Review

Long Non-Coding RNAs: the New Horizon of Gene Regulation in Ovarian Cancer

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Key Words

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Abstract

Long non-coding RNAs (lncRNAs), a class of non-coding transcripts, have recently been emerging with heterogeneous molecular actions, adding a new layer of complexity to gene-regulation networks in tumorigenesis. lncRNAs are considered important factors in several ovarian cancer histotypes, although few have been identified and characterized. Owing to their complexity and the lack of adapted molecular technology, the roles of most lncRNAs remain mysterious. Some lncRNAs have been reported to play functional roles in ovarian cancer and can be used as classifiers for personalized medicine. The intrinsic features of lncRNAs govern their various molecular mechanisms and provide a wide range of platforms to design different therapeutic strategies for treating cancer at a particular stage. Although we are only beginning to understand the functions of lncRNAs and their interactions with microRNAs (miRNAs) and proteins, the expanding literature indicates that lncRNA-miRNA interactions could be useful biomarkers and therapeutic targets for ovarian cancer. In this review, we discuss the genetic variants of lncRNAs, heterogeneous mechanisms of actions of lncRNAs in ovarian cancer tumorigenesis, and drug resistance. We also highlight the recent developments in using lncRNAs as potential prognostic and diagnostic biomarkers. Lastly, we discuss potential approaches for linking lncRNAs to future gene therapies, and highlight future directions in the field of ovarian cancer research.

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Introduction

Ovarian cancer (OC) is a gynecological malignancy that causes death in women worldwide. The epithelial ovarian cancer (EOC) subtype represents nearly 90% of all OC cases, contributing to 70% of all deaths caused by OC, because of the absence of early-

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stage diagnostic tools [1-5]. In the United States, OC is the fifth most lethal malignancy in women, with 14,000 estimated deaths and 22,000 new cases occurring in 2016 [6]. Despite continuous efforts towards better treatment and/or improvement of the overall survival (OS) rates of patients, OC remains a threat to women because of drug resistance, the distinctive features of each OC subtype, and the lack of clear symptoms at early stages. Identification of biomarkers enabling diagnosis at the initial stage of OC and developing new therapies remain fundamental goals for researchers in the field of OC.

Continuous advancements in genomics technologies have revolutionized the world of RNA biology, particularly in the field of non-coding RNAs (ncRNAs), which has provided new research directions. As such, high-throughput sequencing technology has enabled the discovery of transcribed RNA molecules that lack protein-coding potential, but function beyond that in simply bridging DNA to protein through translational processes. Of ncRNAs, long non-coding RNAs (lncRNAs, greater than 200 nucleotides) are structurally complex transcripts that are involved in multiple cellular functions [7-9].

Continuous efforts have shed insights into the biological roles of lncRNAs in various normal and pathological physiological processes, such as development, metastasis, apoptosis, stem cell pluripotency, proliferation, DNA damage, differentiation, and cancer [9-18]. Unlike microRNAs (miRNAs) and other non-coding transcripts, lncRNAs are large and complex [19], and their ability to govern genes in virtually all transitional states is an indication of their potency. Indeed, lncRNAs control gene transcription epigenetically in combination with chromatin remodeling [3, 20-22], translation [23], splicing [24, 25], and post-translational stability [26].

The functional role of lncRNAs in almost all hallmarks of cancer is increasingly recognized and has augmented our knowledge, leading to a better understanding of the biology of different cancer types such as OC [27], hepatocellular carcinoma [28-31], endometrial cancer [32], lung [33-35], gliomas [36, 37], and prostate cancer [38, 39]. A few reports have demonstrated the classic involvement of lncRNAs in different OC stages with various modes of action, providing the opportunity to intervene at specific points in OC development [22, 40, 41]. Individual OC studies have described the involvements of some lncRNAs along with their prognostic and therapeutic relevance; however, many studies have not revealed an underlying mechanism. A previous genome-wide transcriptome study uncovered a link between cancer and lncRNAs [17].

Although the roles of only a few lncRNAs in virtually all features of OC cells have been uncovered, unforeseen roles and mechanisms of action will likely be discovered in the future. Hence, in this review, we provide a comprehensive view of the current literature highlighting prominent lncRNA biomarkers, as well as the strategies and therapeutic value of targeting lncRNAs to treat OC.

lncRNA variants are associated with the risk and functionality of OC

A handful of studies have identified non-coding genetic variants, such as single-nucleotide polymorphisms (SNPs), chromosomal rearrangements, and somatic copy-number alterations (SCNAs). However, less attention has been paid to ncRNA variants owing to the dogma that they are unable to transmit information and perform functional roles [42]; however, several studies have identified multiple SNPs in lncRNAs linked to the risk of developing OC [14, 43]. Data from a recent study showed that SNPs are also capable of modulating the features of OC cells, suggesting that non-coding variants can potentially transmit cellular signals [44]. Notably, future work will define the algorithm through which ncRNAs contribute to OC cellular phenotypes.

A genome-wide association study (GWAS) identified an A>T genetic variant in the exonic region of homeobox A11 antisense (HOXA11-AS) that was associated with a reduced risk for EOC. Further characterization of the identified genetic variant revealed that EOC cells carrying the minor allele (T) showed reduced survival, migration, and invasion abilities

compared to EOC cells carrying the common allele (A) [44]. In a similar study, low HOXA11-AS expression was found in OC cells, indicating its tumor suppressor property might be attributed to the T allele [44]. Thus, genetic variants of HOXA11-AS may play functional roles beyond being a risk factor for EOC. Such data provide impetus for further exploring the regulatory mechanisms of lncRNAs involved in cancer cell phenotypic changes.

