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Review

LncRNAs in ovarian cancer

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ABSTRACT

Ovarian cancer is one of the most common gynecologic malignancies and has a poor prognosis. Recently, long noncoding RNAs (lncRNAs) have been identified as key regulators of cancer development. Studies have shown that the dysregulation of lncRNAs is frequently observed in ovarian cancer and greatly contributes to malignant phenotypical changes. In this review, we provide perspectives on the involvement of lncRNAs in the proliferation, apoptosis, cell cycle, migration, invasion, metastasis and drug resistance of ovarian cancer based on recent discoveries. Then, we discuss the role of lncRNAs in predicting the prognosis of ovarian cancer. Finally, we provide insight into the potential of lncRNAs for evaluating the diagnosis and prognosis of ovarian cancer.

1. Introduction

Ovarian cancer (OC) is one of the most lethal gynecologic cancers and the most common cause of cancer-related deaths in regard to gynecologic cancers around the world [1]. Despite the optimization of current treatment modalities over the past decade, the 5-year overall survival (OS) rate for this patient population remains at a dismal 30% [2]. The low OS rate might be due to the lack of sophisticated approaches for early diagnosis. Furthermore, the occurrence and development of ovarian cancer is a multistage process, including proliferation, apoptosis, angiogenesis, migration, invasion and metastasis. Therefore, an increased understanding of the molecular mechanisms implicated in ovarian carcinogenesis may result in improved techniques for diagnosis, therapy and prevention.

Long noncoding RNAs (lncRNAs) are a family of nonprotein-coding RNAs with lengths longer than 200 nt [3]. Previously regarded as transcriptional noise, lncRNAs have now been considered to play an important role in multiple physiological and pathological processes, including proliferation, apoptosis, cell cycle, migration, invasion, metastasis and drug resistance in various diseases, especially in cancers [4–7]. More importantly, dysregulated lncRNAs have been recognized to acting as tumor suppressors or oncogenes by binding to their target genes in various cancers, such as bladder cancer [8], colorectal cancer [9], renal cell carcinoma [10], prostate cancer [11], glioma [12], multiple myeloma [13] and ovarian cancer [14,15]. Hence, functional lncRNAs might be used as an emerging alternative target for diagnosing ovarian cancer and determining prognosis.

In this review, we will focus on the action of lncRNAs in the processes of OC cell proliferation, apoptosis, cell cycle, migration, invasion, metastasis and drug resistance and predict the potential roles of lncRNAs in the diagnosis and molecular targeted therapy of ovarian cancer.

1.1. The mode of action of LncRNAs

In recent years, multiple mechanisms have been observed by which lncRNAs exhibit their gene-regulating properties at both the transcriptional and posttranscriptional levels [16]. LncRNAs contain several significant domains, such as RNA-binding domains, DNA-binding domains and protein-binding domains, that allow them to carry out their biological functions [17]. For example, lncRNAs do not only act as a scaffold to recruit transcriptional factors to modulate gene expression but also directly bind to DNA or RNA to affect transcriptional initiation or RNA stability. Moreover, lncRNAs can adjust the posttranslational modification of proteins [18]. Recently, various lncRNAs have been demonstrated to be dysregulated in OC and to play critical roles in tumor development, including proliferation, apoptosis, cell cycle, migration, invasion, metastases and drug resistance through various molecular mechanisms. An increasing number of studies have focused on the regulatory roles of lncRNAs in OC, as listed in Table 1. The underlying mechanisms are addressed as follows.

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1.2. LncRNAs in cell proliferation

Accumulating studies have shown that lncRNAs are positively or negatively correlated with proliferation to a great extent. For example, lncRNA NR_026689 was overexpressed in human ovarian cancer, and the knockdown of NR_026689 suppressed OC cell proliferation by more than 20% [19]. The overexpression of lncRNA lncBRM promoted OC cell proliferation partly by increasing the expression of Sry-related high-mobility-group box 4 (Sox4), which is a member of the Sox family of transcription factors [20]. In addition, Wang, X., et al. [21] found that lncRNA TP73-AS1 was upregulated in both OC tissues and cells. LncRNA TP73-AS1 promoted OC cell proliferation mainly by modulating matrix metalloproteinase 2 (MMP2) and MMP9. Shu, C., et al. [22], Zhang, Y., et al. [23] and Xu, Q. F., et al. [24] also considered that lncRNAs, such as lncARSR, HOXD cluster antisense RNA 1 (HOXD-AS1) and EBIC, enhanced OC cell proliferation by activating the Wnt/beta-catenin signaling pathway. It was also discovered that the inhibition of lncRNA MALAT1 significantly suppressed the proliferation of OC cells [25–29]. The regulation of the MAPK pathways might account for the promoting role of MALAT1 in the proliferation of OC cells [27]. Furthermore, MALAT1 was shown to affect OC cell proliferation by sponging miR-211 and potentially upregulating PHF19 expression [30]. MALAT1 also specifically promoted OC cell proliferation through miR-506-dependent iASPP regulation [31]. In addition, upregulated MALAT1 in OC cells motivated proliferation, increased MMP13, and decreased MMP19 and ADAMTS1 [29].

Recently, it was discovered that the inhibition of LINC00152 suppressed the proliferation of OC cells [32]. Moreover, the downregulation of lncRNA MNX1-AS1 reduced OC cell proliferation by altering the expression of CDK4, cyclin D, Bax and Bcl-2 [33]. Both Li, X., et al. [34] and Han, L., et al. [35] suggested that lncRNA TP73AS1 and SRY-box 2 overlapping transcript (SOX2OT) functioned as oncogenic lncRNAs that enhanced OC cell proliferation. Finally, Huang, Y., et al. [7] found that the overexpression of lncRNA snaR enhanced OC cell proliferation partly by upregulating GRB2-associated binding protein 2 (GAB2) expression. LncRNA ElncRNA1 accelerated OC cell proliferation, which was partially mediated by CDK4, CDK6 and cyclin D1 [36]. Both Kuang, D., et al. [37] and Li, T. H., et al. [38] discovered that taurine-upregulated gene 1 (TUG1) played an important role in promoting the proliferation of OC cells. Furthermore, lncRNA RP11-552 M11.4 was correlated with enhanced proliferation and repressed breast cancer 2 (BRCA2) [39]. The overexpression of ANRIL was able to upregulate Bcl-2 and downregulate P15INK4B, thus inducing OC cell proliferation [40]. The proliferation of OC cells could also be induced by lncRNA CTD-2020 K17.1, and caspase recruitment domain-containing protein 11 (CARD11) was modulated by CTD-2020 K17.1 [41].Zhang, Q., et al. [42] and Yim, G. W., et al. [43] found that DUXAP10 and HOXA11 antisense (HOXA11as) were positively correlated with the proliferation ability of OC cells. LncRNA RAD51 antisense RNA 1 (RAD51-AS1, also known as TODRA) reinforced OC cell proliferation, which was regulated by E2F1 [44]. LncRNA MIR4697HG knockdown significantly decreased OC cell proliferation, which was partly related to the ERK and AKT signaling pathways [45]. It was found that long stress-induced noncoding transcript 5 (LSINCT5) was an oncogene that induced OC cell proliferation by increasing the expression of chemokine receptor 4 (CXCR4) [46]. LncRNA highly upregulated in liver cancer (HULC) exerted its promoting role in OC cell proliferation by reducing ATG7 and inducing ITGB1 [47]. The OC cell proliferation ability was significantly increased by SNHG16 by upregulating the phosphorylation of AKT (P-AKT) and MMP9 [48]. It was also discovered that the upregulated SNHG1 functioned to advance OC cell proliferation [49]. Cui, L., et al. [50] first discovered that the expression of HOTAIR was higher in OC, and this phenomenon might explain the role of HOTAIR in OC. Later, HOTAIR was shown to contribute to OC cell proliferation via the regulation of cell cycle arrest and apoptosis [51]. In addition, AFAP1-AS1, SPRY4-IT1, and H19 were demonstrated to expedite OC cell proliferation [52–54]. Overexpression of ABHD11-AS1 promoted OC cell proliferation, mainly by upregulating the target gene Ras homolog gene family member C (RhoC) and its downstream molecules P70 ribosomal S6 kinase (P70S6K), MMP2 and BCL-xL [55]. Prostate cancer gene expression marker 1 (PCGEM1) plays an important role in inducing OC cell proliferation by upregulating RhoA and the subsequent expression of Yes-associated protein (YAP), P70S6K, MMP2 and Bcl-xL [56]. LncRNA AB073614 exerted its function of advancing OC cell proliferation by targeting ERK1/2 and the AKT-mediated signaling pathway [57].

