

Role of exosomal non-coding RNAs in ovarian cancer (Review)

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Abstract. Ovarian cancer (OC) is a common gynecological disease with a high mortality rate worldwide due to its insidious nature and undetectability at an early stage. The standard treatment, combining platinum-based chemotherapy with cytoreductive surgery, has suboptimal results. Therefore, early diagnosis of OC is crucial. All cell types secrete extracellular vesicles, particularly exosomes. Exosomes, which contain lipids, proteins, DNA and non-coding RNAs (ncRNAs), are novel methods of intercellular communication that participate in tumor development and progression. ncRNAs are categorized by size into long ncRNAs (lncRNAs) and small ncRNAs (sncRNAs). sncRNAs further include transfer RNAs, small nucleolar RNAs, PIWI-interacting RNAs and microRNAs (miRNAs). miRNAs inhibit protein translation and promote messenger RNA (mRNA) cleavage to suppress gene expression. By sponging downstream miRNAs, lncRNAs and circular RNAs can regulate target gene expression, thereby weakening the interactions between miRNAs and mRNAs. Exosomes and exosomal ncRNAs, commonly present in human biological fluids, are promising biomarkers for OC. The present article aimed to review the potential role of exosomal ncRNAs in the diagnosis and prognosis of OC by summarizing the characteristics, processes, roles and isolation methods of exosomes and exosomal ncRNAs.

3. Exosomal ncRNAs
4. Relationship between the tumor microenvironment (TME) and exosomes
5. Discussion
6. Conclusion

1. Introduction

Gynecological cancers are common, and ovarian cancer (OC) is the deadliest due to difficulties diagnosing this disease in the early stages. Specifically, 70-90% of patients with OC are diagnosed at an advanced stage, indicating that the cancer has already spread (1). In 2018, there were ~300,000 reported cases of OC worldwide, with ~18,000 fatalities (2). Epithelial ovarian tumors have the highest incidence, whereas germ cell and sex cord-stromal OC account for ~5% of cases (3). At present, ovarian epithelial tumors are classified into four subtypes with identical pathologies: Serous, endometrioid, mucinous and clear cell (3). These tumors can be classified as either type I or II based on the malignancy. Type II tumors are more aggressive and have poorer survival outcomes compared with type I (4). High-grade serous cancers, a subtype of type II, are the most frequent and account for 80% of OC-related deaths (5,6). Platinum-based chemotherapy and cytoreductive surgery are the primary clinical treatments for OC. However, this treatment strategy is less effective for advanced OC as the lesions are difficult to remove completely, and advanced OC tends to be drug-resistant. Therefore, early diagnosis and targeted medicine are crucial for the effective treatment of OC.

At present, tissue biopsy is the most common method for cancer diagnosis, but it is invasive and time-consuming. Additionally, biopsies carry risks such as tumor implantation and metastasis, making them unsuitable for long-term monitoring (7,8). Thus, novel and sensitive biomarkers are needed for the early and quick diagnosis of cancer. All cell types secrete extracellular vesicles (EVs), particularly exosomes, which transport various cargoes such as lipids, proteins, DNA and most non-coding RNAs (ncRNAs), including circular RNA (circRNA), long ncRNA (lncRNA) and microRNA (miRNA). Exosomes can exchange signals and materials between different cells by carrying and transporting these cargoes (9). Given that exosomes collect, transport and release cargo, they can be considered new targets in OC diagnosis and treatment.

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1. Introduction
2. Exosomes

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Cancer is a genetic disease primarily caused by mutations in the non-coding genome (10). Previous genomic studies have indicated that the non-coding regions of RNA are extensively transcribed (11). The Human Genome Project has demonstrated that 1.5% of the human genome consists of genes that encode proteins; the rest are transcribed without translation into proteins (12,13). The two subtypes of ncRNAs are distinguished based on their size: lncRNA and small ncRNA (sncRNA). sncRNAs can be further classified into miRNA, transfer RNA, PIWI-interacting RNA and small nucleolar RNA (14). Particularly, miRNAs inhibit protein translation and promote messenger RNA (mRNA) cleavage to suppress gene expression (15). Furthermore, miRNAs can migrate into biological fluids (16) and ~10% of circulating miRNAs are secreted via exosomes (17,18). lncRNAs, which are transcripts of >200 nucleotides with potential non-coding functions, exhibit tissue- or cancer-type specificity (19). Serving as readouts of running cellular programs or signals of certain cellular states, lncRNAs can be used to distinguish various cellular pathologies, provide a predictive value or even used to choose appropriate therapeutics for patients with cancer (20). For instance, the circulating lncRNA-GC1, derived from EVs, serves as an early indicator of neoadjuvant chemotherapy (neoCT) effectiveness and is correlated with improved survival outcomes in patients with gastric cancer undergoing neoCT treatment (21). Serum exosomal lncRNA-UCA1, initially discovered in human bladder cancer, can serve as a potential non-invasive biomarker for the diagnosis of bladder cancer. circRNAs are closed RNAs without 5' or 3' ends and are classified into natural or synthetic circRNAs (22). In a number of tissues, endogenous circRNAs are involved in various biological functions such as gene transcription, protein translation, cell division, immune system dysregulation and tumorigenesis (23).

In summary, ncRNAs in exosomes are involved in numerous biological functions, including gene expression and disease development, making them valuable diagnostic tools in clinical settings. The present review summarizes the features, isolation techniques, functions and mechanisms of exosomes and exosomal ncRNAs and predicts their potential in diagnosing and prognosing OC.