An association study of Hox transcript antisense intergenic RNA (HOTAIR) polymorphisms and OC in a Chinese population reported that the rs4759314 and rs7958904 SNPs were associated with EOC susceptibility, although the clinicopathological features need to be defined. Moreover, individuals with C alleles for rs7958904 presented a low risk of acquiring EOC [14]. In a parallel study, Xue et al [45] reported that the HOTAIR SNP rs7958904 was associated with a low risk of colorectal cancer. Another SNP of HOTAIR, rs920778 (C>T), which increases the risk of developing several cancer types such as breast and gastric cancers [46, 47], also appears to be linked to an increased risk for OC and poor prognosis [43]. These SNPs could be used as predictive tools for classifying individuals or populations susceptible to OC. Genetic variants of various lncRNAs can also predispose individuals to other pathologies other than cancer. For example, an SNP in the antisense non-coding RNA in the INK4 locus (ANRIL) lncRNA seems to be associated with increased risks for developing cardiovascular diseases, diabetes, and endometriosis. Nevertheless, the specific SNPs contributing to these diseases are awaiting further investigation [48].

SCNAs, which mainly occur in the non-coding genomic landscape [49], can contribute to carcinogenesis [50]. Pioneering analysis of segregated public databases has become a powerful tool for screening genomic regions harboring lncRNAs genes with SCNAs, which can induce cancer [51], mainly when genomic regions are deleted or amplified. One of the lncRNAs identified within SCNAs and suggested to drive cancer is focal amplified lncRNA on chromosome 1 (FAL1). This lncRNA was shown to play oncogenic roles, and its expression and copy-number alteration (CNA) are associated with OC clinical outcomes [22]. Liu et al. also identified 11 dysregulated lncRNAs, based mainly on their CNAs, which were associated with poor OS in breast cancer. Of these lncRNAs, LINC00657 lncRNA knockout was shown to suppress breast cancer cell growth and proliferation [52], indicating its oncogenic role. Collectively, these data reveal that genetic variants of lncRNAs may serve functional and predictive roles, despite some inconsistent results that urge further study in large cohorts. Hence, a deep understanding of how SNPs and CNAs regulate the expression of lncRNAs will have far-reaching implications in treating cancer and other diseases. Additionally, identification and characterization of genetic variants involved in the canonical biosynthesis of lncRNAs would provide vital information, leading to a comprehensive understanding of the roles of lncRNA variants in human cancers.

Involvement of lncRNAs in OC

Recent reports have indicated that, when dysregulated, numerous lncRNAs are involved in OC initiation, development, progression, and chemoresistance [27, 41]. Some recently identified and classic lncRNAs have been consistently reported to regulate OC tumorigenesis, either alone or in association with partner molecules, which are described herein.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), expressed from chromosome 11q13 and occupying an 8.7-kb genomic area [53], is transcriptionally controlled by the tumor-suppressor p53 gene [54] and has been shown to modulate several cancer types, including OC. Up-regulation of MALAT1 promotes the migration, proliferation, metastasis, invasion, and growth of ovarian tumor cells *in vivo* [55-57]. Microarray analysis after RNA interference (RNAi)-mediated knockdown of MALAT1 expression showed that as many as 449 [55] or 921 [56] genes were transcriptionally regulated and enriched in terms of important OC cells features. In these studies, MALAT1 downregulation abrogated the aggressive behavior of OC cells by arresting cell cycle progression at G0/G1 leading to apoptosis, *in vitro* [55] and repressed tumor growth *in vivo* [56]. MALAT1 was significantly

associated with metastasis and tumor size, and shown to regulate these phenomena through mitogen-activated protein kinase (MAPK) [57]. Although these studies primarily describe the downstream cellular effects of MALAT1 and fail to demarcate the associated mechanisms of actions, MALAT1 seems to be the major focus of therapy for patients with OC.

Of several lncRNAs implicated in OC malignancies, the mechanisms of actions of a few of them are identified and described below. Both overexpression and copy-number amplification of FAL1 are involved in OC. Mechanistic studies revealed that FAL1 is epigenetically associated with the BMI1 proto-oncogene, polycomb ring finger (BMI1), a class of polycomb repressive complexes (PRCs). FAL1 also guides BMI1 to the cyclin-dependent inhibitor 1A (p21) gene locus (a tumor-suppressor gene), thereby inhibiting its transcription. This, in turn, promotes the primary cancer cell cycle progression and facilitates malignant transformation [22] (Fig. 1A). Data from recent studies have evidenced that cancer-associated fibroblasts (CAFs), the main constituent of tumor stroma, can promote carcinogenesis and contribute to drug-resistance in several cancer types, including OC [58, 59]. Recently, Zhao and co-workers implicated long intergenic non-protein coding RNA 92 (LINC00092) in CAF-mediated ovarian tumorigenesis and demonstrated its association with glycolysis regulation in cancer. As indicated in Fig. 1B, the glycolysis-regulatory molecules, fructose-2 and 6-biphosphatase (PFKFB2), bind to the binding site of LINC00092, leading to a reciprocal regulatory loop with CAFs by controlling glycolytic products to maintain the tumor environment and subsequently cancer metastasis [40].

