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Research Progress on Exosomes in the Diagnosis of Ovarian Cancer

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Abstract: Ovarian cancer ranks as the deadliest malignancy among female reproductive system cancers, posing a significant threat to women's health. Around seven out of ten patients are diagnosed only after reaching progressive disease phases, a phenomenon closely linked to three key factors: the disease's hidden onset location, lack of early symptoms, and absence of reliable early diagnostic methods. Therefore, identifying early diagnostic biomarkers and therapeutic targets is critical. Exosomes participate in various phases of ovarian tumorigenesis, including transforming normal cells into cancerous cells, immune regulation, invasion, metastasis, drug resistance, and angiogenesis, making them promising biomarkers for early ovarian cancer detection. This review summarizes current research on exosomal long non-coding RNAs (lncRNAs), miRNAs, and related proteins in ovarian cancer diagnosis. Exosome-based biomarkers have shown potential advantages, including high sensitivity, specificity, stability, and non-invasive accessibility. The study concludes that while exosomes hold significant diagnostic potential for ovarian cancer, additional investigations are required to standardize detection methods, validate clinical applicability, and elucidate underlying molecular mechanisms.

Keywords: Exosomes; Ovarian cancer; Biomarkers; lncRNA; miRNA; Early diagnosis

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1. Introduction

Ovarian cancer, a malignant tumor originating from ovarian epithelial, stromal, or germ cells, is characterized by poor clinical outcomes, high mortality rates, and the highest fatality rate among gynecological cancers [1]. It is highly malignant, and asymptomatic early stages often lead to late diagnosis. Notably, over 70% of cases are diagnosed at advanced stages (FIGO stage III or IV) [2]. According to the latest population-based cancer incidence data compiled by the American Cancer Society in "Cancer Statistics, 2020," the 5-year survival rate can reach 93% if patients are diagnosed at an early stage (FIGO stage I or II) [3]. However, there is currently no widely accepted, highly sensitive, and specific screening tool for early ovarian cancer detection. Diagnosis predominantly relies on nonspecific symptoms (e.g., abdominal pain, bloating), imaging techniques (e.g.,

transvaginal ultrasound), and serum biomarkers such as CA125 [4,5]. Despite its widespread clinical use, CA125 exhibits limited sensitivity and specificity in early-stage ovarian cancer, with CA125 elevation observed in only half of patients with FIGO stage I ovarian cancer. Elevated CA125 levels are also observed in other malignancies (e.g., breast, uterine, gastric, liver, and pancreatic cancers) and benign conditions (e.g., acute pelvic inflammatory disease, adenomyosis, and endometriosis), leading to frequent false positives [6]. These limitations underscore the need for more specific diagnostic, prognostic, and therapeutic biomarkers. Recent research highlights the potential of exosomes, nanoscale extracellular vesicles, as promising biomarkers for ovarian cancer. Exosomes are actively involved in ovarian cancer progression, including immune evasion, metastasis, and drug resistance. They carry molecular cargo such as long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and proteins, which reflect the biological state of tumor cells and have potential as diagnostic and prognostic biomarkers.

This paper explores the application value of exosomes in the diagnosis of ovarian cancer, particularly their potential as a novel tumor biomarker for early diagnosis of ovarian cancer. Through a systematic review and summary of the existing literature, this study focuses on the current applications of exosomal long noncoding RNA (lncRNA), microRNA (miRNA), and related proteins in the diagnosis of ovarian cancer. It analyzes their advantages in terms of sensitivity, specificity, stability, and ease of acquisition and discusses their potential for early diagnosis of ovarian cancer. The significance of this research lies in providing new ideas for the clinical diagnosis of ovarian cancer, exploring a more promising early diagnostic biomarker, and ultimately reducing the incidence and mortality rates of ovarian cancer while improving patients' survival rates and quality of life.

2. Current status of ovarian cancer

With regard to female genital tract neoplasms, ovarian cancer carries the worst case-fatality rate [7]. According to Cabasag *et al*., by 2040, the global incidence of ovarian cancer is projected to reach approximately 428,000 new cases and 307,000 deaths, with a five-year survival rate of only 20–30% for advanced-stage patients, posing a serious threat to women's health [8]. Due to its insidious onset, rapid progression, and high recurrence rate, ovarian cancer is often at an advanced stage, with approximately 70% of cases detected late, contributing to its poor prognosis [9]. The primary reasons for this dire situation are the hidden location of the disease, the absence of noticeable symptoms in early stages, and the lack of effective early diagnostic techniques. Therefore, the identification of reliable biomarkers for early detection and novel therapeutic targets is of paramount importance in improving the prognosis of ovarian cancer patients.

