, metastasis, and low survival rate. Knocking out *lncRNA LBX2-AS1* inhibited the proliferation, migration, and invasion of OC cells. Further studies confirmed that *lncRNA LBX2-AS1* could directly interact with *miR-455-5p* and *miR-491-5p* as competing endogenous RNA (ceRNA), regulate the expression of *E2F2* cancer-promoting gene and play a role as an oncogenic lncRNA in OC. Wang *et al*. [29] found that *lncRNA CDKN2B-AS1* was significantly overexpressed in different OC cell lines and may promote the migration and invasion of OC, inhibit its apoptosis and promote the development of OC through the *miR-411-3p/HIF-1a/VEGF/p38* pathway. Chen *et al*. [30] found that the expression of *lncRNA PVT1* was upregulated in OC samples. Knockout of *lncRNA PVT1* inhibited the proliferation, migration, and invasion of SKOV3 cells. The potential mechanism may be that *lncRNA PVT1* caused the combination of *Enhancer of zeste homologue 2* (*EZH2*) and the *miR-214* promoter, to inhibit the expression of *miR-214*, and then promote the progression of OC. Zhang *et al*. [31] found that the expression of *lncRNA HOXD-AS1* was significantly higher in EOC. *LncRNA HOXD-AS1* competitively adsorbed *miR-133A-3p*, activated Wnt/β-Catenin signal pathway, enhanced the proliferation of EOC cells, regulated the EMT process, accelerated tumor metastasis, and ultimately promoted tumor progression. Shang *et al*. [32] found that the *lncRNAs HOTIP*, *IL-6* and *PD-L1* were highly expressed in OC tissues. Their expression levels were positively correlated. Mechanistic studies showed that the *lncRNA HOTTIP* could promote the secretion of *IL-6*, upregulate the expression of *PD-L1* in neutrophils, and inhibit the activity of T cells, ultimately accelerating the immune escape of ovarian cancer cells and promoting the progression of ovarian cancer.

2.2 Some Other LncRNAs can Inhibit the Occurrence and Development of Ovarian Cancer

LncRNAs have dual effects on OC. Some lncRNAs can promote the occurrence and development of OC, whereas others can inhibit the progress of OC [33–38]. Sun *et al*. [39] found that *lncRNA EPB41L4A-AS2* was expressed at low levels in OC. The SKOV3 cell line was cultured *in vitro* and transfected with *EPB41L4A-AS2* overexpression plasmid. They found that upregulating the expression of *lncRNA EPB41L4A-AS2* could inhibit the proliferation, colony formation, migration, and invasion of SKOV3 cells. In addition, 3–4 weeks old female BALB/c nude mice were injected with transfected SKOV3 cells, and tumor volume was measured and recorded regularly. Animal experiments confirmed that overexpressed lncRNA *EPB41L4A-AS2* inhibited the formation of tumors *in vivo*. Further mechanistic studies have shown that *lncRNA EPB41L4A-AS2* can upregulate the expression of the transcription factor *RUNX1T1* by binding microrNA-103A, inhibit the progression of OC and play a similar role as tumor suppressor genes. Long *et al*. [40] discovered low expression of *lncRNA GAS5* in EOC tissues and HEY, A2780, A2780/DDP, SKOV3, SKOV3/DDP and other seven cell lines through microarray and qRT-PCR. Compared with sensitive cell lines, the expression of *lncRNA GAS5* in cisplatin DDP-resistant OC cell lines decreased more. Cell transfection upregulated the expression of *lncRNA GAS5* in HEY and SKOV3 cells. They found that overexpression of *lncRNA GAS5* could lead to G0/G1 phase arrest, increase apoptosis of OC cells, and significant enhancement of the sensitivity of OC cells to DDP. Tumorigenicity tests in nude mice showed that after 4 weeks of injection, the tumor size and weight of the mice in the group stably expressing *GAS5* were significantly lower than those in the control group, and the sensitivity to DDP was also significantly enhanced. In conclusion, *lncRNA GAS5* could inhibit the progression of OC and enhance sensitivity to chemotherapy. Chen *et al*. [41] detected 40 OC tissues, 40 control samples, ES-2CaOV-3SKOV3 and OVCAR-3 OC cell lines, they found that *lncRNA HAND2-AS1* was expressed at low levels in OC. After upregulating the expression of *lncRNA HAND2-AS1* by cell transfection, the proliferation rate of tumor cells was significantly inhibited, and the apoptosis rate was enhanced. Tumorigenesis test of xenografts in nude mice also showed that overexpression of *lncRNA HAND2-AS1* could inhibit the growth of tumor volume. Gokulnath *et al*. [42] also found low expression of *lncRNA HAND2-AS1* in high-grade serous ovarian cancer (HGSC) in a study of the relationship between lncRNAs and OC. They also confirmed that the downregulation of *lncRNA HAND2-AS1* was caused by promoter methylation in HGSC and played a tumor suppressive role in the HGSC cell line. Upregulation of *lncRNA HAND2-AS1* expression can improve the sensitivity of HGSC cells to the HDAC inhibitor panobinostat. Wang *et al*. [43] found that *lncRNA XIST* was significantly downregulated in EOC cells. *LncRNA XIST* was stably overexpressed in EOC cells after lentivirus transfection. They found that upregulation of *lncRNA XIST* could inhibit proliferation, inva-