2. Exosomes

Characteristics and main isolation techniques of exosomes. Exosomes can be isolated using several methods, such as ultrafiltration, size exclusion chromatography and density gradient ultracentrifugation. Most cells secrete EVs, first reported in 1985 (24). Exosomes are nanoparticles that facilitate cellular waste disposal into the extracellular environment. Increasing evidence suggests that exosomes participate in various physiological and disease-related processes, serving as biomarkers for several diseases (25-27). Extracting exosomes is crucial for understanding their characteristics and functions. Numerous techniques have been developed to separate exosomes based on their main features, such as surface proteins, size, shape and density (Fig. 1 and Table I).

Exosomes in liquid biopsies for cancer diagnosis. Tissue biopsy is currently the gold standard for cancer diagnosis, but it

has limitations. First, tissue biopsy only provides a snapshot of the tumor tissue, possibly neglecting tumor heterogeneity and the different processes and changes that occur during interactions with the immune system and other systems. Additionally, tissue biopsy requires time to detect cancer, thus delaying further therapeutic decisions. Tissue biopsy also cannot show whether a patient responds favorably to current treatment and is impractical for frequent sample collection (28). With the development of science and technology, liquid biopsy is regarded as a non-invasive, real-time, tumor-specific method that can track the advancement and recurrence of cancer and the response to treatment interventions (29). Assessing serum from patients for human epididymis protein 4, carbohydrate antigen-125 (CA-125) and p53 levels is one way to detect and monitor OC progression or the response to treatment (30). However, these methods lacked specificity and sensitivity. Therefore, a novel approach is required to accurately predict, diagnose and determine the prognosis of OC (14). Exosomes are among the most important biological components of liquid biopsy and possess a number of advantages over tumor-educated platelets (TEPs), circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs). For instance, exosomes display exceptional stability within biological fluids, including plasma and urine (31). The immune conditions of the patient and different treatments can affect the RNA content of TEPs. Additionally, both CTCs and ctDNA have brief half-lives and are unstable, making sample collection challenging (32,33).

3. Exosomal ncRNAs

The term 'liquid biopsy' was first proposed in 2010 when researchers used CTCs to enhance breast cancer treatment and prognosis (34). Initially, the use of liquid biopsies focused on identifying CTCs and ctDNA in patients with cancer. However, components of CTCs and ctDNA are scarce in circulating biofluids, making them inappropriate for use as clinical diagnostic biomarkers. Conversely, other molecules secreted from cancer cells (such as ncRNAs) are more abundant than CTCs or ctDNA and are relatively stable in circulating biofluids (35). In recent decades, exosomes have been used to develop novel biomarkers, a primary goal of translational research (26,27). Exosomes are abundant and widely distributed in human bodily fluids, such as serum, saliva and urine. Exosomes carry various biomolecules, including proteins, lipids and nucleic acids, from their parent cells, making them accessible and potential biomarkers for tumor diagnosis, prognosis and monitoring (36). Additionally, exosomes are crucial for tumor development, spread and therapy resistance, particularly chemotherapy, by transferring their contents (37). ncRNAs are pivotal exosome components; exosomal ncRNAs, including miRNAs, lncRNAs and circRNAs are specific biomarkers for cancer diagnosis, prognosis, prediction and monitoring (38). With the advancements in transcriptomic analysis, ncRNAs have been shown to affect and participate in various aspects of OC (39), including cancer progression, metastasis and drug resistance (40).

miRNAs

Characteristics and biological functions of miRNAs. In 1993, Lee *et al* (41) first reported on miRNAs while investigating the

