

# The Role and Applications of Exosomes in Gynecological Cancer: A Review

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## Abstract

Exosomes are phospholipid bilayer vesicles that are released by all types of cells, containing proteins, lipids, and nucleic acids such as DNAs and RNAs. Exosomes can be transferred between cells and play a variety of physiological and pathological regulatory functions. Noncoding RNAs, including micro RNAs, long noncoding RNAs, and circular RNAs, are the most studied biomolecules from exosomes and more and more studies found that noncoding RNAs play an important role in the diagnosis, prognosis, and treatment of diseases, including various types of cancer. Gynecological malignancies such as ovarian, endometrial, and cervical cancer seriously threaten women's life. Therefore, this article reviews the roles and applications of exosomes in gynecological malignancies, including the promotion or inhibition of tumor progression and regulation of tumor microenvironments, and as potential therapeutic targets for treating gynecological cancers.

## Keywords

exosome, miRNA, noncoding RNAs, gynecological cancer, endometrial cancer, ovarian cancer, cervical cancer

## Introduction

Ovarian cancer (OC), endometrial cancer (EC), and cervical cancer (CC) are the three most common gynecological malignancies<sup>1</sup>. Ovarian cancer is the fifth most frequent cause of death in women and the leading cause of death in females diagnosed with gynecological cancers, with about 313,959 new cases and 207,252 deaths worldwide in 2020<sup>2</sup>. The morbidity and mortality of EC are increasing globally, with about 417,367 new cases and 97,370 deaths worldwide in 2020<sup>3</sup>. Cervical cancer was the fourth most common cancer and the fourth leading cause of women dying from cancer, with about 604,100 new cases and 341,831 deaths worldwide in 2020<sup>3</sup>. Thus, treatments for gynecological cancer are needed urgently and extracellular vesicles (EVs), especially exosomes, are receiving more attention for treating gynecological cancers<sup>4</sup>.

Exosomes are one type of EV, ranging in diameter from 30 to 150 nm, making them the smallest nano-size EVs. Nearly all cells produce exosomes, and the cargo of exosomes can be transferred to the neighbor cells, contributing to cell–cell communication and playing important roles in biological processes, including cancer development<sup>5</sup>. Among the cargo of exosomes, miRNAs were broadly studied and showed great potential for diagnosis and prognosis markers as well as therapeutic targets and nanocarrier for treatments. Therefore, we review the research progress of exosomes in gynecological malignancies.

## Exosomes

Exosomes were first identified in platelets in 1967<sup>6</sup>. Exosomes are small vesicles with lipid bilayer membrane structure and are produced by most cells, including immune cells, stem cells, and cancer cells. Exosomes could be detected in body fluid, including plasma, serum, urine, semen, saliva, bronchial fluid, cerebral spinal fluid (CSF), breast milk, amniotic fluid, synovial fluid, tears, lymph, bile, and gastric acid<sup>7</sup>. Exosomes range in size from 30 to 150 nm and contain a variety of biomolecules such as proteins, lipids, and nucleic acids (eg, RNA, DNA)<sup>8</sup>. Exosomal vesicles form by inward budding and envelop the biomolecules, as mentioned above, into intracavity vesicles (ILVs)

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contained in the endosome and mature into multivesicular bodies (MVBs)<sup>8,9</sup>.

The CD63 along with CD9 and CD81 are considered markers for exosomes, and the functions are closely related to exosome production<sup>10</sup>. Exosomes participate in cell–cell communication, cell maintenance, and tumor progression and can be easily sampled by liquid biopsy<sup>11</sup>. Among those biomolecules, miRNAs, either promoting or inhibiting cancer, is the most studied. One miRNA can target several genes, regulating a series of biological functions and serve as a biomarker for diagnosis, prognosis, therapeutic target, and nanocarrier for cancer treatment, including gynecological cancer<sup>12</sup>.