sion, and tumor growth *in vivo*, and increase the chemosensitivity of OC cells to cisplatin by reversing the downregulation of *HSA-miR-214-3p*, thus playing a significant anticancer role. Gokulnath *et al*. [44] found that the expression of *LncRNA MAGI2-AS3* was lower in EOC tissues and cell lines. Further studies showed that *lncRNA MAGI2-AS3* could adsorb *miR-15-5p, miR-374a-5p*, and *miR-374b-5p*, change the downstream signals of some mRNAs through the ceRNA network, and play a tumor inhibitory role in EOC, especially in HGSC. Fang *et al*. [45] confirmed that the expression of *lncRNA GAS8-AS1* was low in OC tissues, COC1, A2780 and SKOV3 cell lines. The overexpression of *lncRNA GAS8-AS1* inhibited the growth of OC cells, whereas the loss of *lncRNA GAS8-AS1* promoted the growth of cancer cells. Further mechanistic studies showed that *lncRNA GAS8-AS1* inhibited the progression of OC by binding with Beclin1 to activate autophagy (Table 1, Ref. [13,16–35,37–41,43–45]).

3. Clinical Significance of LncRNAs in Ovarian Cancer

3.1 LncRNA and Diagnosis of Ovarian Cancer

Most OC patients have no typical symptoms at the initial stage and usually are at an advanced stage when diagnosed, having missed the best treatment opportunity and resulting in high mortality. Therefore, effective early diagnosis methods are of great significance for OC [46–48]. According to relevant literature reports, early detection of OC can reduce mortality by 10%–30% [49]. With the increasing number of studies on lncRNAs, they have been found to be potentially useful as tumor markers for the early diagnosis of OC [50–55]. Liu *et al*. [56] examined the expression level of *lncRNA LOXL1-AS1* in the serum of 185 patients with EOC and 43 healthy volunteers, and constructed an ROC curve to evaluate diagnostic ability of *lncRNA LOXL1-AS1* expression levels in EOC. The result was that the expression level of *lncRNA LOXL1-AS1* in the serum of the EOC patients was significantly higher. The area under the ROC curve (AUC) of *lncRNA LOXL1-AS1* was 0.843, the 95% confidence interval (CI) was 0.756–0.931, the sensitivity was 63.7%, and the specificity was 85.3%. These findings suggest that the detection of serum *lncRNA LOXL1-AS1* expression levels may be helpful for the early diagnosis of EOC patients. In a study of *lncRNA-LINC01554* and OC, Luo *et al*. [57] found that its expression was significantly lower in tumor tissues and can be used for the early diagnosis of OC. The ROC analysis results showed that the AUC value was 0.7827, the 95% CI was 0.7333–0.8322, and the sensitivity and specificity reached 73.32% and 89.67%, respectively. Shen *et al*. [58] found high expression of *lncRNA ROR* in OC tissues, and its level was positively correlated with CA125. The combined detection of plasma *lncRNA ROR* and CA125 has ideal clinical significance for the early diagnosis of OC. Therefore, the *lncRNA ROR* level can be used for OC diagnosis.