Additionally, lncRNAs played a role in OC cell proliferation not only by communicating with target genes but also with miRNAs.

For example, lncRNA colon cancer-associated transcript 1 (CCAT1) could enhance the proliferation of OC cells by sponging miR-1290, a tumor suppressor [58]. In addition, the knockdown of Lnc-OC1 inhibited OC cell proliferation, which was at least partially dependent on sponging miR-34a and miR-34c [59]. Downregulated plasmacytoma variant translocation 1 (PVT1) greatly limited OC cell proliferation, coupled with negatively regulated miR-133a [60]. Similar to the sequestration of miR-373 by HOTAIR, it was found that the inhibition of HOTAIR impeded the expression of Rab22a, which resulted in hindered OC cell proliferation [61]. Furthermore, lncRNA ZFAS1 accelerated OC cell proliferation by targeting miR-150-5p and modulating the transcription factor Sp1 [62]. LncRNA PCA3 significantly enhanced OC cell proliferation by disrupting the expression of miR-106b, thus increasing the protein expression of RhoC, Bcl/xl, P70S6K, and MMP2 [63]. NEAT1, cooperating with miR-124-3p, significantly promoted OC cell proliferation [64]. Downregulation of lncRNA testis development-related gene 1 (TDRG1) suppressed OC cell proliferation by reducing the expression of RhoC, P70S6K, Bcl-xL, and MMP2, which were modulated by miR-93 [65]. The overexpression of lncRNA EWSAT1 accelerated proliferation in OC cells by directly targeting miR-330-5p and promoting Pdia3 expression [66]. LncRNA human ovarian cancer-specific transcript 2 (HOST2) was found by Gao, Y., et al. [67] to quicken the proliferation of OC cells, partly by inhibiting miR-let-7b, a potent tumor suppressor. LncRNA CCAT2 served as a promoter in OC cell proliferation by negatively targeting miR-424 [68].

In contrast, some lncRNAs were downregulated in OC and played inhibitory roles in OC cell proliferation. The expression of lncRNA RP11-190D6.2 was reduced in OC and was positively correlated with its sense partner WW domain-containing oxidoreductase (WWOX) [14]. Consequently, the overexpression of RP11-190D6.2 markedly suppressed OC cell proliferation. The upregulation of LncRNA growth arrest-specific 5 (GAS5) was shown to limit OC cell proliferation partly by regulating cyclin D1, p21 and apoptosis protease activating factor 1 (APAF1) [69]. SPRY4 intronic transcript 1 (SPRY4-IT1) also reduced OC cell proliferation [70]. Moreover, lncRNA growth arrest-specific transcript 5 (GAS5) overexpression greatly restricted the proliferation of OC cells via the inhibition of miR-21 and subsequently increased sprouty homolog 2 (SPRY2) expression [71]. NBAT-1 might exert its inhibitory effect in OC cell proliferation by suppressing the ERK1/2 and AKT signaling pathways [72]. LncRNA maternally expressed gene 3 (Meg3) suppressed OC cell proliferation by regulating ATG3 activity and inducing autophagy [73]. The detailed signaling pathways of lncRNAs and their target genes and miRNAs are shown in Fig. 1.

1.3. LncRNAs in cell apoptosis

LncRNAs also play a regulatory role in OC cell apoptosis. For example, the knockdown of NR_026689 affected cell apoptosis and the activities related to caspase-3 and caspase-9 in the intrinsic apoptotic signaling pathway [19]. Chen, P., et al. [32] considered that the LINC00152/miR-125b/MCL-1 axis played a significant role in regulating the mitochondrial apoptosis pathway in OC cells. Additionally, lncRNA MNX1-AS1 suppressed apoptosis partly by modulating the expression of CDK4, cyclin D, Bax, and Bcl-2 [33]. Both lncRNA TP73AS1