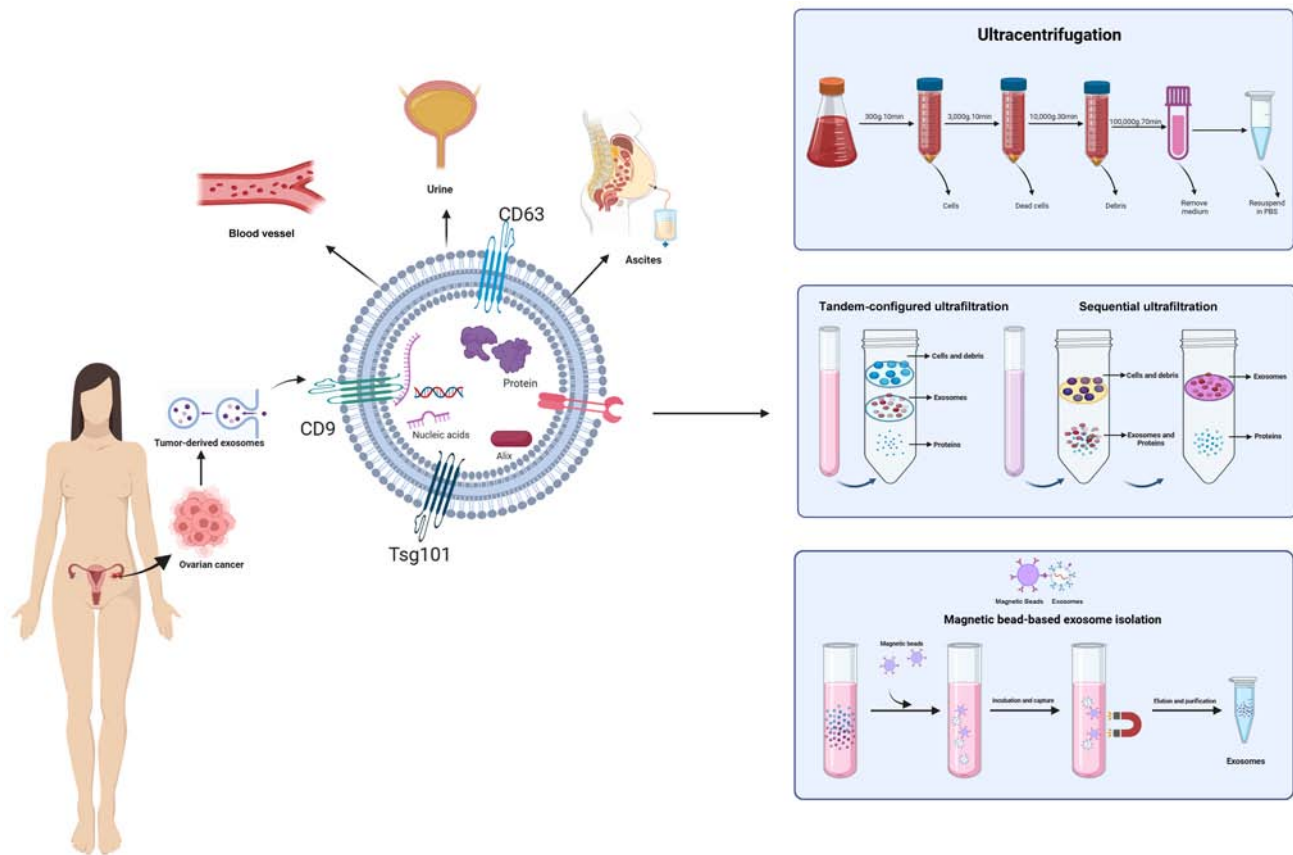


Figure 1. Most cells can secrete extracellular vesicles, which are widely distributed in the human body. Common methods for isolating exosomes include ultracentrifugation, ultrafiltration, magnetic bead-based exosome isolation. The figure was adapted from 'Main isolation techniques of exosomes', by BioRender.com (January 5th, 2024). Retrieved from <https://app.biorender.com/biorend-plates>. Tsg101, tumor susceptibility 101.

developmental timing of *Caenorhabditis elegans*. miRNAs are stable RNA forms found in a number of body fluids, such as blood, urine and saliva (42). There are two types of extracellular miRNAs in biological fluids: One that departs through vesicles, such as apoptotic bodies, microvesicles and exosomes, while the other is attached to proteins, particularly argonaute 2 (AGO2) (43). At present, miRNAs are the most researched ncRNA, which may inform liquid biopsies one day.

The length of a single-stranded miRNA is 18-25 nucleotides (44), and some miRNAs might be protected against degradation by ribonucleases via the microRNA-induced silencing complex (miRISC) (45). There are two RNase III proteins, Drosha and Dicer, which produce miRNAs. The biogenesis of miRNAs is regulated at various levels, including transcription, Drosha and Dicer processing in the nucleus and cytoplasm, RNA editing, methylation, uridylation, adenylation, AGO loading and RNA decay (46). miRNA biogenesis occurs via two pathways: The canonical pathway, which is dominant, and the non-canonical pathway (43). Synthesis of the first miRNA (pri-miRNA) transcript initiates the canonical biogenesis pathway. Drosha and DiGeorge syndrome critical region 8 are components of the microprocessor complex that processes primary miRNA transcripts (47). The cleavage of pri-miRNA by the microprocessor complex generates the precursor-miRNA (pre-miRNA). Subsequently, pre-miRNAs are transferred to the cytoplasm by the exportin 5/RanGTP complex, where they are converted into mature miRNA

duplexes (48). To create a miRISC, the mature miRNA duplex, with either a 5p or 3p strand, is combined with a member of the AGO family (49). miRNAs typically bind to a complementary sequence in the 3'-untranslated region (3'-UTR) of an mRNA. The primary biological role of miRNAs is to regulate the expression of target mRNA, by inhibiting mRNA expression or via mRNA degradation (50). Furthermore, miRNAs interact with additional areas, including gene promoters, the coding sequence and the 5'-UTR (51). Further investigations are necessary to fully comprehend the functional relationship between miRNAs and their target genes. Such strategies that could be used include high-throughput sequencing, bioinformatics and computational tools, RNA immunoprecipitation sequencing, cross-linking and immunoprecipitation sequencing and chromatin isolation by RNA purification. Based on these techniques, researchers will be able to identify the precise binding sites on their targets and determine how miRNAs impact cellular processes and disease states.

In general, miRISCs induce translational inhibition by binding to target mRNA. Then, P-body (GW182) family proteins binding to AGO are recruited, providing a scaffold to recruit downstream effector proteins such as poly(A)-deadenylases, PAN2/3, and the glucose-repressible alcohol dehydrogenase transcriptional effector, carbon catabolite repression 4-negative on TATA-less (52). Ultimately, the chromatin-binding exonuclease, 5'-3' exoribonuclease 1, degrades the decapped mRNA (53,54). While most research

Table I. Different exosome isolation methods.

