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REVIEW

The pivotal role of long non-coding RNAs as potential biomarkers and modulators of chemoresistance in ovarian cancer (OC)

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Abstract

Ovarian cancer (OC) is a fatal gynecological disease that is often diagnosed at later stages due to its asymptomatic nature and the absence of efficient early-stage biomarkers. Previous studies have identified genes with abnormal expression in OC that couldn't be explained by methylation or mutation, indicating alternative mechanisms of gene regulation. Recent advances in human transcriptome studies have led to research on non-coding RNAs (ncRNAs) as regulators of cancer gene expression. Long non-coding RNAs (lncRNAs), a class of ncRNAs with a length greater than 200 nucleotides, have been identified as crucial regulators of physiological processes and human diseases, including cancer. Dysregulated lncRNA expression has also been found to play a crucial role in ovarian carcinogenesis, indicating their potential as novel and non-invasive biomarkers for improving OC management. However, despite the discovery of several thousand lncRNAs, only one has been approved for clinical use as a biomarker in cancer, highlighting the importance of further research in this field. In addition to their potential as biomarkers, lncRNAs have been implicated in modulating chemoresistance, a major problem in OC. Several studies have identified altered lncRNA expression upon drug treatment, further emphasizing their potential to modulate chemoresistance. In this review, we highlight the characteristics of lncRNAs, their function, and their potential to serve as tumor markers in OC. We also discuss a few databases providing detailed information on lncRNAs in various cancer types. Despite the promising potential of lncRNAs, further research is necessary to fully understand their role in cancer and develop effective strategies to combat this devastating disease.

Introduction

Ovarian cancer (OC) is a deadly gynecological malignancy accounting for 3.4% of all cancer cases (Sung et al. 2021). It ranks as the 8th most common cancer among women worldwide (Cancer today 2021), with 313,959 new cases and 207,252 deaths attributed to OC in 2020 (Sung et al. 2021). These numbers account for a significant portion of the 19.3 million new cancer cases and 10 million cancer-related deaths globally. OC is the 5th leading cause of gynecological cancer-related mortalities worldwide (Siegel et al. 2017), and by 2040, the estimated number of OC-related incident and mortality cases is expected to rise to 440,000 310,000, respectively (Cancer Tomorrow 2022). Unfortunately, OC is typically asymptomatic, and the majority of patients are diagnosed at late stages; 51% at stage III and 29% at stage IV, primarily due to the absence of reliable early-stage biomarkers (Torre et al. 2018). This, coupled with drug treatment resistance and recurrence (Norouzi-Barough et al. 2018), is a major cause of poor overall survival (Wang et al. 2019a) (Coticchia et al. 2008). The five year survival rate for early-stage OC is 89%, compared to only 20% for stage IV (Ovarian Cancer 2023). Despite advancements in OC research, fatality rates remain unchanged due to the lack of robust clinical tools for early detection (Galea et al. 2017; Chandra et al. 2019). Therefore, elucidating the process of ovarian cancer pathogenesis and identifying potential biomarkers, such as differentially expressed genes, for OC diagnosis, prognosis, and treatment is crucial (Zheng et al. 2019a).

The pathogenesis of ovarian cancer involves a series of molecular and genetic changes in healthy ovarian cells, leading to the onset and progression of cancer. However, the heterogeneity of OC complicates efforts to understand its

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pathogenesis (Gross et al. 2010; Kurman and Shih 2016). Various theories have been proposed to elucidate the mechanisms underlying OC pathogenesis. According to the theory of incessant ovulation**,** surface epithelial cells, which were previously believed to be the origin of OC, undergo physical damage that is rapidly repaired. The repetitive ovulation during a women's life causes repeated damage to the epithelial cells, resulting in DNA damage. These cells, which are continually exposed to ovarian hormones, promote malignant growth, leading to the neoplastic transformation into cancer cells (Kurman and Shih 2010; Erickson et al. 2013; Budiana et al. 2019).

The dualistic model theory proposed by Kurman and Shih categorizes ovarian tumors into two types, namely Type-I and type-II, based on clinical, genetic, and histological observations (Kurman and Shih 2010; Koshiyama et al. 2014). Type-I ovarian carcinomas include low-grade serous, clear-cell, endometrioid, mucinous, and malignant Brenner tumors. These tumors are characterized by being low grade, indolent, and confined to the ovary at presentation, with better survival outcomes. Type-I tumors exhibit specific genetic mutations such as KRAS, PTEN, BRAF, ARID1A, PIK3CA, and ERBB2, and they are genetically stable (Koshiyama et al. 2014). The progression of Type-I cancers follows a series of sequential steps from benign precursor lesions to malignant lesions.

On the other hand, Type-II ovarian carcinomas encompass high-grade serous, high-grade endometrioid, malignant mixed, undifferentiated tumors, and mesodermal tumors. These tumors are high-grade, aggressive, and associated with unfavorable survival outcomes. They are characterized by TP53 mutations (Ledermann et al. 2013; Koshiyama et al. 2014; Chen et al. 2014; Kurman and Shih 2016; Aluloski et al. 2017; Ricciardi et al. 2018). In Type-II ovarian cancer, the precursor originates from fallopian tube, and TP53 mutations contribute to the neoplastic changes in the epithelial cells of the fallopian tube (Budiana et al. 2019). Subsequently, these cancerous cells metastasize to the ovaries and peritoneal cavities.

Previous studies in cancer have revealed aberrant gene expression that couldn't be explained by methylation or mutation alone. Dysregulated expression of these genes could be due to their regulation by non-coding RNAs (ncRNAs), such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) (Al Saqri et al. 2022; Malgundkar et al. 2022). For many years, cancer research focused primarily on protein-coding genes. However, the discovery that protein-coding genes account for only 1.5–3% of the total genome, while the majority is transcribed to ncRNAs (15–17), has revolutionized the field. The increasing number of studies on ncRNAs suggests that they have functions beyond being an intermediary between DNA and protein. NcRNAs are a class of RNAs with no protein coding ability known to interact with DNA, RNA, or protein to modulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels (Holoch and Moazed 2015).

NcRNAs, particularly lncRNAs, play a crucial role in regulating gene expression in differentiation, development, and human diseases. Given the aberrant expression of lncRNAs, they could also play a significant role in the onset and development of OC. Furthermore, the presence of lncRNAs in biological fluids makes them a promising biomarker for OC. While the list of functionally characterized lncRNAs in the cancer field is rapidly expanding, the question arises as to whether lncRNAs are solely transcriptional noise or have biological functions. Moreover, the study of lncRNAs is not as extensive as that of miRNAs, and many unknowns exist regarding their function and involvement in cancer, including OC (Salamini-Montemurri et al. 2020).