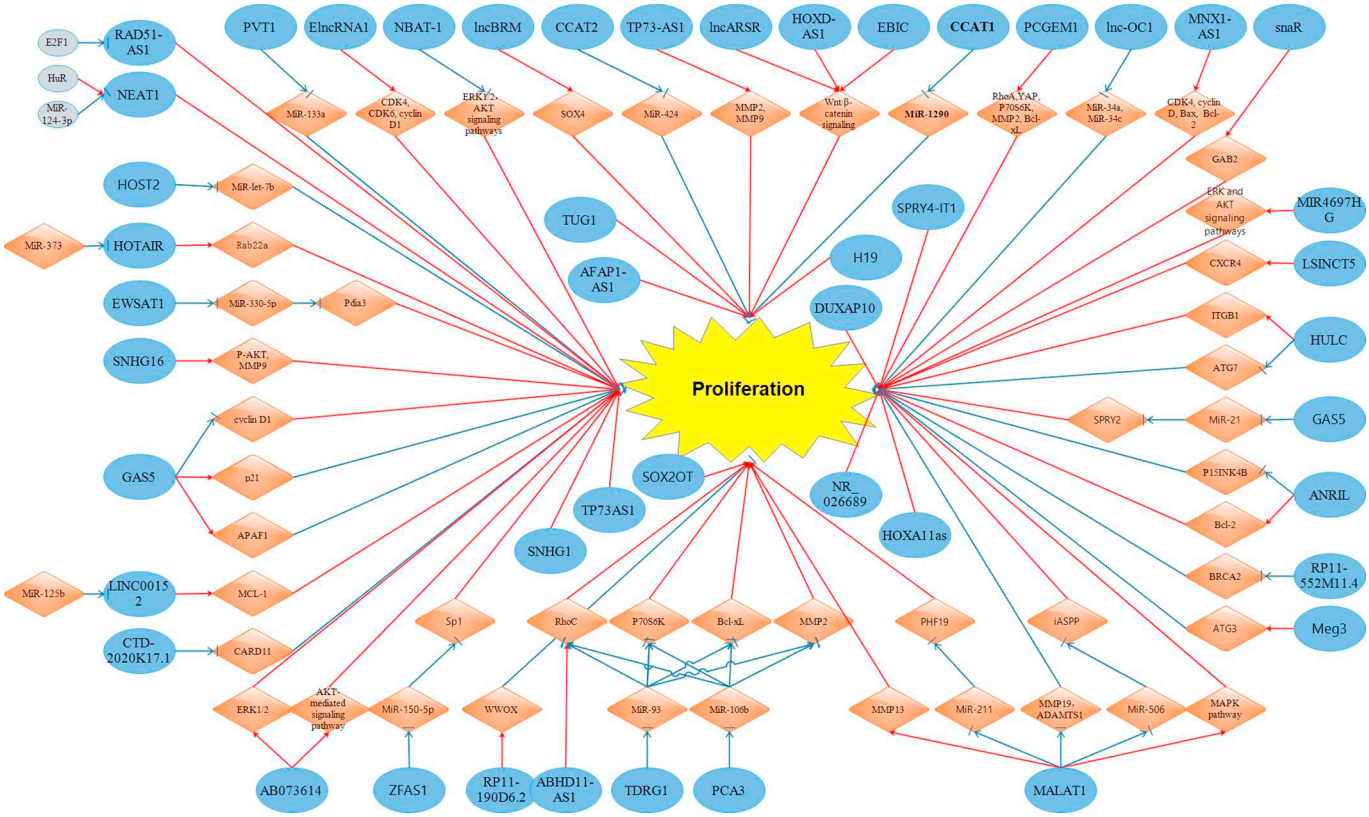

Fig. 1. LncRNAs targeted genes such as CDK4/6, cyclin D1, ERK1/2, SOX4, MMP2/9/13/19, RhoA, YAP, P70S6K, Bcl-xL, Bcl-2, Bax, GAB-2, ERK, CXCR4, ITGB1, ATG3/7, P15INK4B, ADAMTS1, RhoC, WWOX, CARD11, MCL-1, APAF1, P21 and Rab22a to regulate OC cell proliferation. LncRNAs also targeted miRNAs such as miR-133a, miR-424, miR-1290, miR-34a/c, miR-21, miR-506, miR-211, miR-106b, miR-93, miR-150-5p, miR-330-5p and miR-let-7b to regulate OC cell proliferation.

and RP11-552 M11.4 were shown to be oncogenic lncRNAs that reduced OC cell apoptosis [34,39]. Furthermore, the knockdown of lncRNA MALAT1 and TUG1 significantly promoted OC cell apoptosis [26,28,38,74]. It was also shown by Zhang, X., et al. [44] and Yang, S. L., et al. [52] that the suppression of lncRNA RAD51-AS1 and AFAP1-AS1 expedited apoptosis in OC cells. HULC overexpression hindered OC cell apoptosis by regulating ATG7 and ITGB1 expression [47]. The knockdown of HOTAIR contributed to the induction of apoptosis by certain apoptosis-related proteins [51]. LncRNA ANRIL decreased P15INK4B and promoted Bcl-2 expression, thus preventing apoptosis [40]. LncRNA ABHD11-AS1 played an inhibitory role in the apoptosis of OC cells by regulating its target gene RhoC [55]. Downregulated MALAT1 served as a motivator of OC cell apoptosis partly by regulating MMP13, MMP19, and ADAMTS1 [29]. MALAT1 could also markedly influence OC cell apoptosis through the MALAT1/miR-211/PHF19 axis [30]. Silencing lncRNA SNHG1 promoted the apoptosis of OC cells, with the expression of pro-apoptotic proteins significantly upregulated [49]. The overexpression of H19 contributed to the inhibition of OC cell apoptosis through the action of certain apoptosis-related proteins [54]. Upregulated PCGEM1 decreased cell apoptosis by upregulating RhoA, YAP, MMP2, Bcl-xL, and P70S6K [56]. Silencing AB073614 resulted in a dramatic increase in apoptosis, partly by targeting ERK1/2 and the AKT-mediated signaling pathway [57]. CCAT2 knockdown accelerated OC cell apoptosis partly by targeting miR-424 [68].

On the other hand, some lncRNAs were adept at promoting apoptosis. LncRNAs GAS5 and SPRY4-IT1 were found to facilitate apoptosis in OC cells [70,75]. LncRNA ENST00000457645 notably increased the expression of Bax and cleaved caspase-3 in cisplatin-resistant OC cells [76]. Xiu, Y. L., et al. [73] considered that lncRNA Meg3 notably quickened OC cells apoptosis by modulating ATG3 activity. The overexpression of lncRNA As-SLC7A11 conspicuously increased OC cell apoptosis and suppressed the expression of SLC7A11 [77]. Finally, based on the lncRNAs mentioned above, the related signaling pathways can be seen in Fig. 2.

1.4. LncRNAs in the cell cycle

The downregulation of lncRNA MNX1-AS1 acted to promote cell cycle arrest at the G0/G1 phase by regulating the expression of CDK4, cyclin D, Bax, and Bcl-2 [33]. The knockdown of SOX2OT acted to arrest the cell cycle in the G0/G1 phase by reducing the expression of key cell cycle regulators, cyclin B1 and cell division cycle 25C [35]. ANRIL decreased P15INK4B and promoted Bcl-2 expression, thus contributing to cell cycle progression [40]. LncRNA SPRY4-IT1 overexpression also dramatically arrested the cell cycle [70]. The inhibition of HOTAIR gave rise to the induction of cell cycle arrest through the action of certain cell cycle-related proteins [51]. Upregulated Meg3 induced cell cycle arrest in the G2 phase in OC cells [73]. Silencing lncRNA SPRY4-IT1 arrested the cell cycle at the G0/G1 stage in OC cells [53]. The knockdown of H19 resulted in the induction of cell cycle arrest, partly by regulating certain cell cycle-related proteins [54]. The knockdown of AB073614 significantly arrested OC cells in the G1 phase of the cell cycle [57]. The knockdown of CCAT2 promoted OC cell cycle arrest at the G0/G1 phase mainly by targeting miR-424 [68]. The knockdown of MALAT1 expression in OC cells resulted in G0/G1 cell cycle arrest [29]. According to the lncRNAs mentioned above, more detailed signaling pathways are shown in Fig. 3.