Method	Advantages	Disadvantages	Principle	Purity	Sample volume	(Refs.)
DUC	i) Low cost; ii) for a large volume; and iii) no other markers will be induced	i) Expensive equipment; and ii) exosomes can be destructed	Varied sedimentation coefficients of particles	Low	-	(31,32)
Density gradient ultracentrifugation	i) Higher purity than DUC; and ii) classification of exosomal subpopulations	i) Low productivity; and ii) complex operation	Localization of different particles at a specific gradient medium	-	Medium	(142)
UF	i) Low cost and ii) simple operation	i) Exosome destruction; and ii) membrane blockage	Utilization of membranes with a specific pore diameter or MWCO to separate sample particles	Medium	Medium	(143)
SSEC	i) Time efficiency; and ii) protects the integrity and biology of the exosome	i) Possibility of pollution; and ii) expensive equipment	Exosome classification according to hydrodynamic radii	-	Small	(144)
Immunoaffinity capture	i) Simple operation; and ii) selectivity	i) High cost; and ii) exosome destruction	Antigen-antibody recognition and binding	High	Small	(145)
Polymer precipitation	i) Protection of the integrity and biology of exosomes; ii) simple processing; and iii) time efficiency	Possibility of pollution	Exosomes surrounded and precipitated by polymers	Low	Small	(146)

DUC, differential ultracentrifugation; MWCO, molecular weight cut-off; SEC, size-exclusion chromatography; UF, ultrafiltration.

Table II. Summary of the miRNAs in ovarian cancer.

First author/s, year	miRNA	Expression	Pathway	(Refs.)
Mo <i>et al</i> , 2023	miR-141 (an exosomal miRNA)	Up	YAP1/GRO α /CXCRs signaling cascade	(123)
Knarr <i>et al</i> , 2020	miR-181a	Up	RB1	(147)
Wu <i>et al</i> , 2022	miR-96-5p	Up	MTSS1/Wnt signaling	(148)
Luo <i>et al</i> , 2018	miR-10a- α	Up	-	(149)
Ying <i>et al</i> , 2016	miR-222-3p (an exosomal miRNA)	Up	SOCS3/STAT3	(150)
Cappellesso <i>et al</i> , 2014	miR-21 (an exosomal miRNA)	Up	PDCD4	(151)
Meng <i>et al</i> , 2016	miR-373, miR-200a, miR-200b and miR-200c (an exosomal miRNA)	Up	-	(152)
Zavesky <i>et al</i> , 2016	miR-92a (an exosomal miRNA)	Up	-	(153)
Zhou <i>et al</i> , 2015	miRNA-30a-5p	Up	-	(154)
Hong <i>et al</i> , 2023	miR-21-5p (an exosomal miRNA)	Up	-	(155)
Zhang <i>et al</i> , 2019	miR-9	Up	BRCA1/DNAJB6/KLF4/AKT1	(156)
Li <i>et al</i> , 2023	miR-1246, miR-141-3p, miR-203a-3p and miR-429	Up	-	(157)
Yu <i>et al</i> , 2021	miR-29	Down	lncRNA H19/miR-29b/ COL1A1 axis	(158)
Liang <i>et al</i> , 2018	miR-101-3p	Down	ZEB1	(84)
Li <i>et al</i> , 2024	miR-136	Down	PIK3R1	(115)
Záveský <i>et al</i> , 2015	miR-106b	Down	-	(159)
Zhou <i>et al</i> , 2015	miR-636, miR-3170, miR-671-5p, miR-583, miR-6076, miR-3682-3p, miR-4688, miR-3646, miR-3621, miR-4497, miR-5195-3p, miR-4656, miR-5001-5p, miR-3679-5p, miR-5006-5p, miR-6087, miR-4532, miR-6510-5p, miR-4655-5p, miR-4459, miR-328, miR-4463, miR-3935, miR-3940-5p, miR-4745-5p, miR-3911, miR-4466, miR-4739, miR-638, miR-1224-5p, miR-4672, miR-6125, miR-4644, miR-197-3p, miR-6090, miR-2861 and miR-3188	Down	-	(154)

COL1A1, collagen type I α 1 chain; CXCRs, CXC chemokine receptors; DNAJB6, DnaJ heat shock protein family (Hsp40) member B6; lncRNA, long non-coding RNA; miR/miRNA, microRNA; MTSS1, MTSS I-BAR domain containing 1; PDCD4, programmed cell death 4; RB1, RB transcriptional corepressor 1; SOCS3, suppressor of cytokine signaling 3; YAP1, yes-associated protein 1; ZEB1, zinc finger E-box binding homeobox 1.

has focused on miRNAs that prevent target gene expression, other studies have revealed that certain miRNAs can increase gene expression. For instance, AGO2 and FMR1 autosomal homolog 1 are linked to certain miRNAs, such as let-7, which stimulate translation during cell cycle arrest (55).

miRNAs in OC. miRNAs are divided into two main categories based on their target genes: Tumor suppressor miRNAs and oncogenic miRNAs (56). Tumor suppressor miRNAs silence uncontrolled genetic proliferation, thereby preventing

cancer progression; tumorigenesis may occur when these miRNAs are downregulated in tumor cells (57). Oncogenic miRNAs increase oncogene expression and promote tumor development; tumorigenesis may occur when these miRNAs are upregulated in tumor cells (58).