Reduced expression of brain cytoplasmic RNA 200 (BC200; also known as brain cytoplasmic RNA1) and growth arrest-specific 5 (GAS5) has been observed in ovarian tumor tissues and cell lines [60, 61]. Further inhibition of BC200 enhances the proliferative capacity of cancer cells *in vivo* [60], and overexpression of GAS5 offsets the aggressive behavior of OC cells both *in vitro* and *in vivo* [61]. Subsequent experiments revealed that GAS5 contributes to OC tumorigenesis through downstream effects on genes related to cell cycle progression, namely, *CDKN1A*, cyclin D1, and apoptotic protease-activating factor (*APAF1*). The oncogenic functions of these lncRNAs seem to be favored at low expression, unlike most lncRNAs. In contrast to BC200 and GAS5, overexpression of ANRIL, colon cancer associated transcript 2 (CCAT2), taurine up-regulated gene 1 (TUG1), and C17/f90 promotes cancer cell proliferation, invasion, and migration. These lncRNAs were also reported to be associated with a high tumor grade and FIGO stage, and distant metastasis [62-65]. Subsequent microarray and *in vitro* analyses identified met proto-oncogene (MET) and matrix metalloproteinase 3 (MMP3) as downstream targets of ANRIL [63]; a pro-metastatic gene, c-mycelocytomatosis (MYC) was targeted by C17/f90 [64]. TUG1 knockdown abrogated cancer cell phenotypes, reversed EMT, and initiated apoptosis, while epithelial makers and apoptosis-related proteins were dysregulated [65] *in vitro*, indicating that molecules downstream of TUG1 could represent valuable therapeutic targets. However, further study is required to discern the molecular mechanisms underlying the function of these lncRNAs in OC.

The study undertaken by Richard et al [44], indicated that HOAX11as functions as a tumor suppressor in OC cell lines and its expression was down-regulated in a cohort of 18 patients with EOC. However, this report has been challenged by Yim et al [66], who observed that HOAX11as expression was up-regulated in a cohort of 129 patients with serous OC (SOC) and it promoted cell proliferation, metastasis, and invasion *in vitro*. Conversely, small interfering RNA (siRNA)-induced HOAX11as down-regulation impaired cancer cell phenotypes *in vitro*, concomitantly regulating angiogenesis, motility, and the epithelial-mesenchymal transition (EMT) [66].

Contradictory results have been reported for sprouty 4 intronic transcript 1 (SPRY4-IT1) lncRNA, where enhanced and low expression promoted OC progression and metastasis in a cohort of 124 [67] and 15 [68] patients with OC, respectively. In further experiments, SPRY4-IT1 promoted OC tumorigenesis by affecting cell cycle progression [67], and EMT and cell cycle processes [68]. Given the complexity of cancer cells, it is not surprising that a gene can act as an oncogene or tumor-suppressor in cells with the same histotypes. This observed discrepancy is likely attributable to mutations, sample sizes, and the techniques

Fig. 1. Heterogeneity of the molecular mechanisms of action of lncRNAs in OC tumorigenesis. A. FAL1 interacts with BMI1, a component of PRC1, and promotes recruitment of the complex to the p21 promoter to suppress its transcription, leading to malignant transformation. B. lncRNA LINC00092 binds to the mRNA of PFKFB2 and promotes glycolysis, thereby providing feedback to CAFs for sustaining cancer tumor cells. FAL1, focally amplified lncRNA on chromosome 1; BMI1, BMI1 proto-oncogene, polycomb ring finger; PRC1, polycomb repressive complex 1; p21, cyclin-dependent inhibitor 1A; CAFs, cancer-associated fibroblasts; PFKFB2, fructose-2, 6-biphosphatase; LINC00092; long intergenic non-protein coding RNA 92.

used. Studies using a large cohort of patient samples are warranted to clearly characterize these lncRNAs as either oncogenes or tumor-suppressors. The regulatory roles of lncRNAs in OC, explored in various studies are presented in Table 1, while their specific functions are discussed above.

LncRNA signature as a diagnostic and prognostic biomarker of OC

LncRNAs are considered potentially novel clinical tools for patient management owing to their tissue- and/or cell-specific expression patterns. Given their cell-specific expression, lncRNAs have been described as potential biomarkers in various cancers types such as gastric [72], lung [73], prostate [74], and hepatocellular carcinoma [75]. Similarly, several lncRNAs have been identified as potential biomarkers in cells with different OC histotypes, where their expressions levels are altered. In cases where dysregulated lncRNAs are associated with OC, lncRNAs might potentially serve as biomarkers, as summarized in Table 2 and discussed in detail below.

Li et al. attempted to assess the clinical relevance of C17orf91 lncRNA in OC, using public datasets deposited in the Gene Expression Omnibus database and noticed differential expression of C17orf91 between omental metastases and primary tumors. Subsequent *in vitro* evaluation indicated that C17orf91 can be employed as prognostic biomarker for patients with OC [64]. Similarly, meta-analysis of four independent datasets derived from 954 human samples of 4 different cancer types, including OC, revealed that higher expression of human urothelial carcinoma associated 1 (UCA1) was linked to reduced survival, suggesting UCA1 as a predictive biomarker [76]. Furthermore, Hu and colleagues identified a key oncogene lncRNA, FAL1, as a prognostic biomarker of OC by employing bioinformatics at the genomic scale [22].