3.2 LncRNA as Therapeutic Targets in Ovarian Cancer

The main therapies for OC are surgery and chemotherapy, supplemented by radiotherapy, targeted therapy, and immunotherapy [59–62]. The treatment of OC is becoming increasingly advanced with the rapid development of medical technology, but it still faces many difficulties, such as missing the best operation opportunity, chemoresistance, poor radiotherapy sensitivity, and so on [63–65]. LncRNAs are abnormally expressed in OC and promote or inhibit tumor development. Therefore, lncRNAs are potential therapeutic targets for OC [66–72]. Liu *et al*. [73] found that the expression of *lncRNA PCA3* in EOC tissues was higher than that in normal ovarian tissues. Overexpression of *lncRNA PCA3* can promote the progression of EOC through the *miR-106b/RhoC* pathway. Knockout of *lncRNA PCA3* inhibited cell proliferation and invasion and slowed down tumor progression. Therefore, inhibiting the expression of *lncRNA PCA3* may be an effective gene therapeutic strategy for the treatment of OC. Cheng *et al*. [74] showed that siRNA targeting *lncRNA AB073614* can effectively inhibit the growth and metastasis of HO-8910 and OVCAR3 cells, leading to cell arrest in the G1 phase of the cell cycle and promoting apoptosis. Therefore, *lncRNA AB073614* can be used as a therapeutic target for OC. A large number of studies have shown that lncRNAs are closely related to chemotherapy resistance and radiotherapy sensitivity in OC [75–82]. Zhang *et al*. [83] found cell models that have high expression of *lncRNA HOTIAR* and low expression of *miR-138-5p* in SKOV3/DDP and A2780/DDP OC. Knockdown of *lncRNA HOTAIR* can increase *miR-138-5p* expression; *miR-138-5p* can regulate the expression of the cisplatin resistance-related proteins EZH2 and SIRT1, thus improving the sensitivity of cisplatin-resistant cells to cisplatin. The *lncRNA HOTAIR/miR-138-5p* axis can regulate cisplatin resistance of OC cells through the potential targets EZH2 and SIRT1, which may provide a new therapeutic strategy for OC. Wang *et al*. [84] found that *lncRNA-UCA1* is significantly overexpressed in paclitaxel-resistant OC cells. *LncRNA-UCA1* increases the resistance of OC cells to paclitaxel by regulating *miR-129/ABCB1*. The research team proposed that l*ncRNA-UCA1/miR-129/ABCB1* could be used as a new regulatory axis of PTX resistance in OC, providing a potential therapeutic target for clinical treatment. Li *et al*. [85] observed that *lncRNA-UCA1* expression was also upregulated in the tissues and cells of cisplatin-resistant patients, and knockout of *lncRNA UCA1* inhibited the proliferation of OC cells and promoted cisplatin-induced apoptosis. Mechanistic studies have shown that *lncRNA UCA1* can regulate cisplatin resistance in OC through the *miR-143/FOSL2* pathway. Yang *et al*. [86] found that *lncRNA CRNDE* was highly expressed in the acquired radiotherapy-resistant cell line CAOV3/R. Silencing of *lncRNA CRNDE* expression by siRNA could significantly enhance the sensitivity of CAOV3/R cells to radiotherapy and inhibit clone

Table 1. Function of LncRNAs in Ovarian Cancer.