This review aims to elucidate the involvement of lncRNAs in OC, providing insights into the mechanisms by which lncRNAs contribute to the disease and their potential as diagnostic and therapeutic targets. Additionally, we will discuss several key findings on lncRNAs as biomarkers for OC.

ncRNAs and its classification

RNA is divided into two categories: messenger RNA (coding RNA) and non-coding RNA (ncRNA). Messenger RNA (mRNA) is the most well-known and studied type of RNA, constituting only 2% of the coding part of the human genome. Non-coding RNAs are further classified as structural or regulatory. House-keeping ncRNAs include transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNAs (snoRNAs), and small nuclear RNAs (snRNAs). Regulatory ncRNAs are sub-classified as short or long ncRNAs based on their length. Short ncRNAs include piwi-interacting RNAs (piRNAs), circular RNA (circRNAs), microRNAs (miRNAs), and short interfering RNAs (siRNAs) (Nagano and Fraser 2011; Aliperti et al. 2021; Ahadi 2021) Fig. 1.

miRNAs are short ncRNAs composed of 22 nucleotides, with a key role in post transcriptional level gene silencing. miRNAs achieve this through binding to specific sequence (3' untranslated region) known as miRNA recognition element (MRE) on target mRNA transcripts (Ha and Kim 2014; Yang et al. 2017; Treiber et al. 2019). A previous finding revealed > 60% mRNA were regulated by miRNAs (Friedman et al. 2009). mRNAs that are perfectly complementary to the miRNA undergo cleavage via endonucleolytic activity. On the contrary, in case of partial complementarity, mRNAs are subjected to translational repression (Magri et al. 2018). Several miRNAs have been reported to be aberrantly expressed in OC, and was found

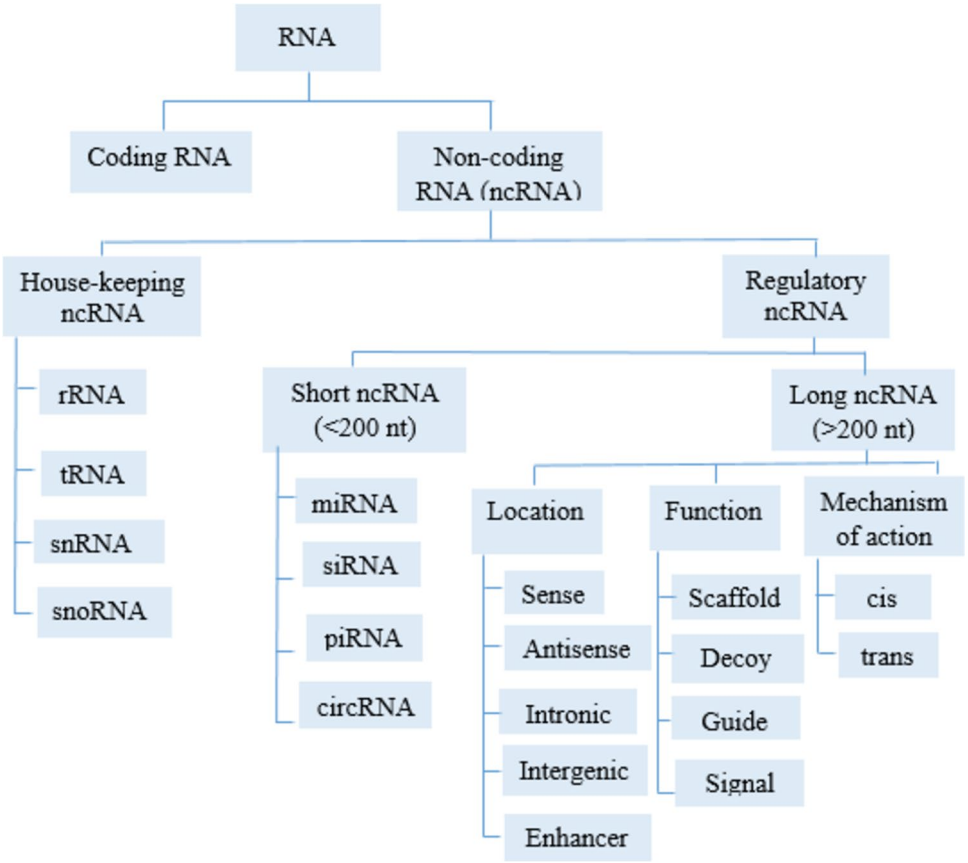

Fig. 1 Classification of RNA molecule

to be involved in OC pathogenesis (Zaman et al. 2012; Pal et al. 2015; Mahdian-Shakib et al. 2016).

The oncogenic or tumor suppressive effects of miRNA occur through the regulation of either tumor suppressive or oncogenic protein coding genes (Svoronos et al. 2016). Overexpression of oncogenic miRNAs silences tumor suppressive genes, thereby promoting cancer. Similarly, lower levels of tumor suppressive miRNAs enhances oncogene expression (Otmani and Lewalle 2021). Aberrant miRNA expression have the ability to regulate cancer related processes such as inducing invasion, metastasis, angiogenesis, evading growth suppressors, maintaining cell growth signals (Rishabh et al. 2021).

While miRNAs acts as post-transcriptional regulators in the cytoplasm, lncRNAs occur in the cytoplasm and nucleus indicating its potential to serve as epigenetic modifiers of chromatin thereby regulating gene expression (Kapranov et al. 2010; Derrien et al. 2012; Fort et al. 2014). Furthermore, abnormal levels of miRNA have been closely associated with lncRNAs (Ye et al. 2018). The regulatory interactions between lncRNAs and miRNAs occur in two distinct ways. Firstly, lncRNAs can modulate miRNAs by serving as its precursor or can act as miRNA sponge. Secondly, miRNAs can control lncRNA expression through epigenetic mechanism. Moreover, miRNAs could trigger lncRNA degradation via argonaute (Nukala et al. 2022).

Several miRNAs have been identified as being aberrantly expressed in OC and have been implicated in its pathogenesis (Zaman et al. 2012; Pal et al. 2015; Mahdian-Shakib et al. 2016). For instance, *miR-600* was found to be significantly over-expressed in OC tissue samples, leading to the downregulation of KLF9 expression and promoting OC cell proliferation and metastasis (Shan et al. 2022). Similarly, *miR-149-3p* facilitated EMT and cisplatin resistance in OC by reducing TIMP2 and CDKN1A levels (Wang and Liu 2021).

Another study revealed the downregulation of *miR-425* in OC tissues and cell lines, which was correlated with poor overall survival. Furthermore, miR-425 was shown to inhibit OC cell migration, invasion, and proliferation by regulating PAK4 levels (Wang et al. 2022). Also, investigating the lncRNA-miRNA-mRNA network could provide insights into the mechanisms underlying OC pathogenesis, such as *OIP5-AS1-miR-203a*-ZEB2 axis, which regulates OC progression through EMT and metastasis (Pronina et al. 2022). Abnormal levels of miRNA have been found to be closely associated with lncRNAs (Ye et al. 2018). This study will exclusively focus on describing the role of lncRNA in OC.

Overview on lncRNAs

Recent studies have revealed that a significant portion of the human genome (80%) is actively transcribed into RNA, despite having no protein-coding potential (Derrien et al. 2012; Djebali et al. 2012; de Hoon et al. 2015). A large subset of these transcripts, exceeding 200 nucleotides in length, is known as lncRNA (Nagano and Fraser 2011). LncRNAs are transcribed from the human genome by RNA Polymerase II and lack protein-coding open reading frames (Gibb et al. 2011). In a wide-scale analysis of 91,013 transcribed human genes across more than 7250 tissue samples, lncRNAs constituted around 70% (58,648 in number) of human transcripts, with 79% of these being unannotated (Iyer et al. 2015). Although over 90,000 lncRNAs have been identified in some studies, only 16,000 have been annotated in GENCODE (Harrow et al. 2012; Iyer et al. 2015). Given that the majority of the human genome is non-protein coding, and the potential of these non-coding genes to serve as biomarkers, research focus has shifted to lncRNAs, which were previously considered to be transcriptional noise (Shi et al. 2016).