Various miRNAs are associated with OC progression, diagnosis, prognosis and monitoring, which is summarized in Table II. miR-34a, which inhibits nearly 700 target genes, is a classical tumor suppressor (58). miR-34a can also encode

a microprotein, termed miRPEP133, through an open reading frame (ORF) in the pri-miRNA-34a. A study overexpressed miRPEP133 in the SKOV3 OC cell line, finding that it may increase apoptosis and limit cell survival (59). Numerous studies have assessed the expression of miR-1246 in various cancer cell lines using various miRNA profiling techniques. The upregulation of miR-1246 has been noted in lung and liver tissues. Compared with normal colonic mucosa, the marked upregulation of miR-1246 in colorectal cancer tissues bolsters its status as a promising biomarker and suggests a role in the pathogenic processes of colorectal cancer (60-62). OC exosomes show significant levels of oncogenic miR-1246 expression (63). Based on data from The Cancer Genome Atlas, OC cells can be sensitized to paclitaxel in patients with OC receiving anti-miR-1246 therapy and exhibiting caveolin 1 (Cav1) upregulation. Moreover, miR-1246 inhibits Cav1 by acting on platelet derived growth factor receptor β receptor, preventing cell proliferation (64). miR-221 plays both oncogenic and tumor-suppressive roles in human cancer. miR-221 is capable of suppressing the proliferation of lung cancer cells, potentially through S phase arrest (65). miR-221 is upregulated in OC tissues compared with matched normal tissues. Furthermore, patients with high miR-221 expression have shorter overall survival (OS) and disease-free survival times than those with low expression. miR-221 targets protease activating factor 1 (APAF1), which induces apoptosis via gene inhibitors (66). Expressing higher levels of APAF1 by transfecting OC cell lines with miR-221 inhibitors prevents the proliferation, migration and invasion of cancer cells *in vitro* (66). According to a previous study, miR-27b-5p expression is lower in OC cell lines and tissues than in surrounding tissues. Furthermore, the OS rate was lower in patients with low miRNA-27b-5p expression. This study also verified that C-X-C motif chemokine ligand 1 (CXCL1), which is involved in OC malignancy, is a target gene of miR-27b-5p. Additionally, reverse transcription-quantitative PCR and immunoblotting analyses showed that the CXCL1 mRNA and protein levels were decreased in A2780 and OVCAR3 cells following miR-27b-5p overexpression (67).

In total, four molecular subtypes of OC, characterized by low overall survival rates, have been identified through extensive transcriptional profiling of cancer tissues: Immunoreactive, differentiated, proliferative and mesenchymal (68,69). To further investigate the different patterns of immune cell infiltration in OC, Liu *et al* (70) utilized the expression deconvolution algorithm, CIBERSORT, to confirm the distinct infiltration of immune cells in the four subtypes. Concentrated in plasma cells, the mesenchymal subtype of high-grade serous ovarian cancer (HGSOC) can induce the mesenchymal features of OC by releasing exosomes. Exosomal miRNA profiling revealed that plasma cell-derived miR-330-3p is an essential modulator of mesenchymal identity in OC. miR-330-3p increases the transcription of junctional adhesion molecule 2 through enhancer-induced gene activation pathways (71).

lncRNAs

Characteristics and biological functions of lncRNAs. lncRNAs were first described in 1990 (72). One of the earliest known lncRNA genes, the imprinting H19 gene, encodes a 2.3-kb

ncRNA molecule, which aids in the development of a number of tumor types, including OC (72,73). Previously, lncRNAs were acknowledged as non-coding molecules. However, advances in proteomics and genetic technologies have revealed that a growing proportion of lncRNAs have small ORFs (sORFs). Certain sORFs have the ability to encode micropeptides or proteins that are essential for basic biological functions (74). Similar to miRNAs, RNA polymerase II is responsible for the conventional biosynthesis of lncRNAs. After transcription, the 5' and 3' ends of lncRNAs are independently capped and polyadenylated (75). Compared with protein coding genes, the overall sequence of lncRNAs frequently exhibits substantially lower evolutionary conservation (76).

The promoter regions of lncRNA genes are conserved, similar to those of protein-coding genes, and the production of lncRNAs controlled by these genes is tissue-specific (77). At present, different methods are used to classify lncRNAs, mainly depending on their function, interactions with protein-coding genes, structure, sequence and metabolism (78). lncRNAs can be categorized into four functional groups: Skeleton, guide, signal and bait molecules. In terms of interactions with protein-coding genes, lncRNAs fall into four categories: Overlapping, bidirectional, intron and cis-antisense (79). lncRNAs are crucial for various biological processes, including: i) Engaging with chromatin complexes to support the regulation of epigenetic genes; ii) acting as proteins or multiprotein compound modulators; iii) influencing transcriptional expression by binding proteins linked to DNA/RNA; iv) controlling the stability of DNA by forming triple helices and R-loops; and v) assisting in the creation of higher-order chromatin structures (80).