1.5. LncRNAs in drug-resistance

Surgery combined with platinum/paclitaxel is the main therapy for patients with advanced stage OC [78]. Unfortunately, most patients

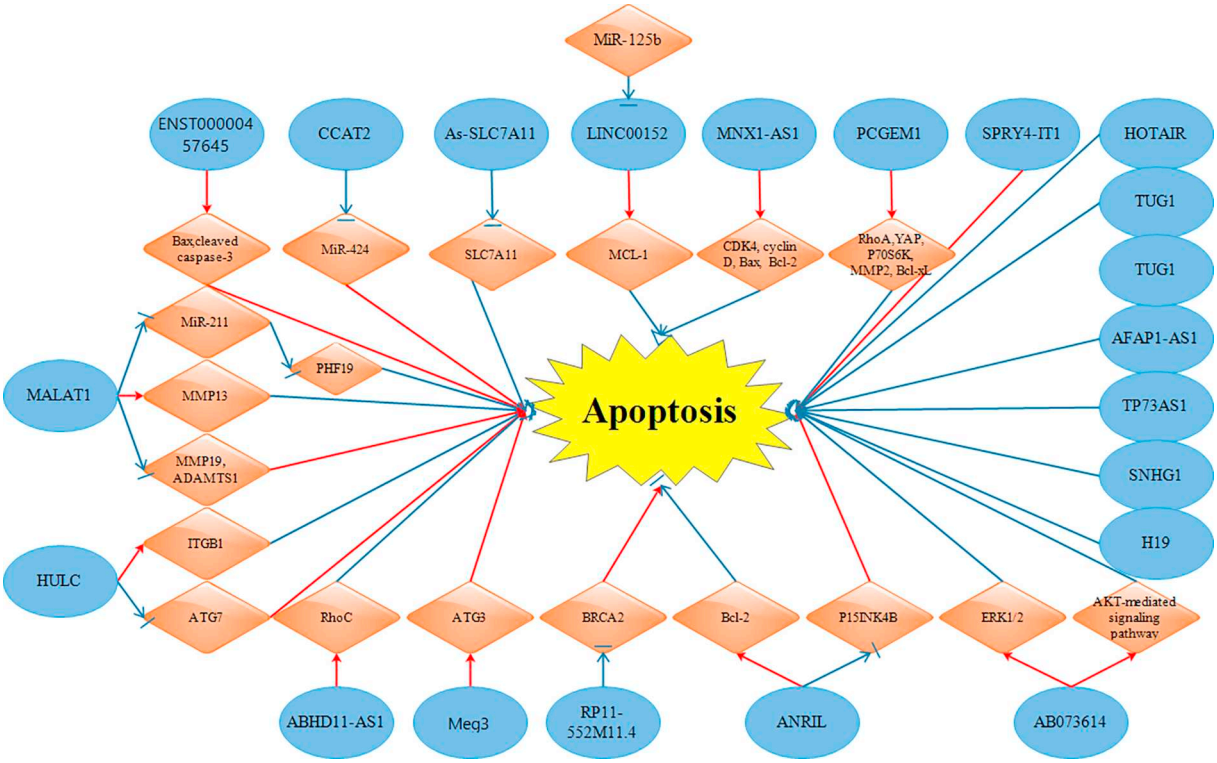

Fig. 2. LncRNAs targeted genes such as Bax, cleaved caspase-3, SLC7A11, MCL-1, CDK4, cyclin D, BCL-2, RhoA, RhoC, YAP, P70S6K, MMP2/13/19, BCL-xL, ERK1/2, P15INK4B, BRCA2, ATG3/7, ITGB1 and ADAMTS1 to regulate OC cell apoptosis. LncRNAs also target miRNAs, such as miR-424 and miR-211, to regulate OC cell apoptosis.

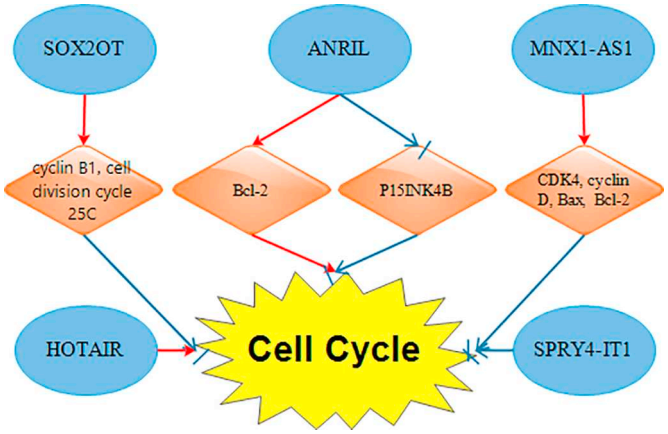

Fig. 3. LncRNAs targeted genes, including cyclin B1, cell division cycle 25c, Bcl-2, P15INK4B, CDK4, cyclin D and Bax, to regulate the OC cell cycle.

developed chemoresistance after chemotherapy, and the 5-year survival rate is only 30% [79]. Recently, an increasing number of lncRNAs related to chemotherapy resistance have been discovered, such as lncRNA Linc00623, lncRNA-UCA1, and LncRNA PVT1 [80,81].

LncRNA EBIC functioned to promote OC cell cisplatin resistance by activating the Wnt/beta-catenin signaling pathway [24]. Li, J., et al. [82] also considered that HOX antisense intergenic RNA (HOTAIR) was positively correlated with chemoresistance and increased chemoresistance by activating the same pathway in OC cells. The overexpression of LncRNA PVT1 reinforced cisplatin resistance in OC cells by regulating typical genes in apoptotic pathways, such as TGF-beta1, p-Smad4 and caspase-3 [83]. The knockdown of lncRNA NEAT1 strengthened OC cell sensitivity to paclitaxel through PTX-induced apoptosis, mediated by the miR-194/ZEB1 axis [84]. Silencing lncRNA HOTAIR negatively influenced the activity of drug-resistant OC cells and suppressed the expression of HOXA7 [85]. Wang, F., et al. [86] explained the promoting role of lncRNA UCA1 in inducing cisplatin resistance with the involvement of SRPK1. The overexpression of ZFAS1 strengthened chemoresistance in OC cells partly by modulating miR-150-5p and SP1 [62].

In contrast, lncRNA Linc00312 could considerably enhance the sensitivity of cisplatin-resistant cells to cisplatin by activating the Bcl-2/caspase-3 signaling pathway [87]. The signaling pathways involved in the drug resistance of OC are shown in Fig. 4.

1.6. LncRNAs in migration, invasion, metastasis and EMT of OC

Tumor metastasis is the primary challenge for the treatment of various types of cancers. Distant metastasis within the abdomen is often observed at the time of diagnosis in most patients with ovarian carcinoma [88]. Next, we summarized the existing research on the role of lncRNAs in the migration, invasion, metastasis and EMT of OC. For instance, lncRNA NR_026689 depletion inhibited OC cell migration and invasion [19]. The migration and invasion of OC cells could also be enhanced by the overexpression of TP73-AS1 by positively targeting MMP2 and MMP9 [21]. In addition, the upregulated lncRNA EBIC increased migration and invasion through the Wnt/beta-catenin signaling pathway in OC [24]. Lai, X. J. and H. F. Cheng [58] also demonstrated that the downregulation of lncRNA CCAT1 suppressed OC cell migration and invasion.