LncRNA	Experimental models	Expression	Function	Mechanism	Refs.
THOR	Cell lines, Clinical samples, Mice	Up	Promote	Promote OC cells growth, metastasis and self-renewal by activating IL-6/TAT3 signal	[13]
TP73-AS1	Cell lines, Clinical samples, Mice	Up	Promote	Promote OC cells proliferation and metastasis via MMP2 and MMP9	[16]
LINC00858	Cell lines, Clinical samples	Up	Promote	Aggravate the development of OC through miR-134-5p/RAD18 signal	[17]
MALAT1	Cell lines, Clinical samples, Mice	Up	Promote	Enhance OC Cell stemness by enhancing YAP translocational activity; promote OC progress through miR-211/PHF19 signal	[18,20]
LINC00176	Cell lines, Clinical samples, Mice	Up	Promote	Promote OC progress by increasing ceruloplasmin expression via BCL3	[19]
ROR	Cell lines, Clinical samples	Up	Promote	Promote EMT through the miR-145/FLNB regulatory axis in OC	[21]
SRA	Cell lines, Clinical samples, Mice	Up	Promote	Promote cell migration, invasion, and progression of OC via NOTCH and EMT	[22]
H19	Cell lines	Up	Promote	Promote TGF-β-induced EMT by acting as a ceRNA of miR-370-3p	[23]
UCA1	Cell lines, Clinical samples, Mice	Up	Promote	Regulate tumor stem cells and promote EMT	[24]
PTAR	Cell lines, Clinical samples, Mice	Up	Promote	Promote EMT in SOC through miR-101-3p/ZEB1 signal	[25]
RHPN1-AS1	Cell lines, Clinical samples, Mice	Up	Promote	Promote OC progress by combining miR-596 and upregulaing LETM1	[26]
DANCR	Cell lines, Clinical samples	Up	Promote	Promote OC progress through negative regulation of UPF1 expression	[27]
LBX2-AS1	Cell lines, Clinical samples Mice	Up	Promote	Drive OC progress via the miR-455-5p and miR-491-5p	[28]
CDKN2B-AS1	Cell lines, Mice	Up	Promote	Combine with miR-411-3p, promote OC progress through HIF-1a/VEGF/P38 pathway	[29]
PVT1	Cell lines, Clinical samples	Up	Promote	Regulate EMT process and interact with EZH2 represses miR-214 expression in OC cells.	[30]
HOXD-AS1	Cell lines, Clinical samples	Up	Promote	Promote EOC progress through miR-133a-3p and Wnt/β-Catenin signal pathway	[31]
HOTTIP	Cell lines, Clinical samples, Mice	Up	Promote	Upregulate the expression of PD-L1 and IL-6, enhance the immune escape of OC cells, and promote tumor progression	[32]
SNHG9	Cell lines, Clinical samples	Down	Inhibit	Inhibite OC progress by sponging microRNA-214-5p	[33]
NPBWR1-2	Cell lines	Down	Inhibit	Affect the expression of IGFBP7 through miRNA and play an inhibitory role in tumor	[34]
LEMD1-AS1	Cell lines, Clinical samples, Mice	Down	Inhibit	Suppress OC progress by sponging miR-183-5p and regulation of TP53	[35]
WDFY3-AS2	Cell lines, Clinical samples, Mice	Down	Inhibit	Inhibite tumor progress by sponging microRNA-18a in OC cells	[37]
ASAP1-IT1	Cell lines, Clinical samples	Down	Inhibit	Suppress OC progress by regulating Hippo/YAP signaling	[38]
EPB41L4A-AS2	Cell lines, Clinical samples, Mice	Down	Inhibit	Suppress OC progress by adsorbing microRNA-103a and upregulating the expression of RUNX1T1	[39]
GAS5	Cell lines, Clinical samples, Mice	Down	Inhibit	Inhibit tumor progress of EOC via GAS5-E2F4-PARP1-MAPK axis	[40]
HAND2-AS1	Cell lines, Clinical samples, Mice	Down	Inhibit	Upregulate expression of BCL2L11 by competitively binding with miR-340-5p, act as a tumor suppressor in OC	[41]
XIST	Cell lines, Mice	Down	Inhibit	Inhibit EOC progress through hsa-miR-214-3p	[43]
MAGI2-AS3	Cell lines	Down	Inhibit	Inhibit OC progress by sponging miR-15-5p, miR-374a-5p and miR-374b-5p	[44]
GAS8-AS1	Cell lines, Clinical samples, Mice	Down	Inhibit	Suppress OC progress through activating Beclin1-mediated autophagy	[45]

Table 2. Clinical application of lncRNAs in ovarian cancer.