Characteristics and classification of lncRNAs

LncRNAs share similarities with mRNAs, which distinguishes them from short ncRNAs that can be easily differentiated from mRNAs (Ponting et al. 2009). While lncRNAs possess a 5' cap, exons, and poly-A tails like mRNA, they do not have functional open reading frames or protein-coding functions (Fang and Fullwood 2016). Approximately 50% of lncRNAs have a polyA tail, and nearly all are spliced (Derrien et al. 2012). Like mRNAs, lncRNA are transcribed by RNA Polymerase II (Derrien et al. 2012), but they typically have fewer exons and are longer in length (Cabili et al. 2011; Harrow et al. 2012). Despite lacking sequence conservation, LncRNAs can play a modulatory role due to the highly conserved secondary and tertiary structures of lncRNAs (Li et al. 2016b). However, their primary structure conservation is poor (Aliperti et al. 2021), as lncRNAs lack evolutionary conservation and exhibit differential expression, as revealed by the presence of epigenetic markers (Guttman et al. 2009).

In contrast to mRNAs, only 11–29% of lncRNAs are expressed in all tissues and at low levels (Derrien et al. 2012; Djebali et al. 2012). Additionally, lncRNAs exhibit high tissue specificity (~78%) compared to mRNAs (~19%) (Cabili et al. 2011). Certain lncRNAs undergo transcriptional and post-transcriptional modifications identical to protein-coding genes (Ponting et al. 2009). Furthermore, lncRNAs exhibit characteristic functions in different physiological processes, as indicated by their tissue-cell type-specific expression compared to mRNAs (Cabili et al. 2011; Derrien et al. 2012; Djebali et al. 2012).

Almost thirty years ago, the first lncRNAs, H19 and XIST, were discovered and studied for their roles in chromosome dosage compensation and genomic imprinting (Brannan et al. 1990; Brown et al. 1991). According to Brannan et al. (1990), the RNA molecule H19 was found to be distinct from classical mRNAs despite being transcribed by RNA polymerase II, undergoing splicing and polyadenylation. This distinction was due to the absence of a conserved open reading frame in the H19 RNA molecule.

Recently, lncRNAs was identified to play a crucial role in several biological processes, including RNA splicing, cell proliferation, cell differentiation, epigenetic silencing, transcription (Guttman et al. 2009), cell cycle regulation (Kitagawa et al. 2013; Heydarnezhad Asl et al. 2022), DNA methylation (Yang et al. 2022), antiviral immunity (van Solingen et al. 2022), specifying cell identity (Hu et al. 2012) and apoptosis (Jiang et al. 2021). LncRNAs achieve their functions by regulating gene expression at the epigenetic, transcriptional, and post-transcriptional levels (Kornienko et al. 2013; Fatica and Bozzoni 2014; Renganathan and Felley-Bosco 2017). The majority of lncRNAs are enriched in the nucleus, where they regulate post-transcription (Wang and Chang 2011; Quinn and Chang 2016). Additionally, lncRNAs can act as competing endogenous RNA (ceRNA) by serving as a miRNA sponge, regulating miRNA abundance, and competing with mRNA for miRNA binding (Ye et al. 2018). Furthermore, Tian et al. identified a direct association between the lncRNA WDR7-7 and the mRNA GPR30 (Tian et al. 2017), highlighting its ability to regulate gene expression through means other than the well-known ceRNA network.

Classifying lncRNAs is challenging due to their structural variations, poor sequence conservation, various molecular mechanisms of action, and differential subcellular localization (Mattick and Rinn 2015). LncRNAs can be broadly classified based on their location in the genome, mechanism of action, and function. They are categorized as intronic, intergenic, enhancer, and antisense lncRNAs based on location. Intronic lncRNAs arise from the intronic region of protein-coding genes, intergenic lncRNAs arise from the region between two protein-coding genes, enhancer lncRNAs are produced from the promoter enhancer region, and antisense lncRNAs arise from the antisense strand of the gene (Ma et al. 2013). Based on function, lncRNAs are categorized as signaling, guiding, decoy, and scaffold lncRNAs. Signaling lncRNAs are linked to specific signaling pathways, guiding lncRNAs are associated with regulatory protein complexes and direct them to particular

target gene promoters, thereby regulating downstream gene expression (Wang and Chang 2011). Decoy lncRNA titrates the transcription factors away from the target gene promoters, preventing them from binding and promoting or inhibiting gene expression. Additionally, scaffold lncRNAs serve as platforms for several protein complexes, directing them to specific gene locations (Wang and Chang 2011; Ma et al. 2013).

Gene expression profiling techniques

Most of the lncRNA based research involve the use of bioinformatic analysis, RNA sequencing, microarray, functional assays for the identification and characterization of lncRNAs in cancer. Integrating multiple approaches for experimental validation and functional analysis is important to determine and characterize the lncRNAs.

Gene expression technology can be used to identify the link between genetic aberrations and OC pathogenesis, providing insight into the process of cancer onset and progression. These techniques also have the potential to reveal novel OC biomarkers (Zhang et al. 2011). The field of functional genomics has rapidly developed due to advanced computational approaches and high-throughput sequencing technologies (65, 66). Recently, sophisticated molecular biology techniques such as Next Generation Sequencing (NGS), microarrays, and Chromatin immunoprecipitation (ChIP) have been used to identify differentially expressed genes, including lncRNAs. These genes can potentially be used as biological biomarkers in epithelial ovarian cancer (EOC) (El Bairi et al. 2017).

NGS technology enables the simultaneous sequencing of millions of gene fragments (Kamps et al. 2017), providing insight into the various signaling pathways involved in OC progression (Gov et al. 2017). The most commonly employed techniques for the discovery and annotation of novel lncRNA transcripts of low abundance is RNA-seq, which also detects the lncRNA isoforms. (as reviewed in (Chowdhary et al. 2021)), however it is time consuming and costly (Lee and Kikyo 2012). Currently, RNA sequencing techniques have led to the detection of several lncRNAs, although only a few have been well characterized (Zhan et al. 2018). For instance, Abildgaard et al. identified the lncRNA *SNHG12*, which regulate carboplatin resistance using RNA sequencing in OC cell lines (Abildgaard et al. 2022). Similarly, RNA sequencing in OC and healthy ovarian tissues revealed 6,764 aberrantly expressed genes (Guo et al. 2020). However, this technique requires sophisticated bioinformatics techniques to interpret the data (as reviewed in Rao et al. 2019) and to predict lncRNAs.

