Review

Long Noncoding RNAs in Ovarian Cancer—Functions and Clinical Applications

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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 posttranscriptional 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-ASI in 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-ASI was significantly higher in EOC cancer tissues and cell lines than in control samples. Further mechanistic studies demonstrated that lncRNA RHPN1-ASI 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/P13K/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 DANCN expression level in OC tissues was significantly higher than that in control samples, and lncRNA DANCN overexpression could promote proliferation, migration and invasion of OC cells. Mechanistic experiments showed that DANCN overexpression resulted in significant downregulation of UPF1, and the expression level of UPF1 was negatively correlated with the expression of DANCN. LncRNA DANCN could enhance the proliferation, migration, and invasion of OC cells by down-regulating 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-441-3p/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 HOTIP 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. Uptregulation 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 HOTIAR 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 HOTIAR/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 LncRNA-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/FOST2 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.

<table>
<thead>
<tr>
<th>LncRNA</th>
<th>Experimental models</th>
<th>Expression</th>
<th>Function</th>
<th>Mechanism</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>THOR</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Promote OC cells growth, metastasis and self-renewal by activating IL-6/TAT3 signal</td>
<td>[13]</td>
</tr>
<tr>
<td>TP73-AS1</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Promote OC cells proliferation and metastasis via MMP2 and MMP9</td>
<td>[16]</td>
</tr>
<tr>
<td>LINC00858</td>
<td>Cell lines, Clinical samples</td>
<td>Up</td>
<td>Promote</td>
<td>Aggravate the development of OC through miR-134-5p/RAD18 signal</td>
<td>[17]</td>
</tr>
<tr>
<td>MALAT1</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Enhance OC Cell stemness by enhancing YAP translocaional activity; promote OC progress through miR-211/PHF19 signal</td>
<td>[18,20]</td>
</tr>
<tr>
<td>LINC00176</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Promote OC progress by increasing ceruloplasmin expression via BCL3</td>
<td>[19]</td>
</tr>
<tr>
<td>ROR</td>
<td>Cell lines, Clinical samples</td>
<td>Up</td>
<td>Promote</td>
<td>Promote EMT through the miR-145/FLNB regulatory axis in OC</td>
<td>[21]</td>
</tr>
<tr>
<td>SRA</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Promote cell migration, invasion, and progression of OC via NOTCH and EMT</td>
<td>[22]</td>
</tr>
<tr>
<td>H19</td>
<td>Cell lines</td>
<td>Up</td>
<td>Promote</td>
<td>Promote TGF-β-induced EMT by acting as a ceRNA of miR-370-3p</td>
<td>[23]</td>
</tr>
<tr>
<td>UCA1</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Regulate tumor stem cells and promote EMT</td>
<td>[24]</td>
</tr>
<tr>
<td>PTAR</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Promote EMT in SOC through miR-101-3p/ZIP1 signal</td>
<td>[25]</td>
</tr>
<tr>
<td>RHPN1-AS1</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Promote OC progress by combining miR-596 and upregulating LETM1</td>