At present, RNAs are the main targets for therapeutic and diagnostic strategies. ncRNAs, for instance, show notable variety in nucleotide length and can form different structures when interacting with proteins, DNA and other substances. Notably, lncRNAs are more likely to form intricate secondary or tertiary structures due to their long nucleotide sequences. These structures, similar to enzymes, fulfill biological functions through their unique domains that show reproducibility and conservatism (81). The function of a number of proteins is determined by their distinct structural domains. However, current understanding of the structural domains that determine their functionality and define their interactome is lacking. Recently, various methods have been developed to assess the secondary structure of lncRNAs (82). These techniques are roughly divided into two types: Experimental and computational methods. Experimental techniques include enzymatic footprinting, chemical probing, nuclear magnetic resonance, small-angle scattering, atomic force microscopy and cryo-electron microscopy (81).

lncRNAs in OC. Various mechanisms have demonstrated that lncRNAs are involved in cancer progression. In the clinic, most OC cases have abdominal cavity metastases. Thus, the epithelial-to-mesenchymal transition (EMT) pathway serves a crucial role in tumor cell dissemination. The mechanisms by which lncRNAs mediate EMT in OC are diverse (83). For instance, through bioinformatics analysis, a previous study identified lncRNA pro-transition associated RNA as a lncRNA-mediated competing endogenous RNA (ceRNA) that competitively inhibits miR-101 to modulate the

Table III. Oncogenic lncRNAs in critical signaling pathways in ovarian cancer.

lncRNAs	Pathway	(Refs.)
DLEU1, HOTAIR, HOXD-AS1, LINC00511, NEAT1	p53	(160-164)
CCAT1, HOTAIR	RAS	(165,166)
CCAT1, DQ78624, EMX2OS, HAGLROS, HOTAIR, HOXD-AS1, LINC00511, MALAT1+, NEAT1, PCAT-1	PI3K/AKT/mTOR	(165-169,161,170,163,171-173)
HOTAIR, NEAT1, SCAMP1, TDRG1	NF- κ B	(174,164,175,176)
CCAT1, H19, HOTAIR, LINC00161, MIR4435-2HG, NEAT1	TGF- β	(177-180,172)
CCAT1, H19, HOTAIR, LINC00161, MALAT1+	MAPK/ERK	(177,178,166,179,181)
CCAT1, HOTAIR, LINC00511, MALAT1+, NEAT1, PCAT-1, TDRG1	JAK/STAT	(165,182,163,183,164,173,176)

JAK, Janus kinase; lncRNA, long non-coding RNA; PI3K, phosphoinositide-3-kinase.

expression of zinc finger E-box binding homeobox 1 (84). A number of patients with OC develop carboplatin resistance. Chemotherapy-resistant strategies often involve multipotent mesenchymal stem cells or an increased EMT phenotype in cancer (85,86). In a clinical study, which included 134 primary OC cases (63 treated with carboplatin, 55 treated with cisplatin and 16 without therapy), expression of the lncRNA HOX transcript antisense RNA (HOTAIR) and the corresponding DNA methylation were detected. The research showed that patients with high HOTAIR expression receiving carboplatin had significantly lower survival rates, whereas this effect was not observed in patients who did not receive carboplatin (87). To reduce transcription, HOTAIR attracts polycomb repressive complex 2 (PRC2) to certain polycomb group target (PCGT) genes, particularly in embryonic fibroblasts (88). During differentiation, PCGTs essential for the identity of specialized cells are derepressed (89,90). However, promoters of these stem cell PCGTs are methylated and repressed in cancer (91). In several cancer types, high HOTAIR expression levels are strongly associated with metastasis, cancer invasiveness and poor prognosis (88,92).

The OC process is aided by ferroptosis, an iron-dependent type of cell death. One of the predominant methods used in cancer therapy involves triggering apoptosis to eradicate malignant cells. lncRNAs can regulate ferroptosis, a process that can trigger apoptosis and may therefore be beneficial in cancer treatment (93). A recent study found that lncRNA CACNA1G antisense RNA 1 promotes ferritin heavy chain 1 synthesis by reducing ferroptosis through insulin like growth factor 2 mRNA binding protein 1-mediated N6-methyladenosine (m6A) modification, which enhances the migration and division of OC cells (94). Additionally, another study showed that lncRNA ADAMTS9 antisense RNA 1 sponges miR-587 in OC, preventing ferroptosis and enhancing the expression of solute carrier family 7 member 11 (95).

Numerous studies have shown that lncRNAs can control the expression of tumor suppressor genes to either promote or prevent new tumor growth. Leukemia inhibitory factor receptor antisense RNA1 (LIFR-AS1), a tumor suppressor gene in colorectal cancer, was found to be downregulated in serous ovarian carcinoma (SOC) in a previous study. Generally, patients with SOC and low LIFR-AS1 expression had a poor prognosis. Low LIFR-AS1 expression was also associated with

tumor size, clinical stage, lymph node metastasis and distant metastasis (96). LIFR-AS1 upregulation enhances the production of cleaved caspase-3 and E-cadherin, suppressing the malignant activities of SOC cells, including their migration, invasion and proliferation (96). lncRNAs can also repress tumor progression by regulating oncogene expression. For instance, long intergenic non-protein-coding RNA 857 (LINC00857), which inactivates the Hippo signaling pathway, can accelerate OC progression by regulating yes-associated protein 1 (YAP1), which acts as an oncogene in OC. LINC00857 competitively binds to miR-486-5p to regulate YAP1 expression, which elevates OC progression (97). A summary of the oncogenic lncRNAs in critical signaling pathways in OC is detailed in Table III.

circRNAs

Characteristics and biological functions of circRNAs. When a tumor suppressor gene exon is spliced, circRNAs join in a different order from their genomic sequences. circRNAs were first described in 1976 (98). In 2015, high-throughput technologies were used to ascertain that circRNAs were two times more abundant in EVs than in parental cells (99). Premature mRNAs, which often do not encode proteins, can be alternatively spliced to become circRNAs, which are ncRNAs. circRNAs are more stable than other linear RNAs as they form covalently closed loops without 5'- or 3'-end features (100). This structure makes circRNAs resistant to degradation by classical RNA pathways, leading to their exocytosis from cells (101-103). circRNAs were initially thought to be non-functional byproducts of splicing mistakes. However, as high-throughput technologies and bioinformatics research progress, there is a growing body of evidence indicating that they exist widely in eukaryotic cells, where they regulate miRNAs and proteins to participate in various biological processes (104,105). Moreover, these circRNAs have been found to be stable and extremely conservative (99,106). circRNA expression in tumor tissues differs from that in normal tissues, indicating their involvement in tumorigenesis (107). circRNAs originate from various genomic regions, including intergenic, intronic, antisense and untranslated regions, and are categorized into three groups based on the region from which they are derived: Intronic, exon-intron and exonic (108). circRNAs have three major biological functions (109), including: i) Controlling the expression of

Table IV. Summary of the circRNAs in ovarian cancer.