Microarray is a widely used technique to simultaneously assess the expression of thousands of genes. It provides key data on the molecular differences in tumors, OC prognosis, mechanisms of resistance to chemotherapy, and response to chemotherapy (Spentzos et al. 2004; Konstantinopoulos et al. 2008). The use of microarray for lncRNA research is limited to only known lncRNA sequences, and it cannot detect novel lncRNAs. Microarray analysis has revealed differentially expressed lncRNA in OC samples compared to normal tissues, providing insight into their role as biomarkers (Ding et al. 2017). In a previous microarray study, 4,289 differentially expressed lncRNAs were identified in high-grade serous ovarian cancer (HGSOC) compared to healthy fallopian tissue samples (Lou et al. 2018). Similarly, another study reported 3527 aberrantly expressed lncRNAs in SKOV3 cells compared to IOSE80 cells, while 9706 dysregulated lncRNAs were identified in the cisplatin-resistant variant of SKOV3 cells (Gao et al. 2019a). Therefore, microarray analysis is a crucial tool to understand the function of lncRNAs in OC and provides a means to elaborate on the mechanisms underlying carcinogenesis, helping researchers identify significant lncRNAs for further analysis.

Many important biological processes, such as cell cycle progression, cell differentiation, transcription, DNA replication, and epigenetic silencing, rely on the interactions between DNA and proteins (Mundade et al. 2014). Chromatin immunoprecipitation (ChIP-seq) is an emerging technique that is often used in combination with DNA sequencing to identify the genomic DNA segments bound to the protein of interest, such as transcription factors, co-factors, and chromatin remodeling complexes (Wiehle and Breiling 2016; McColl et al. 2019). Therefore, ChIP is a useful technique for unraveling the molecular mechanisms of gene regulation (Mundade et al. 2014). In a previous ChIP study performed on OC cell lines, several lncRNAs that interact with E2F5, a transcription factor involved in the pathogenesis of EOC, were identified (Malgundkar et al. 2022).

To investigate the interacting partners of lncRNAs, several techniques have been developed. One commonly used technique is RNA immunoprecipitation (RNA-IP), which enables the detection of interactions between specific proteins and RNA molecules. RNA-IP is particularly useful for studying lncRNA-protein interactions and identifying lncRNAs that form complexes with specific proteins of interest (Zhang et al. 2016a). However, one disadvantage of this technique is its potential lack of specificity in identifying RNA interactions (Cao et al. 2019).

Another technique employed to determine RNA–protein interactions is cross-linking and immunoprecipitation (CLIP). This technique involves cross-linking RNA and interacting proteins, followed by immunoprecipitation to isolate RNA–protein complexes (Hafner et al. 2021).To identify the interactions between lncRNAs and chromatin, one widely used technique is chromatin isolation by RNA

purification (ChIRP) (Chu and Chang 2016). For example, ChIRP was used to determine the interaction between the lncRNA *NEAT 1–1* and *RUNX2* promoter (Wen et al. 2020). Similarly, ChIRP was used to identify the interaction between the lncRNA *GAS5* and *miR-18a-5p* in bladder cancer cells to elucidate its mechanism of action (Zhang et al. 2022).

To determine the function of lncRNAs, one common approach is to silence the lncRNA using siRNA and GAPmers and analyze the resulting changes in gene expression to identify the genes influenced by the lncRNA (Chowdhary et al. 2021). Computational approaches for identifying lncRNA function are more challenging due to factors such as tissue specificity, low expression levels, and interactions with multiple molecular components (Chowdhary et al. 2021).

lncRNAs in cancer

LncRNAs has been linked to the onset and progression of several human diseases, including cancer, as the aberrant expression of lncRNAs can function as oncogenes or tumor suppressor genes by regulating tumor cell migration, apoptosis, proliferation, invasion, and metastasis (Li et al. 2021b). Activation of oncogenic signaling pathways, epigenetic modifications, and interactions with other RNA molecules are known to promote cancer progression by modulating lncRNA expression. lncRNAs have been found to be differentially expressed in different types of cancer. For example, the lncRNA *H19* expression levels was reported to be higher in breast cancer cell lines and tissue samples. Moreover, by regulating *TNFAIP8* levels, *H19* was found to promote cell migration, invasion, proliferation, and EMT, (Li et al. 2020). *H19* was also found to be upregulated in gastric cancer cell lines and tissues, which resulted in activation of the Wnt/β catenin pathway by promoting nuclear translocation of β catenin. This in turn resulted in EMT and metastasis of gastric cancer cells (Liu et al. 2021). In OC, *H19* was significantly higher in OC samples and cell lines, which promoted invasion, migration, proliferation and EMT through modulation of the PI3K/ AKT pathway (Xu et al. 2021). Table 1 summarizes how lncRNAs can regulate OC by functioning as scaffolds, guides, decoys, or signaling molecules.

lncRNAs reflect the physiological condition of the cell due to their specific expression in tissues and development specific expression (Chowdhary et al. 2021). High-grade serous OC is the most lethal subtype of OC, characterized by low five-year survival rates and a poor prognosis. Detecting the genes associated with OC onset and progression, as well as understanding their regulatory mechanisms, is crucial for managing OC (Lou et al. 2018). Analyzing the expression status of lncRNA has the potential to classify cancer subtypes (Flippot et al. 2016). In a previous microarray profiling study, differential expression of 663 lncRNA transcripts was observed in healthy ovarian samples, benign ovarian cysts, and EOC samples. Among these, 182 lncRNAs were overexpressed, and 481 were under-expressed in EOC samples, suggesting their function as tumor suppressor/oncogene and biomarkers (Wang et al. 2016). (Wang et al. 2016). Another microarray analysis comparing high-grade serous OC samples and healthy fallopian tube samples revealed that 1,511 lncRNAs were overexpressed, while 2,778 lncRNAs were down-regulated in OC (Lou et al. 2018). The study identified several upregulated lncRNAs, including *RP11-199F11.2, FAS-AS1, AC093818.1,* and *AK130076,* as well as the downregulation of *GTSE1-AS1.*

Additionally, the expression of associated mRNA, such as *GSTE1, PDK1, TP53, PTEN,* and *FAS,* was found to be altered in high-grade serous OC samples, suggesting the involvement of both mRNA and their associated lncRNAs in OC progression (Lou et al. 2018). Furthermore, dysregulated lncRNA expression was associated with lymph node metastases and OC FIGO stages in high-grade serous OC patients' samples, indicating its potential association with ovarian carcinogenesis and tumor development (Lou et al. 2018).

The lncRNA *MALAT-1* was significantly upregulated in primary OC samples compared to healthy ovarian tissues. Moreover, *MALAT-1* expression was associated with the FIGO stage, indicating its involvement in OC progression (Zhou et al. 2016). On the other hand, the lncRNA *MEG3*, a tumor suppressor, was significantly downregulated in primary OC samples as well as metastatic tumors compared to

Table 1 Examples of regulatory mechanisms of lncRNAs in OC

Function	lncRNA	Mechanism	References
Scaffold	*SNHG7*	Promotes tumorigenesis by forming a scaffold for the EZH2 thereby repressing *KLF2* expression	(Bai et al. 2020)
Decoy	*SNHG5*	Decoys the *miR-23a* thereby re sensitizing the cells to paclitaxel	(Lin et al. 2020)
Guide	*ATB*	Binds to and guides EZH2 component in PRC2 complex to the promoter of *FOXC1, CDH1, LATS2* genes, thereby inhibiting its expression through the trimethylation of H3K27	(Chen and An 2021)
Signal	*LINC-ROR*	Promotes epithelial-mesenchymal transition (EMT) via the modulation of Wnt/ beta catenin pathway	(Lou et al. 2017)

healthy ovarian and benign ovarian cancer samples. Additionally, *MEG3* expression showed a negative correlation with the FIGO stage (Xiu et al. 2017).