## Noncoding RNAs

Noncoding RNAs mainly include small RNA, such as micro RNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and others<sup>13</sup>. miRNAs were first discovered in *Caenorhabditis elegans*<sup>14,15</sup>, negatively regulating complementary target genes (mRNAs). miRNAs are transcribed by RNA polymerase II as primary miRNAs (pri-miRNAs)<sup>16</sup> and processed to single hairpins termed precursor miRNAs (pre-miRNAs) by RNase III enzyme Drosha, DiGeorge critical region 8 (DGCR8), and others<sup>17</sup>, after exporting pre-miRNAs to cytoplasm and processing to double-strand RNA (dsRNA) by Dicer<sup>18</sup>. These mature miRNAs are 20 to 25 nucleotides in length and bind the Argonaute (AGO) protein, forming the RNA-induced silencing complex (RISC) and mediating gene silencing<sup>19</sup>.

Conversely, lncRNAs are commonly defined on the threshold of 200 nucleotides (nt) of the RNA length, regulating chromatin remodeling, transcriptional controlling, and post-transcriptional processing<sup>20</sup>. The cellular localization of lncRNAs decides their functions. Cytoplasmic lncRNAs regulate mRNA stability, translation, and protein phosphorylation<sup>21</sup> and nuclear lncRNAs modulate gene expressions<sup>22</sup>. Genomic localization and context of lncRNAs include intergenic lncRNAs, intronic lncRNAs, sense lncRNAs, and anti-sense lncRNAs<sup>23</sup>. Unlike mRNA and miRNAs, lncRNAs are poorly evolutionarily conserved among species<sup>24</sup>. lncRNAs may also regulate miRNA biogenesis<sup>19</sup>.

CircRNAs are the covalently linked transcripts formed by the back-splicing of mRNA<sup>25</sup>. Most circRNAs are expressed from known protein-coding genes<sup>26</sup>, including exonic circRNAs, exon–intron circRNAs (EIcircRNAs), circular intronic RNAs (ciRNAs), and mitochondria-encoded circRNAs (mecciRNAs). Except intron-containing circRNAs, most circRNAs are exported to the cytoplasm<sup>27</sup>. Many circRNAs exert important biological functions by acting as microRNA or protein inhibitors (sponges), enhancer of protein function, scaffold and recruitment for protein, and templates for translation<sup>25</sup>.

In summary, noncoding RNAs exert important biological functions and have been implicated in various diseases,

including cancer. Elevated evidence showed that noncoding RNAs were presented in exosomes and regulated the cells in tumor microenvironments (TMEs), such as tumor cells, mesenchymal stem cells (MSCs), and immune cells. Thus, we review the sources of exosomes and the functions in received cells in the TME of gynecological cancers.

## Exosomes in OC

Human epididymis protein 4 (HE4) and carbohydrate antigen-125 (CA-125) are the main application markers in diagnosing OC with lacking sensitivity and specificity. Among the OC subtypes, high-grade serous carcinoma (HGSC, type II) is the most prevalent and lethal, representing more than 70% of OC. Type I tumor includes low-grade serous, endometrioid, clear cell, and mucinous carcinomas, carrying a good prognosis except for clear cell carcinoma. About 60% of OC are diagnosed at a later stage (stage III or IV), associated with poor prognosis<sup>28,29</sup>. Therefore, improving diagnosis and prognosis biomarkers and therapeutic targets is crucial for OC. Exosomes derived from OC or other cells from TME may have great potential to become new biomarkers and therapeutic targets<sup>30</sup>.