Current diagnostics combine symptoms, serum CA125, and imaging (e.g., transvaginal ultrasound). While CA125 is widely used, its limitations in early detection persist. Imaging methods are cost-effective but lack sensitivity and may lead to unnecessary surgeries. Given their non-invasive nature and stability, exosomes have emerged as a promising alternative, though their mechanisms require further exploration (**Table 1**).

Table 1. Current diagnostic methods and their limitations

Method	Examples	Advantages	Disadvantages
Serum biomarkers [1]	CA125, HE4, AFP	Widely accepted	Low sensitivity/specificity in early stages
Imaging [10]	Transvaginal ultrasound	Cost-effective	Limited sensitivity, high false-positive rates
Exosomes [11]	lncRNAs, miRNAs, proteins	Non-invasive, stable, accessible	Mechanisms remaining unclear, early-stage research

3. Exosomes in ovarian cancer diagnosis

Exosomal, lncRNAs, miRNAs, and proteins are broadly studied for early ovarian cancer detection [12].

3.1. Long non-coding RNAs (lncRNAs)

Long non-coding RNAs (lncRNAs) are non-coding RNA transcripts composed of more than 200 nucleotides [13]. Approximately 76% of the human genome is transcribed into lncRNAs, which are widely distributed in both the nucleus and cytoplasm [14]. Dysregulation of lncRNAs plays a critical role in tumorigenesis and is closely associated with the development of human malignancies [15]. The expression of lncRNAs differs significantly between normal and tumor tissues. These molecules can interact with DNA to regulate gene transcription or associate with RNA and proteins to modulate cellular processes such as proliferation, apoptosis, and invasion [16]. Functioning as either oncogenes or tumor suppressors, lncRNAs are key regulators of tumor initiation and progression, which highlights their potential as diagnostic and prognostic markers for multiple malignancies [17].

For instance, Yang *et al*. revealed that the expression of lncRNA HAGLROS is significantly elevated in ovarian cancer tissues than in healthy controls, highlighting its potential for early diagnosis [18]. Similarly, Gong *et al*. found that levels of MIR4435-2HG and TGF-β1 are markedly higher in ovarian cancer patients than in healthy controls [19]. Other lncRNAs, such as HOTAIR, are also upregulated in various types of ovarian cancer tissues [20]. Additionally, frequent epigenetic alterations in the Igf2/H19 domain, focal amplification of FAL1 in epithelial cancers, and elevated expression of ASAP1-IT1, FAM215A, and LINC00472 further underscore the diagnostic potential of lncRNAs in ovarian cancer [21–23]. Collectively, these studies confirm that lncRNAs are highly promising biomarkers for the early detection of ovarian cancer. However, further research is needed to validate their clinical utility and standardize detection methodologies.

3.2. MicroRNAs

MicroRNAs (miRNAs), typically 20–25 nucleotides long, represent a group of small non-protein-coding RNA molecules originating from endogenous genetic material. These molecules control gene expression after transcription mainly through base pairing with target mRNA's 3'-untranslated regions, leading to mRNA degradation or translational repression. This mechanism allows miRNAs to suppress the expression of specific proteins, making them crucial regulators of gene expression [24,25]. Numerous studies have demonstrated the significant role of exosomal miRNAs in early cancer screening. miRNAs encapsulated within exosomes exhibit enhanced stability and play pivotal roles in tumor cell proliferation, invasion, and metastasis, making them promising biomarkers for early detection.

For example, Iorio *et al*. identified miR-141, miR-200a, miR-200b, and miR-200c as significantly overexpressed miRNAs capable of distinguishing normal ovarian tissue from epithelial ovarian cancer (EOC) tissue [26]. Wang *et al*. employed quantitative real-time polymerase chain reaction (qRT-PCR) to analyze the expression of 1722 miRNAs in 15 normal ovarian tissue samples and 48 ovarian cancer samples. They identified a signature comprising 10 miRNAs, which demonstrated a sensitivity of 97% and a specificity of 92% [27]. Additionally, exosomal miR-21 is highly expressed in ovarian cancer patients, while PDCD4 expression is notably reduced [28]. miR-200c demonstrates promising biomarker characteristics for early-stage ovarian cancer diagnosis, while miR-30a-5p shows significantly elevated expression levels in liquid biopsies from ovarian cancer patients [26,29]. Furthermore, miR-205 promotes ovarian cancer metastasis by inducing angiogenesis [30]. These findings collectively underscore the potential of exosomal miRNAs as reliable biomarkers for the early diagnosis of ovarian

cancer, offering a non-invasive alternative to traditional diagnostic methods.