<td>[26]</td>
</tr>
<tr>
<td>DANCER</td>
<td>Cell lines, Clinical samples</td>
<td>Up</td>
<td>Promote</td>
<td>Promote OC progress through negative regulation of UPF1 expression</td>
<td>[27]</td>
</tr>
<tr>
<td>LBX2-AS1</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Drive OC progress via the miR-455-5p and miR-491-5p</td>
<td>[28]</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>Cell lines, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Combine with miR-411-3p, promote OC progress through HIV-1a/VEGF/P38 pathway</td>
<td>[29]</td>
</tr>
<tr>
<td>PVT1</td>
<td>Cell lines, Clinical samples</td>
<td>Up</td>
<td>Promote</td>
<td>Regulate EMT process and interact with EZH2 represses miR-214 expression in OC cells.</td>
<td>[30]</td>
</tr>
<tr>
<td>HOXD-AS1</td>
<td>Cell lines, Clinical samples</td>
<td>Up</td>
<td>Promote</td>
<td>Promote EOC progress through miR-133a-3p and Wnt/β-Catenin signal pathway</td>
<td>[31]</td>
</tr>
<tr>
<td>HOTTIP</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Up</td>
<td>Promote</td>
<td>Upregulate the expression of PD-L1 and IL-6, enhance the immune escape of OC cells, and promote tumor progression</td>
<td>[32]</td>
</tr>
<tr>
<td>SNHG9</td>
<td>Cell lines, Clinical samples</td>
<td>Down</td>
<td>Inhibit</td>
<td>Inhibit OC progress by sponging microRNA-214-5p</td>
<td>[33]</td>
</tr>
<tr>
<td>NPBWR1-2</td>
<td>Cell lines</td>
<td>Down</td>
<td>Inhibit</td>
<td>Affect the expression of IGFBP7 through miRNA and play an inhibitory role in tumor</td>
<td>[34]</td>
</tr>
<tr>
<td>LEMD1-AS1</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Down</td>
<td>Inhibit</td>
<td>Suppress OC progress by sponging miR-183-5p and regulation of TP3</td>
<td>[35]</td>
</tr>
<tr>
<td>WDFY3-AS2</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Down</td>
<td>Inhibit</td>
<td>Inhibit tumor progress by sponging microRNA-18a in OC cells</td>
<td>[37]</td>
</tr>
<tr>
<td>ASAP1-IT1</td>
<td>Cell lines, Clinical samples</td>
<td>Down</td>
<td>Inhibit</td>
<td>Suppress OC progress by regulating Hippo/YAP signaling</td>
<td>[38]</td>
</tr>
<tr>
<td>EPB41L4A-AS2</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Down</td>
<td>Inhibit</td>
<td>Suppress OC progress by adsorbing microRNA-103a and upregulating the expression of RUNX1T1</td>
<td>[39]</td>
</tr>
<tr>
<td>GAS5</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Down</td>
<td>Inhibit</td>
<td>Inhibit tumor progress of EOC via GAS5-E2F4-PARP1-MAPK axis</td>
<td>[40]</td>
</tr>
<tr>
<td>HAND2-AS1</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Down</td>
<td>Inhibit</td>
<td>Upregulate expression of BCL2L11 by competitively binding with miR-340-5p, act as a tumor suppressor in OC</td>
<td>[41]</td>
</tr>
<tr>
<td>XIST</td>
<td>Cell lines, Mice</td>
<td>Down</td>
<td>Inhibit</td>
<td>Inhibit EOC progress through hsa-miR-214-3p</td>
<td>[43]</td>
</tr>
<tr>
<td>MAGI2-AS3</td>
<td>Cell lines</td>
<td>Down</td>
<td>Inhibit</td>
<td>Inhibit OC progress by sponging miR-15-5p, miR-374a-5p and miR-374b-5p</td>
<td>[44]</td>
</tr>
<tr>
<td>GAS8-AS1</td>
<td>Cell lines, Clinical samples, Mice</td>
<td>Down</td>
<td>Inhibit</td>
<td>Suppress OC progress through activating Beclin1-mediated autophagy</td>
<td>[45]</td>
</tr>
<tr>
<td>LncRNA</td>
<td>OC type</td>
<td>Expression</td>
<td>Number of patients</td>
<td>Clinical application (Diagnosis/Therapy/Prognosis)</td>
<td>Refs.</td>