LncRNA	OC type	Expression	Number of patients	Clinical application (Diagnosis/Therapy/Prognosis)	Refs.
HAGLROS	OC	Up	41	Early diagnosis and prognostic evaluation for OC—Diagnostic biomarker and factor associated with survival	[51]
FLJ33360	OC	Down	32	Participate in OC progression target miR-30b-3p—Diagnostic biomarker and factor associated with survival	[54]
LOXL1-AS1	EOC	Up	185	Early diagnosis and prognostic evaluation for EOC—Diagnostic biomarker and factor associated with survival	[56]
LINC01554	EOC	Down	161	Diagnostic biomarker, therapeutic target and factor associated with survival	[57]
ROR	OC	Up	60	Early diagnosis of OC—Diagnostic biomarker	[58]
NEAT1	OC	Up	32	Promote the resistance of OC to PTX by regulating EMT—Therapeutic target	[66]
CCAT1	EOC	Up	N/A (cell lines, mice)	Promote chemoresistance of OC cells to cisplatin by sponging miR-454—Therapeutic target and factor associated with survival	[68]
TUG1	OC	Up	N/A (cell lines)	Inhibit tumor angiogenesis in OC by regulating LRG1—Diagnostic biomarker and therapeutic target	[70]
CHRF	OC	Up	20	Promote the resistance of OC to cisplatin resistance—Therapeutic target	[72]
PCA3	EOC	Up	36	Treat OC by inhibiting PCA3 expression—Therapeutic target	[73]
AB073614	OC	Up	75	Inhibit OC through SiRNA targeting lncRNA AB073614—Therapeutic target	[74]
NEAT1	OC	Up	32	Enhance paclitaxel (PTX) resistance of OC—Therapeutic target	[75]
ANRIL	EOC SOC	Up	86 (EOC) 68 (SOC)	Affect the sensitivity of EOC to cisplatin—Therapeutic target; Predict poor prognosis of SOC—Factor associated with survival	[76,100]
LINC01125	OC	Down	21	Enhance the cisplatin sensitivity of OC cells by binding to miR-1972—Therapeutic target	[79]
FAM83H-AS1	OC	UP	80	Enhance radioresistance, guide clinical treatment—Therapeutic target	[81]
HOTAIR	OC	Up	N/A (cell lines)	Reverse cisplatin resistance of OC cells through knockdown of HOTAIR—Therapeutic target	[83]
UCA1	OC	UP	56	Reverse the tolerance of OC to chemotherapeutic drugs—Therapeutic target	[85]
CRNDE	OC	Up	N/A (cell lines, mice)	Reverse radiotherapy resistance of OC Cell Strain CAOV3/R by Targeting LncRNA CRNDE—Therapeutic target	[86]
CCEPR	OC	Up	N/A (cell lines)	Predict the poor prognosis of OC patients—Factor associated with survival	[91]
SNHG20	EOC	Up	60	Serve as an independent prognostic predictor in EOC—Factor associated with survival	[95]
LINC00664	OC	Up	N/A (Bioinformatics)	Independent risk factors for OC recurrence—Factor associated with survival	[97]
LINC00667	OC	Up	N/A (Bioinformatics)	Independent risk factors for OC recurrence—Factor associated with survival	[97]
LINC01139	OC	Up	N/A (Bioinformatics)	Independent risk factors for OC recurrence—Factor associated with survival	[97]
LINC01419	OC	Up	N/A (Bioinformatics)	Independent risk factors for OC recurrence—Factor associated with survival	[97]
LOC286437	OC	Up	N/A (Bioinformatics)	Independent risk factors for OC recurrence—Factor associated with survival	[97]
CASC2	EOC	Down	126	Inhibit progression and predicts favorable prognosis in EOC—Therapeutic target and factor associated with survival	[98]
CCAT2	OC	Up	109	Potential prognostic biomarker and therapeutic target for patients with OC	[99]
RP11-284N8.3.1	OC	Up	399	Biomarker for the prognosis of patients—Factor associated with survival	[101]
AC104699.1.1	OC	Up	399	Biomarker for the prognosis of patients—Factor associated with survival	[101]
SNHG3	OC	Up	76	Poor prognosis enhancing malignant progression of OC—Factor associated with survival	[102]