3.3. Proteins

Compared to exosomes derived from normal tissues, ovarian cancer exosomes exhibit significantly increased levels of certain proteins [31]. For instance, CD24 and Claudin-4 are markedly elevated in ovarian cancer exosomes [12]. Claudin-4 is also expressed at higher levels in ovarian cancer patients compared to healthy controls [32]. Heat shock protein 70 (HSP70) is highly expressed in exosomes derived from ovarian cancer cells, and small heat shock proteins are abundant in exosomes from the serum and peritoneal fluid of ovarian cancer patients, suggesting their potential as biomarkers [33,34]. A systematic analysis of these protein biomarkers may facilitate early ovarian cancer detection. Future studies should focus on validating their clinical applicability and integrating them into multi-omics diagnostic models to enhance accuracy and reliability.

4. Diagnostic value of exosomes

Exosomal biomarkers exhibit excellent sensitivity and specificity, demonstrating potential in early ovarian cancer detection. Resnick *et al*. conducted a comparative analysis of miRNA expression profiles between nine tumor samples and four normal controls utilizing the TaqMan Array Human MicroRNA platform with real-time PCR quantification. They found that miR-92, miR-93, and miR-21 could be detected even before CA-125 levels increased, indicating their diagnostic potential for early-stage serous ovarian cancer detection [35]. Elias *et al*. demonstrated through algorithmic analysis that miRNA-based neural networks achieved 100% specificity and superior sensitivity compared to CA-125 [36]. Furthermore, Ma and Li discovered that miR-205 was highly upregulated, whereas let-7f was downregulated in the peripheral blood of ovarian cancer patients, particularly in stage I cases [37]. This finding highlights the high sensitivity of this diagnostic approach, which can significantly improve the accuracy of ovarian cancer diagnosis. The unique membrane composition and structure of exosomes provide a relatively enclosed and stable microenvironment for their internal molecules, protecting them from degradation or excretion in the bloodstream. Mitchell and Pendlebury demonstrated that miRNAs in serum and plasma are resistant to ribonuclease degradation, underscoring their advantages as tumor biomarkers [38,39]. This high biological stability allows exosomal molecules to remain intact even in complex biological environments, maintaining their activity and stability over long-term storage.

More importantly, exosomes are secreted by nearly all types of normal and cancerous cells and are widely present in various biofluids, including serum, plasma, urine, saliva, sputum, pleural effusion, and ascites. Blood, in particular, contains a high and stable concentration of exosomes, making it possible to use blood-based exosome detection as a screening tool for ovarian cancer without the need for invasive tissue biopsies. Traditional biopsy methods are highly invasive and carry significant risks, whereas exosome detection offers a minimally invasive or non-invasive alternative, providing a new and safer diagnostic pathway for ovarian cancer.

5. Conclusion

Early detection plays a crucial role in reducing the mortality rate of ovarian cancer. Exosomes, which are closely associated with the development and progression of ovarian cancer, hold significant value in early diagnosis. The long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and proteins carried by exosomes serve as potential

biomarkers for early-stage identification of diseases. Although the field of biomarker research is still in its developmental stages, it is rapidly advancing. Exosome-based diagnostics present several advantages. Long non-coding RNAs (lncRNAs) exhibit high specificity and versatility, making them suitable as biomarkers for early diagnosis. MicroRNAs (miRNAs) demonstrate high sensitivity and stability, rendering them ideal for non-invasive testing and early screening. Proteins, with their significant expression variability and multifunctionality, are well-suited for detection and diagnosis using conventional techniques. These biomarkers can maintain their stability and functionality across various biological environments, exhibiting higher sensitivity and specificity compared to existing diagnostic methods. However, current research in this area has limitations. For instance, many studies involve relatively small sample sizes, and the precise mechanisms by which these biomarkers function are still not fully understood. Future research should focus on elucidating these mechanisms and validating their clinical potential through large-scale, multi-center studies. Such efforts will help establish the reliability and applicability of exosomal biomarkers in real-world clinical settings. Additionally, the combined use of multiple biomarkers, such as lncRNAs, miRNAs, and proteins, could further enhance diagnostic accuracy. This multi-marker approach may provide a more comprehensive and precise method for early ovarian cancer detection, offering new insights and strategies for improving patient outcomes.

Disclosure statement

The author declares no conflict of interest.

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