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<tr>
<td>HAGLROS</td>
<td>OC</td>
<td>Up</td>
<td>41</td>
<td>Early diagnosis and prognostic evaluation for OC—Diagnostic biomarker and factor associated with survival</td>
<td>[51]</td>
</tr>
<tr>
<td>FLJ33356</td>
<td>OC</td>
<td>Down</td>
<td>32</td>
<td>Participate in OC progression target miR-30b-3p—Diagnostic biomarker and factor associated with survival</td>
<td>[54]</td>
</tr>
<tr>
<td>LOXL1-AS1</td>
<td>EOC</td>
<td>Up</td>
<td>185</td>
<td>Early diagnosis and prognostic evaluation for EOC—Diagnostic biomarker and factor associated with survival</td>
<td>[56]</td>
</tr>
<tr>
<td>LINC01554</td>
<td>EOC</td>
<td>Down</td>
<td>161</td>
<td>Diagnostic biomarker, therapeutic target and factor associated with survival</td>
<td>[57]</td>
</tr>
<tr>
<td>ROR</td>
<td>OC</td>
<td>Up</td>
<td>60</td>
<td>Early diagnosis of OC—Diagnostic biomarker</td>
<td>[58]</td>
</tr>
<tr>
<td>NEAT1</td>
<td>OC</td>
<td>Up</td>
<td>32</td>
<td>Promote the resistance of OC to PTX by regulating EMT—Therapeutic target</td>
<td>[66]</td>
</tr>
<tr>
<td>CCA1</td>
<td>EOC</td>
<td>Up</td>
<td>N/A (cell lines, mice)</td>
<td>Promote chemoresistance of OC cells to cisplatin by sponging miR-454—Therapeutic target and factor associated with survival</td>
<td>[68]</td>
</tr>
<tr>
<td>TUG1</td>
<td>OC</td>
<td>Up</td>
<td>N/A (cell lines)</td>
<td>Inhibit tumor angiogenesis in OC by regulating LRG1—Diagnostic biomarker and therapeutic target</td>
<td>[70]</td>
</tr>
<tr>
<td>CHRF</td>
<td>OC</td>
<td>Up</td>
<td>20</td>
<td>Promote the resistance of OC to cisplatin resistance—Therapeutic target</td>
<td>[72]</td>
</tr>
<tr>
<td>PCA3</td>
<td>EOC</td>
<td>Up</td>
<td>36</td>
<td>Treat OC by inhibiting PCA3 expression—Therapeutic target</td>
<td>[73]</td>
</tr>
<tr>
<td>AB073614</td>
<td>OC</td>
<td>Up</td>
<td>75</td>
<td>Inhibit OC through siRNA targeting lncRNA AB073614—Therapeutic target</td>
<td>[74]</td>
</tr>
<tr>
<td>NEAT1</td>
<td>OC</td>
<td>Up</td>
<td>32</td>
<td>Enhance paclitaxel (PTX) resistance of OC—Therapeutic target</td>
<td>[75]</td>
</tr>
<tr>
<td>ANRIL</td>
<td>EOC</td>
<td>Up</td>
<td>86 (EOC)</td>
<td>Affect the sensitivity of EOC to cisplatin—Therapeutic target; Predict poor prognosis of SOC—Factor associated with survival</td>
<td>[76,100]</td>
</tr>
<tr>
<td></td>
<td>SOC</td>
<td></td>
<td>68 (SOC)</td>
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<tr>
<td>LINC01125</td>
<td>OC</td>
<td>Down</td>
<td>21</td>
<td>Enhance the cisplatin sensitivity of OC cells by binding to miR-1972—Therapeutic target</td>
<td>[79]</td>
</tr>
<tr>
<td>FAM83H-AS1</td>
<td>OC</td>
<td>Up</td>
<td>80</td>
<td>Enhance radiosensitivity, guide clinical treatment—Therapeutic target</td>
<td>[81]</td>
</tr>
<tr>
<td>HOTAIR</td>
<td>OC</td>
<td>Up</td>
<td>N/A (cell lines)</td>
<td>Reverse cisplatin resistance of OC cells through knockdown of HOTAIR—Therapeutic target</td>
<td>[83]</td>
</tr>
<tr>
<td>UCA1</td>
<td>OC</td>
<td>Up</td>
<td>56</td>
<td>Reverse the tolerance of OC to chemotherapeutic drugs—Therapeutic target</td>
<td>[85]</td>
</tr>
<tr>
<td>CRNDE</td>
<td>OC</td>
<td>Up</td>
<td>N/A (cell lines, mice)</td>
<td>Reverse radiotherapy resistance of OC Cell Strain CAOV3/R by Targeting LncRNA CRNDE—Therapeutic target</td>
<td>[86]</td>
</tr>
<tr>
<td>CCEPR</td>
<td>OC</td>
<td>Up</td>
<td>N/A (cell lines)</td>
<td>Predict the poor prognosis of OC patients—Factor associated with survival</td>