OC, ovarian cancer; EOC, epithelial ovarian cancer; SOC, serous ovarian cancer.

formation. In addition, combined with *in vivo* animal experiments, targeted silencing of *lncRNA CRNDE* was found to reverse CAOV3/R radiotherapy resistance and inhibit tumor growth. Therefore, they concluded that *lncRNA CRNDE* could be used as a potential target for OC therapy.

3.3 LncRNAs and Prognosis and Recurrence of Ovarian Cancer

In recent years, with the advancement and diversification of OC therapy, the effects have improved significantly. However, due to the high recurrence rate, the 5-year survival rate is still low. Therefore, screening for reliable prognostic and recurrence markers is of great significance for OC [87–89]. The clinical application of lncRNAs for OC is not only limited to diagnosis and therapy but can also be used to predict prognosis and recurrence [90–96]. Chen *et al*. [97] downloaded OC gene expression data from gene expression database (GEO). Weighted correlation network analysis (WGCNA) and multivariate Cox proportional hazards regression (Cox-PHR) analysis were used to screen prognoses related lncRNAs. Kaplan Meier analysis and Receiver Operating Characteristic (ROC) curve analysis were used to evaluate the prediction ability of selected lncRNAs. Finally, five reliable LncRNAs were identified: *LINC01419, LOC286437, LINC01139, LINC00664* and *LINC00667*. In the test cohort, researchers found that the above LncRNAs were stable in predicting risk of OC recurrence. Multivariate Cox-PHR analysis showed that the above LncRNAs were independent risk factors for OC recurrence and could effectively predict the risk of OC recurrence. Xue *et al*. [98] detected the expression of *lncRNA CASC2* in 126 EOC tissue samples and 5 EOC cell lines (A2780, SKOV3, IGROV-1, OV90 and ES2) by qRT-PCR. The results showed that the expression of *lncRNA CASC2* in EOC tissues and cells was lower than in those of the control group. Further analysis showed that low *lncRNA CASC2* expression was an independent risk factor for low overall survival rate (HR = 0.417; 95% CI = 0.251–0.693; p = 0.001) and low progression-free survival rate (HR = 0.426; 95% CI = 0.260–0.699; p = 0.001) in EOC patients. *LncRNA CASC2* may be a biomarker of poor prognosis in EOC patients. Huang *et al*. [99] analyzed tissue samples of 109 OCpatients and 4 OC cell lines (SKOV3, OVCAR3, A2780 and IGROV1) by qRT-PCR. The results showed that the *lncRNA CCAT2* expression level was high in OC tissues and cells, and it was positively related to Federation International of Gynecology and Obstetrics (FIGO) stage, tumor grade, and distant metastasis. They also found that the overall survival rate and progression-free survival rate of patients with high *lncRNA CCAT2* expression were lower than those with low *lncRNA CCAT2* expression ($p <$ 0.001). Multivariate analysis showed that *lncRNA CCAT2* was an independent factor influencing the poor prognosis of OC patients. Qiu *et al*. [100] analyzed the expression level of *lncRNA ANRIL* in 68 serous ovarian cancer (SOC), 30 non cancer tissues and SK-OV-3, HO8910, SK-OV-3.ip1, HO8910-PM cell lines by qRT-PCR. They found that *lncRNA-ANRIL* expression increased in SOC, which may regulate the progress of SOC cells by regulating MET and MMP3. Knocking out *lncRNA ANRIL* inhibited migration and invasion of OC cells. The study also found that the overall survival (OS) of SOC patients with high expression of *lncRNA ANRIL* was shortened, and *that lncRNA ANRIL* could be used as an independent factor to predict OS of patients with SOC. Thus, *lncRNA ANRIL* could be a potential marker to predict the recurrence and prognosis of clinical OC patients. Guo *et al*. [101] constructed a functional lncRNA-mRNA regulatory network (OVLMN) related to malignant progression of OC through a multi-step method. High-throughput molecular profiles of 399 patients with ovarian serous cystadenoma in The Cancer Genome Atlas (TCGA) were used for comprehensive analysis. They found two protective *lncRNAs*: *AC104699.1.1* and *RP11-284N8.3.1*. They are differentially expressed in OC patients and could activate the immune system response, which is significantly related to patient survival and disease stage. Integrating them into the OC risk model can divide patients into different risk groups and predict their survival rate. Hong *et al*. [102] detected the expression level of *lncRNA SNHG3* in 76 human OC tissue samples and A2780, SKOV3, ES2 and OVCAR3 OC cell lines by qRT-PCR. The results showed that the expression level of *lncRNA SNHG3* was higher in OC tissues and cells than in control samples, and the expression level was positively correlated with FIGO stage and lymph node metastasis of OC patients. Univariate and multivariate Cox regression analyses showed that high expression of the *lncRNA SNHG3* could be an independent prognostic factor for the overall survival rate of OC patients (Table 2, Ref. [51,54,56–58,66,68,70,72–76,79,81,83,85,86,91,95,97–102]).