Overexpression and methylation of the HOTAIR gene mediate the therapeutic resistance of OC cells; thus, HOTAIR is associated with poor OS [77]. Interestingly, as DNA is unlikely to change, HOTAIR DNA-based prognostic biomarkers could be used as reliable classifiers to distinguish patients for personalized treatment. Moreover, a recent meta-analysis of data from 13 studies revealed 8 up-regulated and 5 down-regulated lncRNAs associated with poor prognosis, and of these lncRNAs, higher expression of HOTAIR was associated with shorter OS in patients with OC [78].

Survival outcomes have been evaluated in several OC patients with dysregulated expression of lncRNAs. Among these, the prognosis associated with ANRIL, CCAT2, AB073614,

Table 1. Tumorigenic lncRNAs known to modulate ovarian cancer. ANRIL, antisense non-coding RNA in the INK4 locus; APAFA, apoptotic protease-activating factor; BC200, brain cytoplasmic RNA 200; CCAT2, colon cancer-associated transcript 2; CDKN1A, cyclin-dependent inhibitor 1A; EMT, epithelial-mesenchymal transition; GAS5, growth arrest-specific 5; HOXA11as, homeobox a11 antisense; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; SPRY4-IT1, sprouty 4 intronic transcript 1; TUG1, taurine up-regulated gene

lncRNA	Category	Expression status in patients	Observed effects during in vitro and/or in vivo study in humans (H) and/or mice (M)	Associated molecules and downstream effects	Refs.
AB073614		Upregulation	Down-regulation promotes apoptosis, inhibits proliferation, and invasion in vitro, and inhibits proliferation and retards tumor growth in vivo.	Regulates the expression of EMT, apoptotic and metastatic genes, and involves the ERK1/2 and AKT pathway.	[69]
ANRIL	Antisense	Upregulation	Down-regulation arrests migration and invasion.	Regulates MMP3 and MET genes.	[63]
BC200	Intergenic	Downregulation	Down-regulation promotes proliferation in vitro.	Unknown	[60]
CCAT2	Intergenic	Upregulation	Down-regulation retards proliferation, migration, and invasion in vitro.	Unknown	[62]
C17orf91		Upregulation	Down-regulation inhibits migration, invasion, and viability in vitro.	Regulates pro-metastatic genes	[64]
GAS5	Bidirectional	Downregulation	Overexpression represses migration, invasion, and proliferation and promotes apoptosis in vitro, while reducing tumor growth in vivo.	CDKN1A, cyclin D1, and APAFA are downstream targets.	[61]
HOXA11as		Downregulation	Down-regulation attenuates migration, invasion, and proliferation in vitro.	Modulates motility and angiogenesis-related genes	[66]
MALAT1	Intergenic	Upregulation	Down-regulation inhibits tumorigenesis in vivo and in vitro.	Alters the expression of genes associated with metastasis and proliferation.	[55, 70]
NR-026689		Upregulation	Down-regulation suppresses migration and invasion, and induces apoptosis in	Regulates apoptotic proteins	[71]
		Upregulation	Down-regulation inhibits proliferation.	Down-regulation arrests the cell cycle at G0/G1 phase.	[67]
SPRY4-IT1	Intronic	Downregulation	Overexpression enhances apoptosis and cell cycle progression.	Regulates expressions of EMT-associated genes	[68]
TUG1	Intergenic	Upregulation	Knockdown promotes apoptosis, inhibits proliferation, and halts EMT in vitro.	Regulates apoptosis-related proteins and EMT factors	[65]

NEAT1, and GAS5 has been studied in patients with OC. For example, poor prognosis (shorter OS) is associated with high expression of nuclear paraspeckle assembly transcript 1 (NEAT1) [79], ANRIL [63], and AB0736614 in patients with OC [69]. Furthermore, both shorter OS and disease-free survival (DFS) were associated with up-regulated CCAT2 [62] and HOXA11as [66], whereas low expression of GAS5 was associated with shorter OS and DFS in patients with OC [61]. Another lncRNA, SPRY4-IT1, was found to be highly expressed in OC and could be used as an independent prognostic agent for OS and PFS, and a diagnostic marker for tumors in patients with OC [67].

Table 2. lncRNAs associated with OC clinical outcomes. ANRIL, antisense non-coding RNA in the INK4 locus; CCAT2, colon cancer-associated transcript 2; GAS5, growth arrest-specific 5; HOTAIR, hox transcript antisense intergenic RNA; HOXA11as, homeobox AS11 antisense; NEAT1, nuclear paraspeckle assembly transcript 1; UCA1, urothelial carcinoma associated; ↓= low expression; ↑= high expression.