First author/s, year	circRNA	Expression	Pathway	(Refs.)
Li <i>et al</i> , 2024	circPLPP4	Up	miR-136/PIK3R1	(115)
An <i>et al</i> , 2020	circKRT7	Up	miR-29a-3p/COL1A1	(184)
Wang <i>et al</i> , 2023	circATP2B4	Up	miR-532-3p/SREBF1/PI3K α /AK	(185)
Wu <i>et al</i> , 2023	circ_0010467	Up	miR-637/LIF/STAT3	(186)
Li <i>et al</i> , 2022	circITGB6	Up	GF2BP2/FGF9/RNA-PROTEIN	(187)
Wu <i>et al</i> , 2022	circFBXO7	Down	miR-96-5p/MTSS1	(148)
Luo <i>et al</i> , 2018	circ-ITCH	Down	miR-10a- α	(149)
Zou <i>et al</i> , 2018	circLARP4	Down	-	(188)
Zhang <i>et al</i> , 2019	circPLEKHM3	Down	miR-9/BRCA1/DNAJB6/KLF4/AKT1	(156)

circRNA, circular RNA.

target genes by competitively binding to miRNAs, similar to lncRNAs, acting as sponges for miRNAs or ceRNAs (110); ii) controlling the transcription, splicing, translation and interaction of genes with RNA-binding proteins to control the expression of genes (111); and iii) serving a role in polysomes, initiating putative ORFs and the AUG codon, and encoding regulatory peptides (112).

circRNAs in OC. circRNAs are involved in the development, metastasis and carcinogenesis of numerous human disorders (113,114). For instance, in platinum-resistant OC, the expression of circPLPP4 is notably elevated. Functionally, circPLPP4 operates as a molecular sponge for miR-136, effectively sequestering it. By doing so, circPLPP4 competitively increases the expression of PIK3R1, thereby contributing to resistance against cisplatin (115). Hsa_circ_0004712 exhibits abundant regulation in both OC tissues and cellular models, and functions by specifically targeting and reducing the expression of miR-331-3p. FZD4 was identified as a downstream target of miR-331-3p, experiencing repression when miR-331-3p levels were high, yet its expression was notably enhanced in the presence of hsa_circ_0004712, illustrating a regulatory axis between the circular RNA, microRNA and target gene (116). A summary of the oncogenic circRNAs in critical signaling pathways in OC is detailed in Table IV.

4. Relationship between the tumor microenvironment (TME) and exosomes

The majority of the tumor mass consists of the TME, which is mostly composed of tumor stroma (117). Stem cells, fibroblasts, endothelial cells, immune cells and numerous other cells that produce growth factors and cytokines are found in the TME (118). EVs are essential for communication between stromal and tumor cells in both nearby and distant microenvironments. EVs support tumor growth and establish a complex microenvironment called the pre-metastatic niche (PMN). The PMN has been primed by the primary tumor in distant organs or regions free of tumors, anticipating metastasis spread (119). The characteristic features of the PMN include extracellular matrix remodeling and deposition,

lymphangiogenesis, vascular permeability, angiogenesis and immunological suppression (120).

Among the deadliest gynecological cancers, OC frequently results in peritoneal metastases, leading to higher recurrence rates and resistance to standard platinum-based treatments, which can result in a poor prognosis (121,122). Metastatic cancer cells spread to secondary sites, where they find a supportive TME owing to the biological components of the host. For instance, OC-generated EVs target YAP1, a key effector of the Hippo pathway. This interaction reduces the nuclear YAP1/transcriptional co-activator with PDZ-binding motif protein ratio and increases CXCL1 production by stromal fibroblasts. Pro-inflammatory cytokines, such as CXCL1, play a crucial role in promoting tumor development and metastasis (123). This finding indicates that pro-inflammatory CXCL1 is extensively expressed in the TME of ovarian malignancies and has oncogenic-promoting properties (123). Exosomes derived from OC that contain activating transcription factor 2 and metastasis-associated protein 1 may enhance angiogenesis (124). Tumor-secreted EVs (TEVs) are taken up by macrophages and lymphocytes in animal models, significantly decreasing the cross-presentation of tumor antigens from dendritic cells, which in turn affects CD8⁺ T cell activity (125). Another study demonstrated that TEVs expressing programmed cell death ligand 1 reduced the number of CD8⁺ T cells that invaded the lymph nodes (126). Phosphatidylserine, which impedes T-cell activation by obstructing intracellular signaling cascades, is present in some exosomes from OC (127). To counteract the immunosuppressive effects, normal cells, particularly immune cells, also produce EVs. These findings highlight the critical role of EVs in controlling the immune system. For instance, exosomes release cytokines, respond to specific antigens and mitogens, stimulate or inhibit B cell antibody production and directly kill target cells (128). Cytotoxic EVs are also released by natural killer (NK) cells. Fais *et al* (129) provided the first evidence that NK-derived EVs are lethal to cancer cells. It was shown that NK cells obtained from healthy donors, both in the resting and active states, were capable of killing a range of cancer cell lines and extending their cytotoxicity to resting immune