Chen, Q. et al., [89] first discovered that MALAT1 was closely associated with distant metastasis in patients with OC. Additionally, the suppression of MALAT1 inhibited tumorigenicity in OC cells [74]. Later, it was demonstrated that downregulated MALAT1 suppressed OC cell migration and invasion and modulated the MAPK pathway through various mechanisms, such as inhibiting phosphorylation of MEK1, ERK1, p38 and JNK1 [27]. Wu, L., et al. [26] discovered that exogenous knockdown of MALAT1 considerably restricted the migration of OC cells. In detail, MALAT1 was positively associated with the migration of

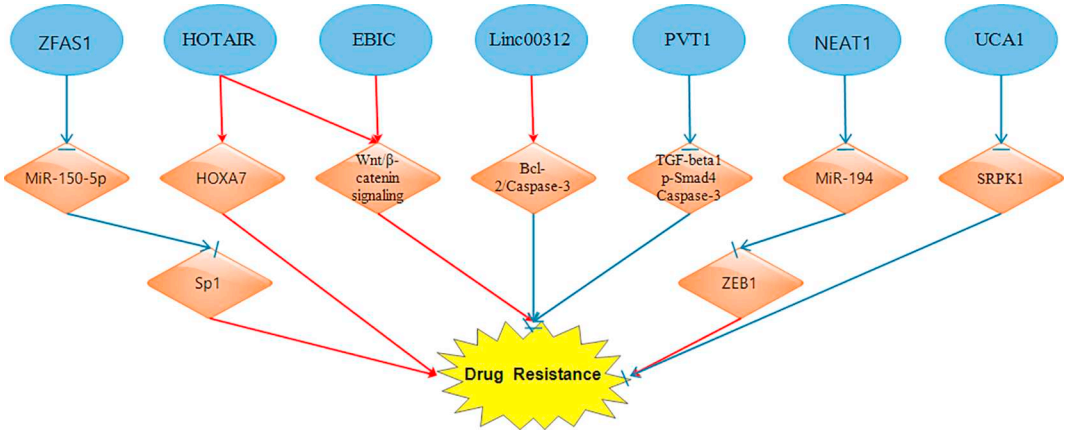

Fig. 4. LncRNAs targeted genes such as HOXA7, Bcl-2, TGF-beta 1, p-Smad4, caspase-3 and SRPK1 to regulate OC cell drug resistance. LncRNAs also targeted miRNAs such as miR-150-5p and miR-194 to regulate OC cell drug resistance.

OC cells, which was partly accompanied by increased MMP13 and decreased MMP19 and ADAMTS1 [29]. Additionally, silencing MALAT1 impeded epithelial-mesenchymal transition (EMT) and metastasis of OC cells by downregulating the PI3K/AKT pathway [25]. Guo, C., et al. [28] suggested the MALAT1 exerted its suppressive function in OC cell migration mainly though the Wnt/beta-catenin signaling pathway. Pa, M., et al. [90] proved that MALAT1 might serve as an oncogene that is positively associated with the migration and invasion abilities of OC cells and that MALAT1 carries out its biological function by regulating miR-200c expression. Furthermore, there was also an important synergy involved in which other factors, such as rosmarinic acid and ubiquitin E3 ligase MARCH7, functioned along with MALAT1 to modulate the metastases of OC cells [91,92]. In addition, the MALAT1/miR-211/PHF19 axis played an important role in influencing the migration of OC cells [30].

The suppression of lncRNA MNX1-AS1 decreased OC cell migration by targeting CDK4, cyclin D, Bax, and Bcl-2 [33]. The inhibition of SOX2OT restricted OC cell migration and invasion by downregulating the expression of mesenchymal protein N-cadherin and upregulating the expression of epithelial protein E-cadherin [35]. The knockdown of TUG1 greatly inhibited invasion by reversing EMT in OC cells [37]. In addition, lncRNA RP11-552 M11.4 promoted OC cell migration and invasion partly by reducing BRCA2 [39]. LncRNA CTD-2020 K17.1 overexpression induced migration and invasion of OC cells through the regulation of CARD11 [41]. Furthermore, HOXA11as overexpression exerted a stimulative effect on the invasion, migration and EMT of OC cells accompanied by the modulation of vascular endothelial growth factor (VEGF), matrix metalloproteinase 9 (MMP-9), B-catenin, E-cadherin, Snail, Twist, and vimentin [43]. The knockdown of MIR4697HG suppressed OC cell migration and invasion capacities and resulted in a decrease in MMP9, phosphorylated ERK, and phosphorylated AKT [45]. Silencing LSINCT5 significantly reduced OC cell migration and invasion by regulating the CXCL12/CXCR4 signaling axis [46]. LncRNA HULC overexpression induced OC cell migration and invasion and was closely related to downregulated ATG7 and upregulated ITGB1 [47]. LncRNA LINK-A promoted the migration and invasion capacity of OC cells, which resulted from the activation of the TGF-beta pathway [88]. ANRIL silencing impaired OC cell migration and invasion, at least in part, by downregulating MET and MMP3 [93]. The low expression of lncRNA HOTAIR significantly increased E-cadherin and decreased Snail expression, which in turn decreased the invasion of OC cells [94]. Yang, X. S., et al. [48] also found that SNHG16 activated p-AKT and MMP9 to enhance OC cell invasion and migration. Inhibiting SNHG1 suppressed the invasion and metastasis of OC cells, which was associated with the inhibition of the EMT process and MMPs [49]. The migration and invasion of OC cells could also be markedly enhanced by lncRNA PCGEM1 by upregulating RhoA, YAP, MMP2, Bcl-xL, and P70S6K expression [56]. LncRNA AB073614 significantly induced OC cell invasion by modulating ERK1/2 and the AKT-mediated signaling pathway [57]. Mechanistic studies revealed that LINC00092 quickened metastasis by increasing glycolysis and sustaining the local supportive function of CAFs [95]. The upregulated ABHD11-AS1 in OC cells expedited migration and invasion by facilitating the expression of RhoC and its downstream molecules P70s6k, MMP2 and BCL-xL [55]. Silencing As-SLC7A11, which was negatively correlated with the expression of SLC7A11, motivated OC cell migration [77].

Similarly, lncRNAs also exerted their functions in the migration, invasion and metastasis of OC not only by targeting genes but also by sponging miRNAs. For example, lncRNA lncBRM facilitated the migration and invasion of OC cells by modulating Sox4 expression and competitively interacting with miR-204 [20]. LncRNA lncARSR induced EMT and invasion of OC cells by modulating ZEB1 and ZEB2 and competitively binding miR-200 s [22]. The invasion and EMT process of OC cells could also be enhanced by lncRNA HOXD-AS1 by targeting miR-133a-3p and activating the Wnt/beta-catenin signaling pathway [23]. LncRNA lnc-OC1 accelerated OC cell invasion and migration partly by sponging miR-34a and miR-34c [59]. LncRNA PVT1 was regarded as an oncogene in promoting the migration and invasion capabilities of OC cells, which was partly dependent on downregulated miR-133a [60]. Furthermore, HOTAIR, targeted by miR-373, expedited the migration and invasion of OC cells, partly by regulating the expression of Rab22a [61]. The metastasis of OC was distinctly increased by lncRNA NEAT1 by modulating the miR-382-3p/Rho associated coiled-coil containing protein kinase 1 (ROCK1) axial [96]. Chai, Y., et al. [64] also found that the ectopic expression of NEAT1, stabilized by HuR and inhibited by miR-124-3p, could markedly enhance OC cell invasion. LncRNA TDRG1 served as an oncogene in promoting OC cell migration and invasion by modulating the expression of RhoC, P70S6K, Bcl-xL, and MMP2 proteins, which were regulated by miR-93. LncRNA EWSAT1 suppressed miR-330-5p expression and promoted Pdia3 expression, thus increasing OC cell invasion [66]. Xia, B., et al. [62] discovered the significant role of the ZFAS1/miR-150-5p/Sp1 axis in advancing OC cell migration activity. The overexpression of lncRNA PTAF upregulated SNAI2 by competitively targeting miR-25, thus promoting EMT and invasion of OC cells [98]. LncRNA CCAT1 acted as an oncogene in the EMT and metastasis of OC cells mainly by modulating the CCAT1-miR-152/miR-130b-ADAM17/WNT1/STAT3/ZEB1 regulatory network [99]. Liu, Y., et al. [63] proclaimed that downregulated lncRNA PCA3 obviously slowed OC cell migration and invasion by upregulating miR-106b and decreasing RhoC, Bcl/xl, P70S6K, and MMP2. The migration and invasion of OC cells could also be stimulated by HOST2 by sponging miR-let-7b, which posttranscriptionally suppressed the expression of some oncogenes [67].