lncRNA	Involved cases vs. normal (no.)	Marker type	Observed clinical information	Ref
AB073614	Case-control (75 patients with OC vs. 75 normal subjects)	Prognostic	↑AB073614 was associated with shorter OS.	[69]
ANRIL	Case-control (38 patients with SOC vs. 30 normal subjects)	Prognostic and metastasis	↑ANRIL was associated with shorter OS and positively correlated with lymph node metastasis, advanced FIGO, and high histological grade.	[63]
CCAT2	Case-control (109 patients with OC vs. 45 normal subjects)	Prognostic	↑CCAT2 was associated with shorter OS and DFS and positively correlated with tumor grade, FIGO, and distant metastasis.	[62]
C17orf91	Case-control (9 patients with OC vs. 9 normal subjects)	Prognostic	↑C17orf91 was associated with shorter PFS and OS.	[64]
GAS5	Case-control (63 patients with OC vs. 63 normal subjects)	Prognostic	↓GAS5 was associated with shorter OS and DFS and negatively correlated with tumor size, depth of invasion, and TNM stage.	[61]
HOTAIR	Case-control (68 patients with OC vs. 30 normal subjects)	Prognostic and diagnostic	↑HOTAIR was associated with poor OS and positively correlated with high histological grade, advanced FIGO, and tumor size.	[3]
HOXA11as	Case-control (129 patients with SOC vs. 38 normal subjects)	Prognostic	↑HOXA11as was associated with shorter OS and PFS.	[66]
NEAT1	Case-control (149 patients with OC vs. 149 normal subjects)	Prognostic	↑NEAT1 was associated with shorter OS and positively correlated with tumor grade, FIGO stage, and distant metastasis.	[79]
UCA1	Meta-analysis of 117 OC studies	Prognostic	↑UCA1 was associated with shorter PFS and OS.	[76]

In attempting to identify and characterize an OC biomarker for prognosis based on an lncRNA expression signature, Zhou et al. utilized publicly available data from 544 patients with OC and identified 8 lncRNAs, which were used to stratify patients into different risk statuses. Furthermore, these lncRNAs and their prediction outcomes were associated with chemotherapy responses and BRCA1/2-mutated and BRCA1/2 wild-type tumors, suggesting

that these lncRNAs are independent biomarkers and therefore instrumental for identifying patients who may respond well to chemotherapy and those for whom alternative treatments should be prescribed [80].

Similarly, Martini and colleagues identified a molecular signature of 4 lncRNAs (PVT1, lnc-SERTD2-3, lnc-SOX4-1, and lnc-HRCT1) in tumor biopsies from a cohort of 202 patients with stage-I EOC, whose expressions were associated with risk of relapse. Of these lncRNAs, based on the expressions of PVT1 and lnc-SERTD2-3 together with hsa-miR-200c-3p, a risk score was derived to cluster patients into different risk statuses based on the median cut-off value, and patients with high and low risks had OS of 36 and 123 months, respectively (OR = 15.55, 95% CI = 3.8-63.36) [81]. These lncRNAs provide an immense contribution for the early detection of EOC which has been a major hurdle associated with this disease, emphasizing the ability of the integrated use of biomarkers to improve prognosis or diagnostic performance. In support of this view, better diagnostic performance was attained when SPRY4-IT1, NEAT1, and ANRIL expressions were combined than when each was analyzed separately in non-small-cell lung cancer [82].

Owing to their clinical significance, it is essential to detect lncRNAs in bodily fluids of patient with OC and define their expression and stability, in order to employ them as biomarkers. In favor of this prospect, although no lncRNAs were reported in the bodily fluids of patient with OC, recent studies have identified elevated plasma lncRNA levels in patients with other cancer types such as non-small-cell lung cancer [83], hepatocellular carcinoma [84], thyroid cancer with lung metastases [85], esophageal squamous cell carcinoma [86], and renal cell carcinoma [87].

Targeting lncRNA and miRNA networks for therapeutic development

The post-transcriptional interaction between miRNAs and the mRNAs of target genes modulates gene expression, thereby determining the fate of cells in many normal and pathological processes, which has attracted the interest of pharmaceutical industries. In the past 15 years, numerous miRNAs have been identified in the human genome and are implicated in various cellular functions [88, 89]. The functional involvement of miRNAs in OC initiation, development, and spread has been widely demonstrated. Furthermore, their potential use as biomarkers and for therapy has also been explored [90-93]. Most miRNAs play crucial cellular roles, participating in almost all molecular signaling pathways known to regulate cancer cell initiation, progression, metastasis, and survival. Currently, the development of miRNA-based therapy appears to be very promising. However, such therapy will likely be challenged by the mode of delivery to the intended organ, tissue, and cells, as well as by potential off-target effects. Like the interactions between miRNAs and mRNAs, the interactions between lncRNAs and miRNAs have been reported in the pathogenesis of several cancers, including OC [94, 95], gastric [96], hepatocellular carcinoma [97]. Understanding of the interactions between lncRNAs and miRNAs, and their subsequent impacts on the target molecules may facilitate an immense use of lncRNAs as therapeutic targets in future therapies.