<td>[91]</td>
</tr>
<tr>
<td>SNHG20</td>
<td>EOC</td>
<td>Up</td>
<td>60</td>
<td>Serve as an independent prognostic predictor in EOC—Factor associated with survival</td>
<td>[95]</td>
</tr>
<tr>
<td>LINC00664</td>
<td>OC</td>
<td>Up</td>
<td>N/A (Bioinformatics)</td>
<td>Independent risk factors for OC recurrence—Factor associated with survival</td>
<td>[97]</td>
</tr>
<tr>
<td>LINC00667</td>
<td>OC</td>
<td>Up</td>
<td>N/A (Bioinformatics)</td>
<td>Independent risk factors for OC recurrence—Factor associated with survival</td>
<td>[97]</td>
</tr>
<tr>
<td>LINC01139</td>
<td>OC</td>
<td>Up</td>
<td>N/A (Bioinformatics)</td>
<td>Independent risk factors for OC recurrence—Factor associated with survival</td>
<td>[97]</td>
</tr>
<tr>
<td>LINC01419</td>
<td>OC</td>
<td>Up</td>
<td>N/A (Bioinformatics)</td>
<td>Independent risk factors for OC recurrence—Factor associated with survival</td>
<td>[97]</td>
</tr>
<tr>
<td>LOC286437</td>
<td>OC</td>
<td>Up</td>
<td>N/A (Bioinformatics)</td>
<td>Independent risk factors for OC recurrence—Factor associated with survival</td>
<td>[97]</td>
</tr>
<tr>
<td>CASC2</td>
<td>EOC</td>
<td>Down</td>
<td>126</td>
<td>Inhibit progression and predicts favorable prognosis in EOC—Therapeutic target and factor associated with survival</td>
<td>[98]</td>
</tr>
<tr>
<td>CCAT2</td>
<td>OC</td>
<td>Up</td>
<td>109</td>
<td>Potential prognostic biomarker and therapeutic target for patients with OC</td>
<td>[99]</td>
</tr>
<tr>
<td>RP11-284N8.3.1</td>
<td>OC</td>
<td>Up</td>
<td>399</td>
<td>Biomarker for the prognosis of patients—Factor associated with survival</td>
<td>[101]</td>
</tr>
<tr>
<td>AC104699.1.1</td>
<td>OC</td>
<td>Up</td>
<td>399</td>
<td>Biomarker for the prognosis of patients—Factor associated with survival</td>
<td>[101]</td>
</tr>
<tr>
<td>SNHG3</td>
<td>OC</td>
<td>Up</td>
<td>76</td>
<td>Poor prognosis enhancing malignant progression of OC—Factor associated with survival</td>
<td>[102]</td>
</tr>
</tbody>
</table>

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 IncRNA 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 IncRNA CASC2 in EOC tissues and cells was lower than in those of the control group. Further analysis showed that low IncRNA 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 OC patients and 4 OC cell lines (SKOV3, OVCAR3, A2780 and IGROV1) by qRT-PCR. The results showed that the IncRNA CCAAT2 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 IncRNA CCAAT2 expression were lower than those with low IncRNA CCAAT2 expression (\( p < 0.001 \)). Multivariate analysis showed that IncRNA CCAAT2 was an independent factor influencing the poor prognosis of OC patients. Qiu et al. [100] analyzed the expression level of IncRNA ANRIL in 68 serous ovarian cancer 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 RP1I-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. [101] detected the expression level of IncRNA 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 IncRNA 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 IncRNA 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. IncRNA TUG1 is a newly discovered tumor-related lncRNA. Many studies have shown that the expression of IncRNA 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 IncRNA TUG1/miR-186-5p/ZEB1, IncRNA TUG1/miR-29b-3p/MDM2, IncRNA TUG1/miR-1299/NOTCH3, IncRNA 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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