Regulation of gene expression by lncRNA

Regulating gene expression is a fundamental life process, and its modulation is essential for the development of an organism (Schmitt and Chang 2016). Transcription factors, cofactors, chromatin modulators, and aberrant gene regulation can result in a range of malignancies, highlighting the importance of regulating gene expression patterns (Lee and Young 2013). Critical factors in gene expression regulation include DNA methylation, histone modifications, and ncRNA-associated epigenetic mechanisms (Miller and Grant 2013). One of the most significant functions of lncRNA is epigenetic regulation, achieved through interaction with epigenetic modifiers such as Polycomb repressive complexes (PRC) and histone methyltransferases (Hanly et al. 2018). Aberrant regulation of epigenetic mechanisms is a key characteristic of cancer and contributes to its onset and progression (Shen and Laird 2013).

An example of the role of lncRNA in cancer is the lncRNA *KCNQ1OT1,* which was found to reduce the EIF2B5 levels by recruiting DNA methyltransferase to the *EIF2B5* promoter, resulting in OC metastasis (He et al. 2022). Similarly, *UNC5B-AS1* interacts with *EZH2* to promote trimethylation of histone-3 at lysine 27 on the *NDRG2* promoter, thereby promoting OC (Wang et al. 2020a). Only a few studies have highlighted the importance of mutations in lncRNAs as a mechanism regulating their function. Similar to proteins, mutations that cause aberrations in lncRNA expression or structure can result in a range of diseases, including cancer (Cabianca et al. 2012; Xue et al. 2015; Lin et al. 2016; Castellanos-Rubio et al. 2016). Single nucleotide polymorphisms (SNPs) in the interacting site can affect the functional role of lncRNA in terms of genomic alterations in the non-coding region. Additionally, variants can alter the secondary structure of lncRNA, thereby affecting its binding ability (Rao et al. 2017). A recent analysis reported that 495,729 SNPs are prevalent in 17,436 lncRNA genes, potentially affecting their secondary structure (Gong et al. 2015).

Competing endogenous RNA (ceRNA) network in OC

A novel mechanism of gene expression regulation involves the interaction between ncRNAs and mRNAs through shared miRNAs (Karreth and Pandolfi 2013). The participation of ncRNAs in competing endogenous regulatory interactions, also known as the ceRNA network, has been well documented. According to the ceRNA hypothesis, lncRNAs and mRNAs harbor the same miRNA response elements. Furthermore, ncRNAs have the potential to titrate miRNA away from mRNA by recognizing and binding to the miRNA recognition elements (MREs), thereby promoting target gene expression (Salmena et al. 2011; Chan and Tay 2018). Among the ceRNA network, lncRNAs have gained much attention due to their involvement in a range of biological processes. LncRNAs regulate mRNA expression at the post-transcriptional level by acting as a molecular sponge for miRNA through the miRNA-response element (Prensner and Chinnaiyan 2011; Zhou et al. 2019). Therefore, lncRNA behaves as negative regulators of miRNA and positively regulates gene expression (Fig. 2). Aberrations in the lncRNA-miRNA-mRNA network, particularly lncRNAs, have a pivotal contribution to OC pathogenesis (Yan et al. 2015; Bhan et al. 2017; Slack and Chinnaiyan 2019) Table 2.

Involvement of lncRNAs in drug resistance

Chemotherapy, in addition to surgical debulking, is currently used to treat ovarian tumors (Miller et al. 2019). Despite the initial response to chemotherapy, the five-year survival rate of OC patients is low due to late diagnosis and chemoresistance (Coleman et al. 2013; Siegel et al. 2016; Nasioudis et al. 2016). Resistance to chemotherapy remains a major concern in the treatment of OC. One of the significant obstacles in the clinical settings is the lack of ideal platinum resistance associated biomarkers categorizing risk and determining prognosis (Zhu et al. 2022).Elucidating the mechanisms underlying chemoresistance is crucial for developing therapeutic drugs to overcome this resistance (Helleman et al. 2006). Recently, several studies have documented the potential role of lncRNAs in determining the response to standard chemotherapy (Elsayed et al. 2020). These studies have emphasized the role of aberrant lncRNA expression in chemoresistance (Heery et al. 2017; Gao et al. 2019b).

Specific lncRNAs associated with a particular type of cancer require validation in a large cohort of patients. Identifying the cellular localization of lncRNAs is crucial for identifying strategies to inhibit their function. Furthermore, computational approaches to determine the lncRNA function are complicated due to their tissue specificity, low expression levels, and interactions with various molecular components (as reviewed by (Chowdhary et al. 2021)).

Currently, only a few lncRNAs have been thoroughly studied to understand their mechanism of action. Due to the variability of lncRNA levels between different individuals as well as tissues, determining consistent lncRNA markers is challenging. Compared to other RNA molecules, lncRNAs are less stable. Therefore, appropriate methods for sample collection, processing, storage, and assessment are crucial. Despite the therapeutic potential of lncRNAs, developing