In contrast, a set of lncRNAs were identified as suppressors in the

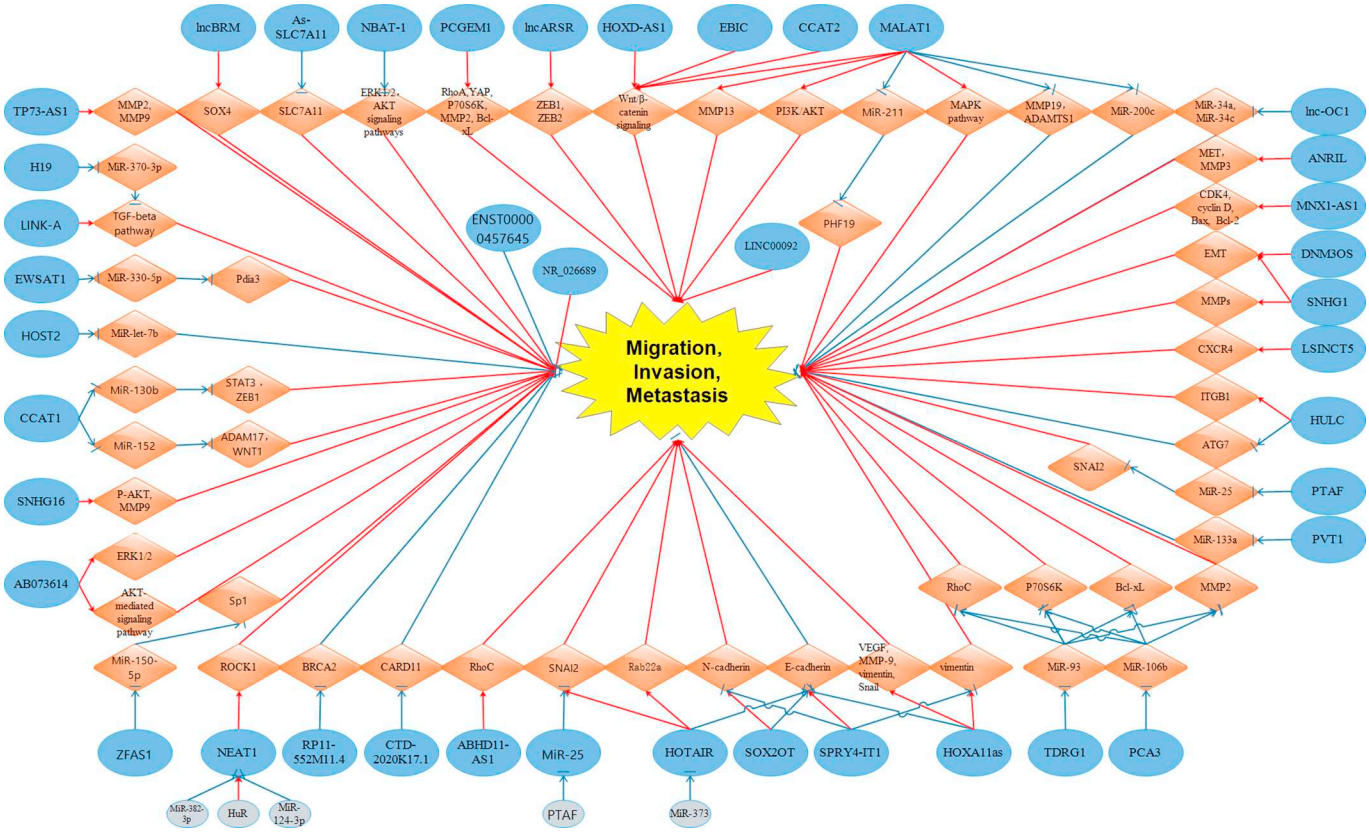

Fig. 5. LncRNAs targeted genes including MMP2/3/9/13/19, SOX4, SLC7A11, ERK1/2, P-AKT, ROCK1, BRCA2, CARD11, RhoA, RhoC, YAP, P70S6K, BCL-xL, ZEB1/2, SNAI2, Rab22a, N-cadherin, E-cadherin, PI3K/AKT, ADAMTS1, MET, CDK4, ITGB1, ATG7, vimentin, VEGF and Snail to regulate OC cell migration, invasion, metastasis and EMT. LncRNAs also targeted miRNAs such as miR-211, miR-200c, miR-25, miR-133a, miR-106b, miR-93, miR-370-3p, miR-330-5p, miR-let-7b, miR-130b, miR-152 and miR-150-5p to regulate OC cell migration, invasion, metastasis and EMT.

migration, invasion and metastasis of OC. For instance, OC cell migration and invasion abilities were notably reduced by RP11-190D6.2 and GAS5 [14,69]. NBAT-1 hindered OC cell invasion and migration and suppressed the ERK1/2 and AKT signaling pathways [72]. LncRNA ENST00000457645 was verified by Yan, H., et al. [76] to be negatively associated with the migration of cisplatin-resistant OC cells.

Moreover, a group of lncRNAs plays a major role in the migration, invasion and metastasis of OC by influencing EMT. Downregulated colon cancer-associated transcript 2 (CCAT2) decreased EMT with the involvement of inhibited beta-catenin and T-cell factor/lymphoid enhancer factor, which are key transcription factors of the Wnt signaling pathway [100]. LncRNA DNM3OS knockdown was associated with altered EMT-linked genes/pathways, EMT, and suppressed OC cell migration and invasion [101]. In addition, lncRNA PTAF, a mediator of TGF-beta signaling, induced the expression of SNAI2 by targeting miR-25, predisposing OC cells to EMT and invasion [98]. OC cell migration and invasion were dramatically restricted following SPRY4-IT1 overexpression, along with increased E-cadherin and decreased N-cadherin and vimentin protein levels, which are key genes in EMT [70]. Transforming growth factor-beta (TGF-beta)-induced EMT was markedly accelerated by lncRNA H19 by notably decreasing the expression of miR-370-3p [102]. According to the complicated role of lncRNAs, we created Fig. 5 to clarify the detailed signaling pathways among lncRNAs, miRNAs and their target genes.