cells but not to activated cells. Another study has reported that NK-derived EVs exhibit characteristic protein markers that are typical of NK cells, showing a propensity to be selectively internalized by SKOV3 cells, and demonstrating cytotoxic effects against OC cells (130). FasL and perforin are expressed in NK-derived EVs. These proteins can induce target cell demise via two pathways: i) A conventional ligand/receptor engagement between the membrane-bound FasL of NK-derived EVs and the Fas receptor on the surface of the target cell and; ii) an atypical cytotoxic mechanism initiated upon the uptake of exosomes by the target cells, potentially involving the intracellular release of effector molecules, such as perforin (129).

EVs have become important mediators of immunological evasion and repression of complex interactions between tumors and normal cells. TEVs disrupt immunological functions and diminish the effectiveness of immunotherapy. Normal cells, particularly immune cells, release EVs to counteract these effects.

5. Discussion

Current clinical screening methods for OC include imaging and blood testing. Imaging techniques comprise positron emission tomography, magnetic resonance imaging, computed tomography and ultrasound screening. Serum tests primarily measure CA-125 and cancer antigen 19-9 (131). Common diagnostic methods for OC, such as pelvic examination, ultrasound screening and CA-125 measurement, lack sensitivity and specificity (132), and only 50-60% of individuals diagnosed with stage I or II OC exhibit elevated CA-125 levels (133). Therefore, the discovery of new biomarkers is urgently needed to improve detection rates. Patients with OC show specific miRNA expression patterns in exosomes (134). Thus, these patterns may serve as potential biomarkers for various cancer types, including OC. For instance, ~95 exosomal miRNAs are differentially expressed in patients with epithelial ovarian cancer (EOC) and healthy donors (135). Individuals with EOC exhibit significantly lower levels of miR-320d, miR-4479 and miR-6763-5p than healthy donors. According to a study that used receiver operating characteristic curves to assess the diagnostic efficiency of exosomal miRNAs, these three exosomal miRNAs have diagnostic potential (135). A study also reported that exosomal miR-200b and CA-125, which are used for EOC screening, are associated with OS. According to this study, miR-200b influences cell proliferation and apoptosis. Furthermore, exosomal miR-200b can distinguish patients with EOC from healthy individuals with a 64% sensitivity and 86% specificity (136). Additionally, the level of serum exosomal miR-34a can be used to differentiate patients with early-stage and advanced-stage OC, suggesting that miR-34 is a potential biomarker for OC (137).

Exosomal ncRNAs show promise as potential novel diagnostic biomarkers for OC and are currently in the preclinical stage of development. Numerous prior studies have demonstrated that exosomal ncRNAs can function as prognostic biomarkers for OC. For instance, exosomal metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been linked to more malignant tendencies and a late International Federation of Gynecology and Obstetrics stage of EOC. Based on nomogram modeling and multivariate survival analysis,

serum exosomal MALAT1 may be a potential predictive biomarker for EOC (138). Zhang *et al* (139) demonstrated that OS was associated with high levels of exosomal miR-200b. Additionally, circFoxp1 is identified as an independent factor that can predict survival and disease recurrence in individuals with EOC, according to the International Union of Obstetrics and Gynecology (140). Unlike other human cancer types, OC preferably invades the peritoneal cavity, with a particular potency at interacting with different viscera inside the compartment (121). The exosomes of the primary ovarian tumor could prime the distant TME for an expedited metastatic invasion. Within the TME, exosomes control intercellular communication between tumor cells and the normal stroma, cancer-associated fibroblasts and local immune cells.

6. Conclusion

Globally, epithelial ovarian cancer leads to >185,000 fatalities annually. HGSOC, the predominant variant, contributes to ~60% of these deaths. Despite advancements in surgical techniques and chemotherapy protocols, the mortality rate for HGSOC has remained high over the past several decades (141). The primary cause is the lack of reliable biomarkers for early diagnosis. Exosomes, which contain numerous ncRNAs, have increasingly been recognized as key players in intercellular communication. ncRNAs, including circRNAs, lncRNAs and miRNAs, are crucial for tumor development. Exosomal ncRNAs can be packaged, secreted and transported by tumor and normal cells to influence each other and complete the establishment of OC. Exosomes from OC could stimulate the establishment of PMNs by immunosuppression, angiogenesis, stromal cell modification and oncogenic reprogramming to promote tumor metastasis and growth. Although exosomes and exosomal ncRNAs are innovative indicators for the prognosis and diagnosis of OC, several issues hinder their use in clinical settings. First, only a limited quantity of exosomes is present in biological fluids. Second, there is limited knowledge about the biological functions of ncRNAs. Despite these challenges, exosomes and ncRNAs are promising biomarkers for the identification and management of OC.

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Authors' contributions

XW was responsible for writing and revising the manuscript. MY participated in the literature review and provided feedback. JZ and YZ provided substantial contributions to conception and design. GL was responsible for revising the manuscript and providing financial support. Data authentication is not

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Competing interests

The authors declare that they have no competing interests.

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