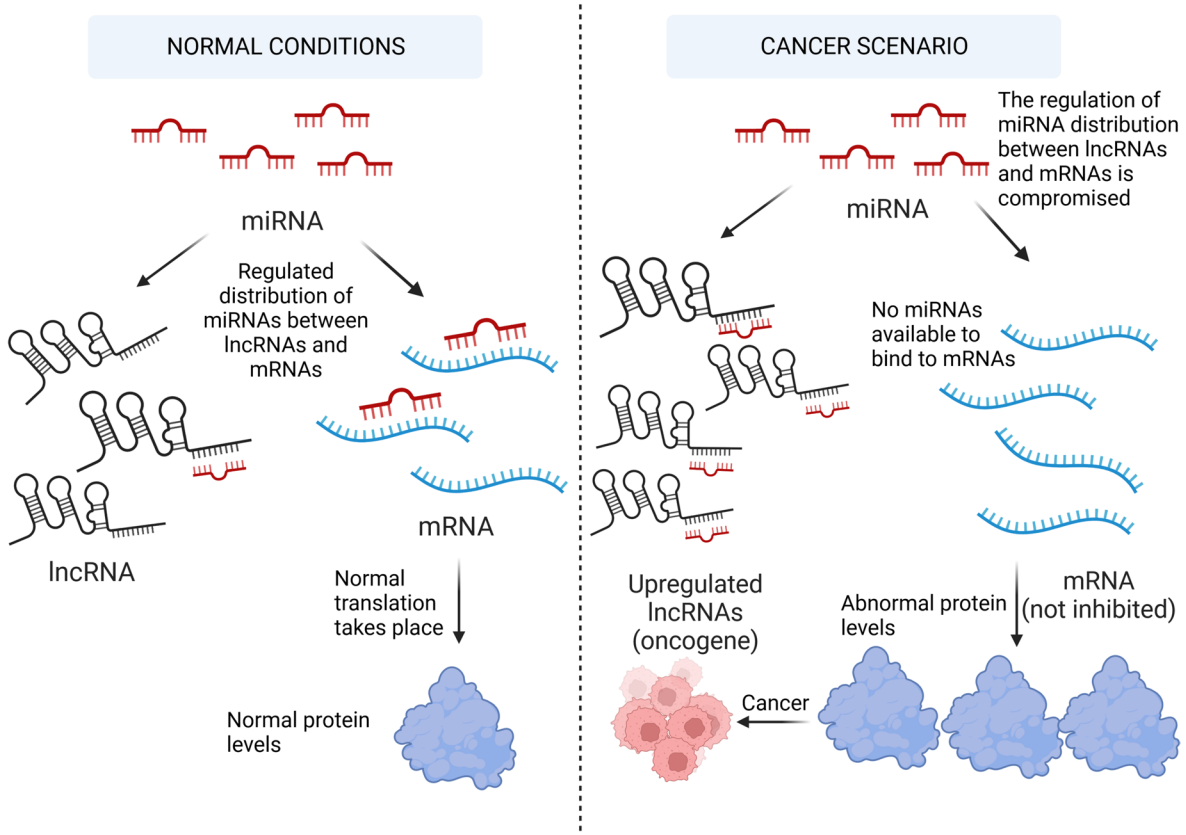

Fig. 2 Competing endogenous RNA network. Created with BioRender.com

Table 2 Examples of ceRNA network comprising lncRNA, miRNA and mRNA in OC

lncRNA/miRNA	Target mRNA	Role in OC progression	References
HOTAIR/miR-373	Rab22a	Elevated levels of *HOTAIR* sponges *miR-373* resulting in the over expression of Rab22a and promoting metastasis	(Zhang et al. 2016b)
HOTAIR/miR-206	CCND1 and CCND2	Elevated levels of *HOTAIR* results in the sponging of miR-206, thereby elevating CCND1 and CCND2, thereby promoting proliferation, cell cycle progression, migration and invasion	(Chang et al. 2018)
DANCR/miR-145	VEGF	Elevated levels of *DANCR* results in the sponging of *miR-145*, thereby elevating VEGF and promoting angiogenesis	(Lin et al. 2019)
ANRIL/let-7a	HMGA2	Elevated levels of *ANRIL* results in the sponging of *let-7a*, thereby elevating HMGA2 and promoting cisplatin resistance	(Miao et al. 2019)
UCA1/miR-485-5p	MMP14	Upregulation of *UCA1* in OC, which functions as a sponge for *miR-485-5p* and promotes over expression of MMP14, thereby leads to metastasis	(Yang et al. 2016, p. 1)

small molecule drugs to target them poses challenges (Jin et al. 2021).

Silencing of *ACTA2-AS1* was found to revert cisplatin resistance by sponging *miR-378-3p* and regulating Wnt5a level (Lin et al. 2022). Similarly, the lncRNA *UCA1* was upregulated in chemoresistant OC cell line as compared to its sensitive counterpart, and silencing *UCA1* reverted the resistance to cisplatin through the ceRNA network involving *miR-27a-5p*. Furthermore, downregulating *UCA1* resulted in lower levels of the *miR-27a-5p* target *UBE2N*, which promoted higher expression of pro-apoptotic protein BIM (Wambecke et al. 2021). Several lncRNAs have been found to regulate chemoresistance by modulating various cancer-related cascades. For example, the lncRNA *HOTAIR* promoted chemoresistance in multiple myeloma to dexamethasone by modulating the JAK/STAT3 pathway (Guan et al. 2019). Similarly, the Myc target lncRNA *LINC00839* enhances chemoresistance in breast cancer through the

PI3K/AKT signaling cascade (Chen et al. 2020). In colorectal cancer, the lncRNA *LINC00689* acts as a tumor suppressor, inhibiting cell metastasis, proliferation, and chemoresistance by upregulating *LATS2* expression and suppressing YAP/ β-catenin levels (Du et al. 2020).

Understanding the mechanism of action of lncRNAs on tumorigenic properties and their ability to serve as biomarkers for determining chemotherapy efficiency is essential (Peng et al. 2020). Dysregulated lncRNAs can induce chemotherapeutic resistance by inhibiting cell death, inducing protective autophagy, epithelial-mesenchymal transition, promoting cell proliferation, and dysregulating glycolysis (Li et al. 2021a). A conserved cellular mechanism through which cells degrade impaired cytoplasmic components utilizing the lysosomal compartments to uphold energy equilibrium is known as autophagy. Recent studies have revealed that autophagy contributes to the development of cisplatin resistance in cancer (Elsayed et al. 2020). In OC, the lncRNA Taurine up-regulated 1 (*TUG1*) promoted autophagy by sequestering *miR-29b-3p,* leading to chemoresistance. Silencing *TUG1* reduces Beclin-1 levels and impairs the conversion of LC3B-I to LC3B-II, thereby affecting paclitaxel sensitivity (Gu et al. 2020).

Another mechanism of chemoresistance employed by lncRNAs is DNA damage repair, which involves interconnected signaling cascades coordinating the repair of DNA damage to prevent detrimental genetic changes. This network includes NF-KB, the tumor suppressor, gene TP53, and p21. However, in cancer, DNA damage repair protects cancer cells from the effects of chemotherapy, promoting cell survival (Elsayed et al. 2020). In OC, the lncRNA *HOTAIR* is over expressed in recurrent platinum-resistance OC samples compared to primary OC samples, and it initiates DNA damage repair following platinum treatment (Özeş et al. 2016).

Previously, the lncRNA *CTSLP8* was found to be overexpressed in chemo-resistant OC samples, promoting cell proliferation and cisplatin resistance. Moreover, *CTSLP8* enhances chemoresistance by facilitating the interaction of PKM2 with the c-myc promoter, thereby promoting its expression and contributing to glycolysis (Li et al. 2022). Some other examples of drug resistance mechanism involving lncRNAs is described in Table 3

One of the areas of cancer research gaining wide attention is re-sensitizing cancer cells to drug for overcoming chemoresistance. In glioblastoma, the lncRNA *SNHG12* was over expressed in temozolomide resistant cells and tissues, and silencing the lncRNA reversed the resistance implying its role as a therapeutic target (Lu et al. 2020). In cisplatin resistant gastric cancer cells, the lncRNA *CRAL* was downregulated which led to cisplatin resistance observed to the gastric cancer cells to cisplatin. *CRAL* reversed the chemoresistance via the ceRNA network involving miR505/ cylindromatosis/ AKT (Wang et al. 2020c). Another lncRNA, *PGM5-AS1* was downregulated in oxaliplatin resistant colorectal cancer tissues and cell lines. Further, *PGM5-AS1* had tumor suppressive function as it inhibited cell migration, proliferation and acquired resistance to oxaliplatin in colon cancer cells. Engineered exosomes for simultaneous delivery of oxaliplatin and *PGM5-AS1* re-sensitized the colon cancer cells to the drug (Hui et al. 2022).

lncRNAs in extracellular milieu

Recently, extracellular vesicles, such as exosomes, have been identified as messengers responsible for cell-to-cell communication (Dragomir et al. 2018). The human lncRNA database available at https://bigd.big.ac.cn/lncbook/index, indicates that a substantial number (~80,000) of the lncRNAs have been associated with exosomes.