1.7. LncRNAs in OC diagnosis and prognosis

According to numerous studies, the aberrant expression of specific lncRNAs could predict the progression of cancers, and these lncRNAs might appear as independent biomarkers for diagnosis and prognosis. Guo, L., et al. [103] defined an integrated miRNA-lncRNA signature including two lncRNAs (LINC01234 and CCDC144NL-AS1) and two miRNAs (miR-637 and miR-129-5p), and this integrated miRNA-lncRNA signature acted to accurately classify OC patients with wild-type BRCA1/2 into groups: patients with a good outcome or patients with a poor outcome. Additionally, a few lncRNAs were downregulated in OC cell lines and were significantly associated with pathological grade, FIGO stage and lymph node metastases, such as CPS1-IT1, TUBA4B, NBAT-1, and GAS5 [69,72,104,105]. A number of upregulated lncRNAs were found to be closely related to histological grade, FIGO stages, lymph node metastasis, CAI125 expression level, progression-free survival (PFS), overall survival (OS) and poor prognosis of patients with OC, including lncBRM, lncARSR, ANRIL, CCAT1, CCAT2, SPRY4-IT1, CXCL14, HOTAIR, HOXA11as, TP73AS1, Lnc-OC1, EIBC, BANCR, NEAT1, SOX2OT, MNX1-AS1 and C17orf91 [20,22,24,34,35,43,53,58,59,93,95,99,106–111].

2. Potential clinical applications of lncRNAs

HOXD-AS1 was positively correlated with advanced FIGO stage, poor overall survival, and lymph node metastasis in OC patients [23]. Shen, L., et al. [112] identified seven lncRNAs that may help the understanding of OC oncogenesis by exploring existing OC microarray datasets in the Gene Expression Omnibus database. Yang, K., et al. [113] identified a six-lncRNA signature (RUNX1-IT1, MALAT1, H19, HOTAIRM1, LOC100190986 and AL132709.8) that was associated with OC recurrence, based on the data extracted from GSE9891 and GSE30161. From the conclusions above, we confirmed that HOTAIR was tightly related to OC cell invasion, apoptosis, proliferation and the cell cycle. HOTAIR and its surrogate DNA methylation were verified by

Table 1
LncRNAs in OC cells proliferation, apoptosis, migration, invasion, metastasis and drug-resistance.

	LncRNAs	Targets	Reference	Participateion
Upregulated	NR_026689		Zhang, X., et al.	Proliferation (+) Apoptosis(−) Migration (+) Invasion (+)
	lncBRM	Sox4	Xi, J., et al.	Proliferation (+) Migration (+) Invasion (+)
	TP73-AS1	MMP2,MMP9	Wang, X., et al.	Proliferation (+) Metastasis (+)
	lncARSR	Wnt/β-catenin ZEB1,ZEB2	Shu, C., et al.	Proliferation (+) Invasion (+)
	CCAT1	MiR-1290	Lai, X. J. and H. F. Cheng Cao, Y., et al.	Proliferation (+) Migration (+)
		CCAT1-miR-152/miR-130b-ADAM17/WNT1/STAT3/ZEB1		Metastasis (+)
	LINC00152	MCL-1	Chen, P., et al.	Proliferation (+) Apoptosis(−) Growth (+)
	HOXD-AS1	Wnt/β-catenin	Zhang, Y., et al.	Proliferation (+) Invasion (+)
	EIBC	Wnt/β-catenin	Xu, Q. F., et al.	Proliferation (+) Metastasis (+) Cisplatin-resistance (+)
	Lnc-OC1	miR-34a, miR-34c	Tao, F., et al.	Proliferation (+) Migration (+)
	MNX1-AS1	CDK4, cyclin D, Bax, Bcl-2	Lv, Y., et al.	Proliferation (+) Migration (+) Apoptosis (−)
	TP73AS1		Li, X., et al.	Proliferation (+) Apoptosis (−)
	SnaR		Huang, Y., et al.	Proliferation (+)
	MALAT1	PI3K/AKT pathway	Jin, Y., et al. Wu, L., et al. Zou, A., et al.	Proliferation (+) Migration (+) Apoptosis (−)
		Wnt/beta-catenin signaling MMP13,MMP19, ADAMTS1	Guo, C., et al.	Invasion (+) Metastasis (+)
		miR-200c	Zhou, Y., et al.	
		MALAT1/miR-211/PHF19 miR-506/iASPP	Wu, L., et al. Pa, M., et al. Chen, Q., et al. Tao, F., et al. Lei, R., et al.	
	ElncRNA1	CDK4, CDK6, cyclin D1	Qiu, J. J., et al.	Proliferation (+)
	NEAT1	miR-382-3p/ROCK1	Liu, Y., et al. Chai, Y., et al.	Metastasis (+) Proliferation (+)
		ZEB1 miR-194	An, J., et al.	Cisplatin-resistance (+)
	TUG1	EMT	Kuang, D., et al. Li, T. H., et al.	Proliferation (+) Metastasis (+) Apoptosis (−)
	RP11-552 M11.4	BRCA2	Huang, K., et al.	Proliferation (+) Migration (+) Invasion (+)
	SOX2OT	cyclin B1 cell division cycle 25C N-cadherin E-cadherin	Han, L., et al.	Proliferation (+) Migration (+) Invasion (+)
	ANRIL	Bcl-2 P15INK4B	Qiu, J. J., et al.	Proliferation (+)
	CTD-2020 K17.1	CARD11	Zhu, L., et al.	Proliferation (+) Migration (+) Invasion (+)
	DUXAP10		Zhang, Q., et al.	Proliferation (+)
	HOXA11as	VEGF, MMP-9, B-catenin, E-cadherin, Snail, Twist, vimentin	Yim, G. W., et al.	Proliferation (+) Migration (+) Invasion (+) EMT (+)
	PVT1	miR-133a TGF-beta1 p-Smad4 Caspase-3	Yang, Q., et al. Liu, E., et al.	Proliferation (+) Migration (+) Invasion (+) Cisplatin-resistance (+)
	RAD51-AS1		Zhang, X., et al.	Proliferation (+) Apoptosis (−)

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Table 1 (*continued*)