Some miRNAs originate from non-coding genomic sequences and, of these, nearly 10% are harbored in lncRNA genes [98]. Many lncRNAs interact with miRNAs either by sequestering, harboring, or blocking them (Fig. 2A3, 2A1, and 2A2), thereby regulating the transcriptional activities and expression of target genes, which in turn leads to OC development and progression [94, 99]. However, miRNA binding to lncRNAs can dysregulate their expression, thereby controlling OC cell functions [26]. The oncogenic or tumor-suppressor effects of some (but not all) lncRNAs are partially or fully dependent on miRNAs, suggesting that endogenous competing RNA is significant in OC. Given the importance of the miRNA-lncRNA axis in OC, targeting lncRNA-miRNA networks is of interest for developing effective therapeutics. The imprinted, maternally expressed transcript, H19, is among the most studied lncRNA in normal cellular physiology and in carcinogenesis. H19 is involved

Fig. 2. Schematic overview of lncRNA-miRNA biogenesis and routes of interaction. A. miRNA biogenesis from miRNA host gene. A1. An lncRNA binding miRNAs and guides them to their sites of action. A2. An lncRNA blocking the transport of miRNAs and preventing their activities. A3. An lncRNA sequestering miRNAs and isolating them, inhibiting their activity. B. LncRNA genes are transcribed and processed to lncRNAs and miRNAs. B1. miRNAs destabilize lncRNAs and regulate OC.

in multiple cancers and exerts its cellular effect by interacting with miRNAs. H19 activation promotes the migration and invasion of OC cells. Intriguingly, these events can be modulated by inhibiting let-7 to subsequently enhance expression of the target genes, *HMG2*, *C-MYC*, and *IGF2BP*, which can promote metastasis and activate downstream targets [94]. Human OC-specific transcript 2 (HOST2) is highly expressed in ovarian tumor tissue and promotes carcinoma cell line migration, invasion, and proliferation *in vitro* and tumor growth *in vivo*. A gain and loss-of-function study revealed that HOST2 down-regulation caused up-regulation of let-7, a tumor suppressor, leading to inhibited oncogenic behavior of OC cells and reduced tumor growth. Concomitantly, the expression levels of four let-7b target genes, namely *c-MYC*, *HMG2*, *IMP3*, and double-stranded RNA-specific endoribonuclease (*DICER*), were down-regulated both at the mRNA and protein levels. Furthermore, HOST2 overexpression resulted in the up-regulation of *MYC*, *HMG2*, *DICER*, and *IMP3* at the protein and mRNA levels, indicating that HOST2 acts as a sequestering agent (Fig. 2A3) and subsequently suppresses the levels of let-7b to prevent binding to the 3'-untranslated regions of its target mRNAs [99]. The observed phenomena strongly indicate that both HOST2 and let-7b can be targeted to develop a combination therapy.

Aberrant expression of HOTAIR is linked to OC. Like HOST2, HOTAIR overexpression promotes oncogenic OC cell behavior. The expression level of miRNA-373 increased following HOTAIR knockdown, thereby suppressing the viability, migration, and proliferation of OC cells. HOTAIR overexpression inhibited the activity of miRNA-373 and restored the behavior of cancer cells by acting as an endogenous sponge and regulating the Ras-related-protein, RAB-22 (RAB22A) [100]. Occasionally, miRNAs regulate the expression of lncRNAs, controlling their function as lncRNAs do. Higher expression of NEAT1 has been observed in both OC cell lines and tumors at the same time the expression levels of 124-p and HuR (a protein-binding RNA) were decreased and increased, respectively [26]. Mechanistically, HuR stabilizes NEAT1 expression, whereas 124-p suppresses it [26]. As discussed above, the actions and interactions of the identified lncRNAs and miRNAs in OC provide compelling evidence calling for the design of combination therapies, as patients may benefit from the additive or synergetic effects of both entities. In this context, a particular oncogene could be targeted by silencing both miRNAs and lncRNAs. Notably, following siRNA-mediated down-regulation of ephrin type-A receptor-2 (EphA2), an ovarian oncogene, tumor growth was reduced, and this effect was amplified by additional inhibition of EphA2 by its target miRNAs [101], strongly demonstrating the potential importance of combination treatment.

Targeting lncRNAs by CRISPR/Cas-9 for therapy

The clustered regularly interspaced palindromic repeats (CRISPR)/Cas-9-based approach for genome editing has been ubiquitously used for wide applications in various model organisms. Despite its usefulness in functional studies of the non-coding genome, it has mainly been leveraged to study coding transcripts. Nevertheless, a few functional studies (silencing, activation, and knockout) of lncRNAs using CRISPR/Cas-9 have been reported. In human cell lines, CRISPR-mediated knockout of lncRNAs such as UCA1, AK023948, and lncRNA 21A has been achieved [102]. Of these lncRNAs, UCA1 promoted tumorigenesis and drug resistance in OC cells [76, 103], indicating that it can be targeted by CRISPR. Moreover, inhibiting UCA1 expression by double-guided RNA CRISPR/Cas-9 impaired bladder cancer cell phenotypes *in vitro*. In another study, high-throughput genomic deletion of lncRNAs was achieved by using paired-guide RNA CRISPR/Cas-9, leading to the identification of as many as 51 functional lncRNAs in human cancer cells on the genomic scale [104]. Taken together, these findings indicate that lncRNAs can potentially be targeted as an OC-treatment option using the CRISPR/Cas-9 system.