The shift towards investigating the function of lncRNAs in exosomes highlights their importance in cancer onset and progression. In a study, sequencing of human plasma-derived exosomal RNA sequences revealed that miRNAs constituted the major component of exosomal RNA (42.32%), while lncRNAs accounted for only 3.36% of the total RNAs (Huang et al. 2013). However, lncRNAs were primarily encapsulated and protected within the exosomes (Li et al. 2015b). Clinical trials (***NCT03738319***) are underway to identify and validate lncRNAs as biomarkers in OC.

Several exosomal lncRNAs have been identified to play a crucial function in OC pathogenesis. For instance, exosomal lncRNA *ATB* contributed to OC development through the modulation of miR-204-3p and TGFβ2 (Yuan et al. 2022). Similarly, another study reported higher expression of *SOX2-OT* in the plasma exosomes derived from OC patients.

Table 3 Examples of lncRNA related drug resistance mechanism in OC

Mechanism of action	Examples
Drug efflux pump	*UCA1* promotes paclitaxel resistance through the modulation of ABCB1 expression via sponging *miR-129* (Wang et al. 2018)
Apoptosis related	*UCA1* promotes cisplatin resistance through the up regulation of Bcl2 and downregulation of Bax, caspase-3, and caspase-9 (Wang et al. 2015)
EMT related	*NEAT1* promoted PTX resistance by activating EMT (An et al. 2017)

Furthermore, exosomal *SOX2-OT* promoted proliferation and inhibited apoptosis in OC cells, implying its role as a therapeutic target (Lai et al. 2021).

Approaches to elucidate lncRNA function

Despite lncRNAs constituting the majority of RNA transcripts, their functional roles are not fully elucidated. This could be due to the lack of efficient tools for the functional characterization of lncRNAs (Awwad 2019). Currently, RNAi involving siRNA and antisense oligonucleotides (ASO), along with CRISPR/Cas9 system, are being used for the functional analysis of lncRNAs (Qian et al. 2020), with RNAi being the most commonly used strategy (Fathi Dizaji 2020). To date, only ~ 5% of lncRNAs have been functionally characterized. Gapmers, synthetic antisense oligonucleotides, have been described as one of the most useful approaches to analyzing nuclear-enriched lncRNAs (Maruyama and Yokota 2020).

lncRNAs as diagnostic and prognostic markers in OC

Currently, the majority of tumor markers are proteins, despite only 2% of the human genome coding for proteins. However, with the identification of over 102,000 lncRNAs, cancer treatment based on lncRNAs shows promise as a tool (Zhao et al. 2016; Cuykendall et al. 2017). Furthermore, the functional characterization of lncRNAs has revealed their great potential as biomarkers. Identifying circulating lncRNAs in bodily fluids could differentiate cancer patients from healthy individuals at early stages and serve as prognostic factors for cancer patients (Shi et al. 2016). Pathological examination of tissues derived from cancer is currently the standard for cancer diagnosis. However, liquid biopsies characterizing cancer-derived components in the blood and other body fluids provide a new direction for cancer research and are increasingly exploited for cancer detection (Trinidad et al. 2020). LncRNAs, with their presence in bodily fluids, tissue-specific expression, and involvement in various aspects of cancer progression, can be extracted through non-invasive means and used as diagnostic and prognostic markers (Qian et al. 2020). Currently, PCA3 is the only FDA-approved lncRNA for clinical use as a biomarker in prostate cancer (Groskopf et al. 2006).

MALAT1 has been identified as a potential biomarker for ovarian tumorigenesis and metastasis, as its higher expression promotes cell proliferation, migration, and invasion (Liu et al. 2013; Zhou et al. 2016, p. 1). Similarly, *UCA1* has an oncogenic function in EOC, promoting cell proliferation, invasion, metastasis, and drug resistance (Liu et al. 2013). Elevated *UCA1* expression is an independent poor prognostic marker, and its levels in EOC reflect the response to chemotherapy (Liu et al. 2013). *UCA1* serves as a sponge for *miR-485-5p*, upregulating *MMP14* expression and leading to metastasis (Yang et al. 2016).

The lncRNA *Growth-arrest-specific 5* (*GAS5*) has a tumorigenic role in EOC, and its reduced expression indicates a poor prognosis. *GAS5* suppresses tumorigenesis by inducing mitochondria-mediated apoptosis and disrupting the mitochondrial membrane potential. This increases cleaved caspase-3, cleaved caspase-9, BAX, and BAK levels in EOC patients, making *GAS5* a promising therapeutic target (Gao et al. 2015; Li et al. 2016a, p. 5).

Martini et al. identified four lncRNAs (*PVT1, SERTAD2-3, SOX4-1, HRCT1-1*) as prognostic markers for relapse and survival (Martini et al. 2017). The network comprising *PVT1* and *SOX4-1* included oncogenes participating in AKT, PI3K, and MAPK pathways, promoting tumor relapse in stage-I EOC patients by regulating cell proliferation and progression through the cell cycle (Martini et al. 2017). Despite the surge in the number of functionally characterized lncRNAs, only one has been approved for clinical use as a biomarker. This suggests the need for further research in this field to identify useful lncRNAs with biomarker potential.

lncRNAs as therapeutic targets

Targeting lncRNAs is a promising approach for OC therapy due to their tissue-specific expression (Wang et al. 2019b). Previous studies have suggested modulating the expression of tumor- suppressive lncRNAs as a possible therapeutic strategy for treating cancer. This can be achieved by designing vectors to promote *GAS5* expression or administering synthetic mimics of *TERRA*. Similarly, inhibiting oncogenic lncRNA is another suggested strategy to fight cancer (Gutschner and Diederichs 2012). Several different strategies can be used to target and regulate lncRNAs, such as using siRNAs against lncRNAs, preventing RNAs-protein associations, or blocking expression via inhibitors that bind to their promoter (Arun et al. 2018). The use of lncRNAs in precision medicine will be enhanced by the emergence of advanced techniques for identifying molecules expressed at low levels (Bonetti and Carninci 2017).

Database related to lncRNAs

The exponential increase in data generation, facilitated by sophisticated techniques such as next generation sequencing (NGS) and microarray, highlights the critical role of data management and analysis in advancing our understanding of biology and therapeutic interventions (Tao et al. 2017). This has led to the development of computational and bioinformatic approaches for analyzing biological information, particularly in cancer research (Mitra et al.

2013). The use of bioinformatics methods to identify differentially expressed genes holds promise for elucidating the underlying mechanisms of OC pathogenesis.

In recent years, there has been a rise in the number of new databases exclusively for lncRNA annotation and differential expression analysis reflecting their significant involvement in cancer. These databases offer valuable resources for investigating lncRNAs in OC and shed light on their roles and mechanisms of action in this disease. One such database is lnCAR, which compiles and integrates information on the functional roles of lncRNAs in cancer. This database collects data on the expression patterns of lncRNAs, their regulatory mechanisms, and their functions in cancer (Zheng et al. 2019b). Similarly, the UALCAN database provides a list of lncRNAs with potential prognostic biomarker roles in several cancer types, including OC (Chandrashekar et al. 2022). According to the LncExp database, the number of lncRNAs associated with normal tissue, organ development, exosomes, and virus infection exceeds that of mRNAs, highlighting their importance. The exoRBase 2.0 database is a comprehensive resource that enables the identification of lncRNAs enriched in extracellular vesicles. exoRBase provides information that aids in understanding the roles of lncRNAs in intercellular communication (Li et al. 2018). Several databases have been developed to facilitate access to the structural, functional, and expression data of lncRNAs, as well as their disease associations (Gong et al. 2021). Frequently accessed databases are listed in Table 4:

While some lncRNAs have been well studied, a significant portion of lncRNAs remains poorly understood. This highlights the need for the development of novel tools and databases to facilitate investigations on lncRNA. For instance, the lncRNAdb database provides details on lncRNAs, including their functions and associations with diseases. Furthermore, it also contains elaborate annotations for each lncRNA. However, it lacks efficient tools for data assessment, and its coverage of lncRNAs is limited compared to other databases (Quek et al. 2015).