	LncRNAs	Targets	Reference	Participateion
	CCAT2	Wnt/beta-catenin pathway miR-424	Wang, B., et al. Hua, F., et al.	EMT (+) Proliferation (+) Apoptosis (−)
	DNM3OS		Mitra, R., et al.	EMT (+)
	PTAF	miR-25/ SNAI2	Liang, H., et al.	EMT (+) Invasion (+)
	MIR4697HG	MMP9 phosphorylated ERK phosphorylated AKT	Zhang, L. Q., et al.	Proliferation (+) Migration (+) Invasion (+)
	ANRIL	MET, MMP3	Qiu, J. J., et al. Qiu, J. J., et al.	Invasion (+) Metastasis (+) Proliferation (+) Apoptosis (−)
	LINK-A	TGF-beta pathway	Ma, J. and M. Xue	Migration (+) Invasion (+)
	LSINCT5	CXCL12/CXCR4	Long, X., et al.	Proliferation (+) Migration (+) Invasion (+)
	PTAF	PTAF-miR-25-SNAI2 axis	Liang, H., et al.	EMT (+) Metastasis (+)
	HULC	ATG7, ITGB1	Chen, S., et al.	Proliferation (+) Migration (+) Invasion (+) Apoptosis (−)
	HOTAIR	E-cadherin,snail miR-373- HOTAIR- Rab22a Wnt/β-catenin HOXA7	Zhou, Y. F., et al. Qiu, J. J., et al. Zhang, Z., et al. Li, J., et al. Liu, S., et al.	Invasion (+) Apoptosis (−) Proliferation (+) Cisplatin-resistance (+)
	SNHG16	P-AKT, MMP9	Yang, X. S., et al.	Proliferation (+) Migration (+) Invasion (+)
	AFAP1-AS1		Yang, S. L., et al.	Apoptosis (−) Proliferation (+)
	H19	miR-370-3p- TGF-beta	Li, J., et al.	EMT (+)
	LINC00092		Zhao, L., et al.	Metastasis (+)
	ZFAS1	ZFAS1/miR-150-5p/Sp1	Xia, B., et al.	Proliferation (+) Migration (+) Drug-resistance (+)
	ABHD11-AS1	RhoC	Wu, D. D., et al.	Apoptosis (−) Proliferation (+) Migration (+) Invasion (+)
	SNHG1	MMPs	Ge, J., et al.	Proliferation (+) Apoptosis (−) Invasion (+) Metastasis (+)
	SPRY4-IT1		Li, H., et al.	Proliferation (+)
	PCA3	miR-106b	Liu, Y., et al.	Proliferation (+) Migration (+) Invasion (+)
	H19		Zhu, Z., et al.	Proliferation (+) Apoptosis (−)
	PCGEM1	RhoA,YAP,MMP2,Bcl-xL,P70S6K	Chen, S., et al.	Proliferation (+) Apoptosis (−) Migration (+) Invasion (+)
	TDRG1	miR-93/RhoC, P70S6K, Bcl-xL, MMP2	Chen, S., et al.	Proliferation (+) Migration (+) Invasion (+)
	AB073614	ERK1/2 and AKT-mediated signaling pathway	Cheng, Z., et al.	Proliferation (+) Apoptosis (−) Invasion (+)
	EWSAT1	MiR-330-5p/ Pdia3	Fu, X., et al.	Proliferation (+) Invasion (+)
	HOST2	miR-let-7b	Gao, Y., et al.	Proliferation (+) Migration (+) Invasion (+)
	UCA1	SRPK1	Wang, F., et al.	Cisplatin-resistance (+)
Downregulated	GAS5	SPRY2	Li, J., et al. Shan, H., et al.	Proliferation (−) Migration (−) Invasion (−)
	RP11-190D6.2	WWOX	Tong, W., et al.	Proliferation (−) Migration (−) Invasion (−)

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Table 1 (*continued*)

LncRNAs	Targets	Reference	Participateion
SPRY4-IT1		Yu, J., et al.	Proliferation (−) Apoptosis (+) Migration (−) Invasion (−)
ENST00000457645		Yan, H., et al.	Migration (−) Apoptosis (+)
Meg3	ATG3	Xiu, Y. L., et al.	Proliferation (−) Apoptosis (+)
As-SLC7A11	SLC7A11	Yuan, J., et al.	Migration (−) Apoptosis (+)
Linc00312	Bcl-2/Caspase-3 signaling pathway	Zhang, C., et al.	Cisplatin-resistance (−)
NBAT-1	ERK1/2, AKT signaling pathways	Yan, C., et al.	Proliferation (−) Migration (−) Invasion (−)

(+): indicated promote; (−): indicated inhibit.

Teschendorff, A. E., et al. [114] to confer resistance to carboplatin. Wu, H., et al. [115] further concluded that rs4759314 and rs7958904, two tagSNPs SNPs of the HOTAIR gene, were significantly associated with EOC risk in a Chinese Han population.

In drug resistance, lncRNAs also have indispensable clinical applications. Wang, L., et al. [116] predicted seven lncRNAs (XR_948297, XR_947831, XR_938728, XR_938392, NR_103801, NR_073113, and NR_036503) that were positively associated with insulin secretion-related pathways and could be utilized to forecast chemoresistance in OC patients with paclitaxel-containing chemotherapy. It was also confirmed by Liu, R., et al. [117] that ZFAS1 expression was crucially related to platinum resistance, based on the data from the Gene Expression Omnibus datasets (GSE9891, GSE63885, and GSE51373). Carboplatin plus docetaxel-regulated lncRNA PVT1 might be positively associated with carboplatin-docetaxel-induced anticancer action in OC, at least in part, though the regulation of p53 and the tissue inhibitor of matrix metalloproteinases-1 (TIMP1) [118].

Moreover, patients with low lncRNA RP5-1120P11.1 expression showed a poorer prognosis than those with high RP5-1120P11.1 expression. The expression of lncRNA RP5-1120P11.1 was positively associated with prognosis in OC patients, possibly by influencing ABCC10 gene expression, which was implicated in resistance to docetaxel treatment [119].

3. Discussions and conclusions

LncRNAs are new participants in the field of cancer, and the understanding of the lncRNA-based molecular mechanisms in the occurrence and development of OC is still in its infancy. However, Zhan, L., et al. [120] explored the dysregulated lncRNAs in OC and discussed the well-characterized mechanisms underlying lncRNAs in OC. For example, they demonstrated that certain kinds of lncRNAs increased OC cell proliferation, migration, invasion and chemo-resistance and inhibited OC cell apoptosis. Worku, T., et al. [121] also summarized the genetic variants of lncRNAs, heterogeneous mechanisms of lncRNAs in OC tumorigenesis and drug resistance. However, it remains unclear whether all lncRNAs function in the same role in the development and progression of OC. In our review, we focused not only on the dysregulation of lncRNAs in OC but also on the two-sided effects of lncRNAs in proliferation, apoptosis, the cell cycle, drug resistance, migration, invasion, metastasis, EMT, diagnosis, prognosis and the potential clinical applications in OC. LncRNAs, such as CCAT1 [99], NEAT1 [64], MALAT1 [89] and SOX2OT [35], appeared to serve not only as therapeutic targets but also as biomarkers in the occurrence and development of OC.

We also explored the correlation between lncRNAs and miRNAs in the occurrence and development of OC. Increasing studies have suggested that there is an interplay between lncRNAs and miRNAs during the tumorigenic process, and lncRNAs might act as molecular sponges for miRNAs [122]. In our review, we concluded that many groups of lncRNAs and miRNAs functioned together to modulate OC cell proliferation, apoptosis, migration, metastasis and so on.

With the development of the depth of sequencing and the recognition of tumor development, lncRNAs were affirmed to be related to materials that had not been noticed previously, such as exosomes and circular RNA. For example, cancer stem-like cell (CSC) exosomes loaded with functional lncRNAs functioned to prepare the local tumor microenvironment and the distant metastatic niche [123]. The connections among lncRNAs, miRNAs, exosomes and circular RNA were interesting and urged us to explore further.

In conclusion, lncRNAs play a major role in OC cell proliferation, apoptosis, the cell cycle, migration, invasion, metastasis, drug-resistance, and so on. Increasing studies might explore the function of lncRNAs and the relationship between lncRNAs and miRNAs in OC. We suggested that typical lncRNAs, such as MALAT1 and HOTAIR, acted as potential therapeutic targets and promising biomarkers in OC.

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