4. Discussion

With the increase in research of lncRNAs, more and more lncRNAs have been proven to be potential biomarkers and targets for the diagnosis and treatment of OC. In particular, some lncRNAs can participate in regulating the occurrence and development of OC in various ways, showing great potential in clinical diagnosis and treatment of OC. *LncRNA TUG1* is one of them. *lncRNA TUG1* is a newly discovered tumor-related lncRNA. Many studies have shown that the expression of *lncRNA TUG1* is up-regulated in OC tissues and cells, and can participate in the occurrence and development, regulate the apoptosis, autophagy, and other processes of OC through multiple pathways such as *lncRNA TUG1/miR-186-5p/ZEB1*, *lncRNA TUG1/miR-29b-3p/MDM2*, *lncRNA TUG1/miR-1299/NOTCH3*, *lncRNA TUG1/miR-582-3p/AKT/mTR*. In addition, they are closely related to the cancer grading, FIGO staging, metastasis, chemotherapy resistance, and efficacy evaluation of OC [103–107]. It is noteworthy that

recent studies have shown that *lncRNA TUG1* can also be targeted by the effective components of Traditional Chinese Medicine. For example, polydatin, the effective component of polygonum cuspidatum, can improve the sensitivity of OC cells to the chemotherapy drug Doxorubicin by reducing the expression of *TUG1* [108]. Our research team is deeply interested in the research of lncRNAs and OC, and has studied Traditional Chinese Medicine and cancer for many years. We will continue to study this, and strive to find new potential targets for the treatment of OC.

More and more lncRNAs have been confirmed to be closely related to OC. However, due to the short period of understanding of lncRNAs, research on the relationship between lncRNAs and OC still faces many problems, such as the following: (a) only a few lncRNAs have been identified for their functions and target genes; (b) lncRNA research and detection methods need to be further improved; and (c) lncRNAs and their target genes form a complex regulatory network. Therefore, it is also a complex research process to clarify which lncRNA plays a role in OC cells through which pathway. Although the research in this field faces many difficulties, it still attracts many research scholars. With the continuous expansion of medical knowledge and the progress of research methods, we believe that lncRNAs will scientifically and effectively guide the early diagnosis, therapy and efficacy prediction of OC.

Author Contributions

LZ—analyze literature and write the paper; XL, YW, BL—collect and sort out literatures; YZ and XD—revise and review the paper. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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