On the other hand, the LNCipedia database offers more comprehensive details on annotated lncRNAs, such as their expression and structure, and provides the option to download data. However, it lacks sufficient tools for data analysis (Volders et al. 2019).

The TCGA database contains RNA sequencing data on lncRNA expression in various cancer types. It also allows for the integration of patient's clinical data with the lncRNA expression. However, utilizing the database effectively requires expertise in analyzing the information and employing bioinformatic tools for detailed exploration.

The Atlas of Noncoding RNAs in Cancer (TANRIC) database provides detailed information on the lncRNA expression and survival outcomes (Li et al. 2015a). However, it focuses exclusively on lncRNAs involved in cancer.

Challenges in lncRNA research

There are several challenges that need to be overcome to incorporate lncRNAs into clinical practice. In order to explore the use of circulating lncRNAs in clinical settings for quantification, it is important to consider critical factors such as the source, primer design, quantitative Real Time PCR (qRT-PCR) procedure, timing of blood sample collection (Gonzalo-Calvo et al. 2022). Moreover standardized procedure for detection and analysis is needed for reproducibility and reliability in the results. Other challenges that need to be addressed for translating lncRNAs into the clinical realm includes comprehensive characterization of the role of lncRNAs in cellular processes, and determining lncRNAs

Table 4 LncRNA related databases

Database	Description	References
NONCODE	Provides location, sequence, source of the lncRNA along with the expression. It has annotations of 173,112 human lncRNAs and elaborates lncRNA-cancer relationships	(Zhao et al. 2016; Fang et al. 2018)
LNCipedia	Provides annotated lncRNA transcripts, protein-coding potential, secondary structure information and microRNA (miRNA) binding sites. It has 56,946 lncRNA genes and 127,802 lncRNA transcripts	(Volders et al. 2019)
Diana-LncBase	It contains information on 200,000 lncRNA-miRNA interactions	(Karagkouni et al. 2020)
LnCeVar	It has information on the genomic variations in lncRNAs such as somatic mutations, copy number variations and SNPs	(Wang et al. 2020b)
lncRNAdb	Provides lncRNA annotations as well as its functions such as gene expression, association with disease, and sequence details	(Quek et al. 2015)
LncRNADisease	Provides information on disease related lncRNA in addition to its name, position, and sequence	(Bao et al. 2019)
Starbase v2.0	Determines lncRNAs according to miRNA-lncRNA interaction, and ceRNA regulatory molecules	(Li et al. 2014)
Lnc2Cancer	Provides an association between lncRNAs and cancer	(Gao et al. 2019c)

specific for a certain cancer type, which requires validation in a large cohort of patients. Identification of the localization of lncRNA in the cell is crucial for identifying strategy to inhibit the lncRNA function. Furthermore, the identification of lncRNA function through computational approaches is complicated since lncRNAs display tissue specificity, low expression levels, and interactions with several different molecular components (as reviewed in (Chowdhary et al. 2021)). Identifying lncRNAs that are specific to particular cancer types necessitate validation in large cohorts of patients. This is a crucial process to confirm the association of specific lncRNAs with certain cancer types and understanding their potential as diagnostic or prognostic markers.

Furthermore, determining the subcellular localization of lncRNAs is vital for developing strategies to inhibit their function. The identification of lncRNA function through computational approaches is challenging due to the tissue specificity, low expression levels, and interactions with several different molecular components (as reviewed in (Chowdhary et al. 2021)).

Currently, only limited number of lncRNAs have been extensively investigated to elucidate their functional mechanisms. The variability of lncRNA levels across individuals and tissues poses challenges in identifying consistent lncRNA markers. Furthermore, lncRNAs exhibit lower stability compared to other RNA molecules, underscoring the importance of employing appropriate methods for sample collection, processing, storage, and assessment.

Despite the therapeutic potential of lncRNAs, the development of small molecule drugs targeting them presents significant challenges (Jin et al. 2021).

Conclusion and future perspectives

LncRNAs have emerged as crucial regulators in the pathogenesis of OC, holding promising potential as new diagnostic and prognostic markers. These ncRNAs regulate various cellular processes, including cell proliferation, migration, invasion, and drug resistance. Despite significant progress in understanding their roles in OC, clinical applications of lncRNAs are still limited. Future research should focus on identifying the signaling pathways regulated by lncRNAs, elaborating their mechanism of action, and identifying potential therapeutic targets in OC. Standardization of protocols for lncRNA detection and quantification, along with the use of computational approaches for lncRNA annotation, will facilitate the translation of lncRNAs into clinical practice for the diagnosis, prognosis, and treatment of OC. With continued research and development, lncRNAs hold great promise for improving the clinical management of OC and other cancers.

While molecular biology techniques such as NGS have advanced the characterization of lncRNAs, the identification and validation of these transcripts still require significant time and resources through experimental approaches. To complement existing experimental methods, computational approaches for lncRNA annotation have been proposed (Baek et al. 2018).

In conclusion, future research is necessary to elucidate the signaling pathways regulated by lncRNAs, elaborate their roles in cancer development and identify promising therapeutic targets for various cancer types. Further efforts are required to unravel the molecular mechanisms underlying the action of lncRNAs by identifying their RNA, DNA, and protein partners in cancer (Gutschner and Diederichs 2012). To utilize lncRNAs as cancer biomarkers and translate them into clinical practice, future studies should focus on standardizing protocols for sample preparation, identifying endogenous lncRNA controls in body fluids, optimizing lncRNA extraction techniques, and monitoring the quality of lncRNA (Shi et al. 2016).

The ability to detect lncRNAs in body fluids through noninvasive methods hold promising option to utilize lncRNAs in routine clinical settings. Moreover, the aberrant expression of lncRNAs upon drug treatment indicates their ability to modulate drug resistance, making them potential therapeutic targets. It is crucial to identify and functionally characterize lncRNAs as early-stage cancer biomarkers, as they could aid in patient stratification. By uncovering the lncRNA-mediated gene regulation network, key cancer-related processes can be elucidated. Future research is required in both science research and in the application of lncRNAs in the clinical realm. To translate the discovery of lncRNA biomarkers to clinical practice, the development of targeted therapies and diagnostic tests is essential. Clinical trials should be conducted to assess the potential use of lncRNAs as therapeutic markers. Further investigation of the molecular mechanisms of lncRNAs action and their interactions with other factors in OC is necessary. Advanced techniques such as CRISPR/Cas9 mediated knockdown or over expression studies are required to analyze the function of lncRNAs.

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