More importantly, in a recent study, Liu and colleagues identified and successfully inhibited nearly 500 lncRNA loci capable of amending cell proliferation by CRISPR-based interference approaches [105]. Indeed, this approach could be extended to identify and target other lncRNA loci associated with high carcinoma cellular features such as tumor expansion, EMT, and metastasis. A remarkable feature of the CRISPR/Cas-9 system is its ability to induce site-specific genomic edition with proper design. Thus, an SNP of HOXA11AS [44] (involved in ovarian tumor development and progression) and an SNP of HOTAIR lncRNA [106] (associated with EOC risk), could be targeted by the CRISPR/Cas-9 system. The CRISPR/Cas-9 system can be used to generate true knockouts of alleles that are functionally involved in OC phenotypic alterations and/or predisposing factors for OC. However, the application of CRISPR/cas-9 to some, but not all, lncRNA regions is challenging because it also dysregulate adjacent genes, leading to risk of disease occurrence. A genomic-wide analysis study revealed that, from 15, 929 lncRNAs, as few as 6, 053 were safely accessible by CRISPR/Cas-9, indicating that targeting lncRNAs in a complex genomic region requires additional approaches that favorably couple with CRISPR/Cas-9 [107]. Additionally, it was previously reported that CRISPR/Cas-9 can span away from the targeted genomic boundary and generate mutations in several model organisms [108, 109], suggesting that accurate CRISPR/Cas-9 targeting is crucial for effectively utilizing it as a genomic editing tool and keep organisms as safe as possible, following gene editing.

Inhibition of chromatin-associated lncRNAs as a therapeutic approach

lncRNAs have various modes of actions in ovarian carcinogenesis, including the interaction with chromatin-remodeling complexes to silence target genes. This phenomenon can be considered to represent a classical mechanism of action in ovarian tumorigenesis. The following lncRNAs function through chromatin remodeling: HOTAIR [3], FAL1 [22], H19 [110], X-inactive specific transcript (XIST) [111], and maternally expressed 3 (MEG3) [112]. Hence, it is reasonable to identify and target lncRNA-mediated chromatin complexes. In OC, expression of the BMI and EZH2 polycomb group protein complexes is mediated by lncRNAs; therefore, they can be either silenced or inhibited by synthetic inhibitors. DZNep was the first inhibitor developed to counter the malignant activity of EZH2 [113], but treatment with DZNep also caused the lysis of other components of polycomb repressive complex 2 (PRC2). In contrast, EPZ005687 [114], GSK126 [115], and EIP [116] specifically inhibit EZH2, suggesting that the oncogenic behavior of lncRNAs associated with EZH2 such as MEG3, H19, and HOTAIR can be reversed.

Silencing lncRNAs using RNAi techniques

As described in this review and elsewhere in the literature, dysregulated lncRNAs contribute to OC initiation, tumorigenesis, and metastasis and the vast majority of lncRNAs share these features. For example, HOXA11AS, UCA1, NEAT1, HOTAIR, and SPRY4-IT1 overexpression contributes to OC development. The oncogenic roles of these lncRNAs could be directly inhibited by employing RNAi techniques, as recently reviewed [28], suggesting remarkable promise as targets for future therapeutic development.

LncRNAs and partner molecules mediate drug-resistance in OC

The resistance of tumor cells to multiple therapeutic approaches remains the biggest barrier for the cancer therapy. Studies performed to determine the therapeutic sensitivity and/or resistance after targeting lncRNAs indicated that some lncRNAs mediate therapeutic resistance in different cancer cell types by involving proteins, miRNAs, DNA, and transcription factors [117, 118]. LncRNAs could serve as chemotherapy-resistance biomarkers, thereby leading to the development of alternative strategies to overcome the disease. BC200 is down-regulated in OC tissue, and carboplatin treatment resulted in increased cell viability, inducing chemoresistance through unknown mechanisms [60]. Future studies will reveal the mechanisms by which BC200 contributes to drug resistance.

HOTAIR is an lncRNA whose influence has been extensively explored in cancer cells presenting therapeutic resistance. In primary OC cells, HOTAIR overexpression and its DNA methylation appeared to induce carboplatin resistance [77], indicating that HOTAIR may contribute to resistance by influencing methylation. In a parallel study, increased HOTAIR expression was observed in the cisplatin-resistant, SKOV-3CDDP/R, ovarian carcinoma cell line model, with subsequent exposure of the cell line to cisplatin upon siRNA-induced knockdown of HOTAIR [16]; this phenomenon was also linked to enhanced apoptosis and cytotoxicity. Another seminal study conducted by Li et al. explored the role of HOTAIR in chemoresistance in OC cells. The study showed that higher expression of HOTAIR in OC cells induced cisplatin resistance through upregulation of the Wnt/ β -catenin signaling pathway and promoting cell cycle progression. Conversely, inhibition of HOTAIR resulted in cisplatin sensitivity, *in vitro* and *in vivo* by suppressing Wnt/ β -catenin signaling and inducing cell cycle arrest at G1 phase [119]. A recent study performed by Ozes and colleagues revealed that HOTAIR mediates chemoresistance in DNA-damage responses through the NF- κ B signaling pathway [41]. The multidimensional involvement of HOTAIR in drug resistance may provide a big opportunity to target it for cancer therapy. Similarly, it has been reported that UCA1 up-regulation promotes OC cellular viability and induces cellular resistance to cisplatin [103]. In the same study, overexpression of the anti-apoptotic protein serine-arginine protein kinase 1 (SRPK1) was observed; however, cisplatin sensitivity was partially restored following SRPK1 downregulation [103].

Indeed, the interaction of lncRNAs and miRNAs is not limited to the modulation of OC cell progression, but also regulates tumor cell chemosensitivity. For example, zinc finger antisense 1 (ZFAS1) was implicated in tumorigenesis, served as a prognostic biomarker in patients with multiple types of solid tumors [120-122], interacted with miRNA-150-5p, promoted the expression of the specific protein 1 (*SP1*) gene, and induced OC cellular resistance to cisplatin and paclitaxel [123]. Some lncRNA-mediated resistance mechanisms are represented in Fig. 3.

Another lncRNA, ENST00000457645, was down-regulated in cisplatin-resistant OC cells and abrogated chemoresistance, thereby regulating the expression of downstream target apoptotic proteins [124]. Furthermore, PVT1 overexpression elicited cisplatin resistance in OC cells and contributed to drug resistance by regulating downstream apoptotic proteins [125].

Fig. 3. LncRNA-mediated drug-resistance mechanisms. Overexpression of HOTAIR mediates drug resistance by activating the Wnt/ β -catenin signaling pathway and thus sustains OC cell cycle progression. Elevated expression of UCA1 activates SRPK1 and increases the expression of anti-apoptotic proteins to promote tumor cell proliferation. ZFAS1 binds to miRNA-150p-5p to regulate the SP1 expression and modulate OC cell chemosensitivity. HOTAIR, hox transcript antisense intergenic RNA; SP1, specific protein 1; SRPK1, serine-arginine protein kinase 1; UCA1, urothelial carcinoma associated 1; ZFAS1, zinc finger antisense 1.

In addition to protein complexes and miRNAs, that associate with lncRNAs during the development of various cancers (including OC), can also mediate drug resistance. For instance, enhancer of zeste homolog 2 (EZH2), a core catalytic subset of PRC2, associates with several oncogenic lncRNAs such as H19, MEG3, HOTAIR, and HEIH [126-128]. EZH2 overexpression promotes invasion and proliferation of OC cells *in vitro* and tumor growth *in vivo* and is associated with poor OS. In contrast, siRNA-mediated knockdown of EZH2 impairs oncogenic cell behavior by arresting cell cycle progression [129]. In a separate study, EZH2 expression was elevated in cisplatin-resistant OC cells, but cisplatin resistance was lost upon EZH2 down-regulation [130]. As mentioned above, lncRNAs can strongly regulate OC chemoresistance via their interactions with different partner molecules (Fig. 3). Taken together, these findings strongly suggest that therapeutic approaches should emphasize on combined strategies instead of focusing on single biological molecules, given that cancer initiation and development involves multiple molecules belonging to specific networks, rather than functioning separately.

Conclusion

LncRNAs are often inscrutable transcriptional products and appear to drive gene-regulation networks, both in normal and pathological cellular processes. Although many lncRNAs have been identified in the last 10 years, their roles have not been characterized and it is difficult to predict their functions, as they are less amenable to analysis with existing genomic tools. Despite their complexities, the normal cellular roles of some lncRNAs have been reported, but not many functions of lncRNAs have been implicated in malignancy, including that in OC. Continued efforts will unveil the functional contribution of lncRNAs in OC biology.

Of the several remarkable attributes of lncRNAs, their tissue-and/or cell-specific expression patterns and involvement in all steps of OC development are important and should be exploited to develop therapies and biomarkers. Most importantly, the ability of lncRNAs to interact with coding and non-coding transcripts, particularly with miRNAs (Fig. 2), is one crossroad that should be focused on during the development of therapies, even though the biogenesis of lncRNAs remains unclear. Further characterization of multiple biogenic pathways of lncRNAs and the molecules involved in these pathways is necessary and will lead to a comprehensive understanding of lncRNAs. As presented in Tables 1 and

2, with few exceptions, most lncRNAs reported in OC are up-regulated both in OC cells and tumor tissue, suggesting that down-regulating their expression is likely to be useful for treating patients. Hence, as mentioned above, RNAi is an important strategy for targeting lncRNAs for therapy, and RNAi-based therapies have been in clinical trials for several years. Interestingly, after much effort, the delivery problem of RNAi-based therapy has been solved [131], and this approach is likely to represent the future gene therapy, although additional work is required for final approval.

Recently, the inhibition of lncRNA loci using CRISPRi technology has garnered attention. Using this approach, Liu et al. inhibited as many as 500 human lncRNA loci [105], and these loci have been found to modify the growth of specific cell types without interfering with neighboring cells. Thus, lncRNA loci, which contribute to cancer development and progression, could be safely targeted for lncRNA-based therapy. Identification of molecules that regulate the transcription (and thus the expression) of lncRNAs is another strategy for targeting lncRNAs. For example, in mouse pluripotent stem cells, Ak028326 and Ak141205 are regulated by the Oct4 and Nanog transcription factors, respectively [132]. The identification of such regulatory molecules might be helpful for targeting lncRNAs. In essence, it might be possible to construct plasmids that can selectively control particular oncogenes and help kill malignant cells. Overall, lncRNAs represent an additional genetic network regulating OC and other genetic disorders by interacting with coding and non-coding molecules and functioning through multiple modes of action via known and unknown pathways. Therefore, further characterization of lncRNAs and their pathways will deepen our understanding and may reveal unforeseen mechanisms, eventually helping to incorporate lncRNAs into future therapies.

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Disclosure Statement

The authors declare that there is no potential conflict of interest.

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