### The Roles of Exosomes for Diagnosis and Prognosis of OC

miR-21, miR-141, miR-200a, miR-200c, miR-200b, miR-203, miR-205, and miR-214 were significantly increased in cancer cells, exosomes, and serum of OC patients (Table 1)<sup>31</sup>. miR-21, miR-100, miR-200b, and miR-320 were significantly enriched, whereas miR-16, miR-93, miR-126, and miR-223 were decreased in exosomes from the plasma of OC patients<sup>32</sup>. Exosomal miR-1260a, miR-7977, and miR-192-5p were significantly decreased in OC patients compared with healthy controls<sup>33</sup>. miRNA-1290 was significantly overexpressed in serum exosomes and tissues compared to the benign ovarian neoplasm<sup>34</sup>. Exosomal miR-21-5p, miR-29a-3p, and miR-30d-5p were overexpressed in ovarian clear cell carcinoma cells<sup>35</sup>. Ascites-derived miR-200a, miR-200b, miR-200c, and miR-1290 were overexpressed, and the high expression level of miR-200b was related to poor overall survival<sup>36</sup>. Serum exosomal miR-484 levels were significantly lower in OC patients, and the combination of miR-484 with CA-125 showed an elevated area under the curve (AUC) of 0.912 in identifying OC patients from controls<sup>37</sup>. The expression level of miR-205 in plasma exosomes was significantly higher in OC patients than in benign and control groups. The level of miR-205 was related to OC staging and lymph node metastasis<sup>38</sup>. Among seven upregulated plasma-derived exosomal miRNAs, miR-4732-5p showed great potential to be a biomarker for diagnosing OC<sup>39</sup>. Conversely, plasma exosomal miR-320d, miR-4479, and miR-6763-5p were significantly downregulated in OC patients and associated with lymph node metastasis<sup>40</sup>.

**Table 1.** Exosomes and Their Components as Biomarkers for Ovarian Cancer.

Biomarker	Trend	Type	Source	Recipient cells	Functions	Application	Ref
miR-21, miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205, miR-214	Increase	miRNA	Cancer cells/serum	—	Biomarker	Early detection in serum	31
miR-21, miR-100, miR-200b, miR-320	Increase	miRNA	Cancer cells/plasma	Cancer cells	Biomarker	Early detection in plasma	32
miR-16, miR-93, miR-126, miR-223	Decrease	miRNA	Cancer cells/plasma	Cancer cells	Biomarker	Early detection in plasma	32
miR-192-5p, miR-1260a, miR-7977	Decrease	miRNA	Plasma	—	Biomarker	Early detection	33
miR-1290	Increase	miRNA	Cancer cells/serum	—	Biomarker	Early detection	34
miR-21-5p, miR-29a-3p, miR-30d-5p	Increase	miRNA	Clear cell carcinoma	—	Biomarker	Early detection	35
miR-200a, miR-200b, miR-200c, miR-1290	Increase	miRNA	Ascites	—	Biomarker	Early detection/prognosis	36
miR-484	Decrease	miRNA	Serum	—	Biomarker	Early detection in serum	37
miR-205	Increase	miRNA	Plasma	—	Biomarker	Prognosis	38
miR-4732-5p	Increase	miRNA	Plasma	—	Biomarker	Early detection in plasma	39
miR-320d, miR-4479, miR-6763-5p	Decrease	miRNA	Plasma	—	Biomarker	Early detection in plasma	40

### The Therapeutic Application of Exosomes in OC

Exosomal miR21 from cancer-associated adipocytes (CAAs) and cancer-associated fibroblasts (CAFs) suppresses OC apoptosis and confers chemoresistance by targeting APAF1 (Table 2)<sup>41</sup>. Exosomal miR-21-5p enhanced migration, invasion, and tumor formation by targeting CDK6 and enhanced chemoresistance through PDHA1<sup>42,43</sup>. Exosomal miR-429, regulated by NF- $\kappa$ B, enhanced the chemoresistance of OC cells by targeting CASR<sup>44</sup>. Ascites-derived exosomal miR-6780b-5p promoted epithelial–mesenchymal transition (EMT) and tumor metastasis in OC cells and correlated to poor patient survival<sup>45</sup>. miR-130a was highly expressed in the exosome from drug-resistant OC cells and promoted angiogenesis<sup>46</sup>. miR-205 was overexpressed in OC tissues, and a high level of miR-205 in serum exosomes was associated with OC metastasis. Besides, exosomal miR-205 promoted angiogenesis by regulating the PTEN-AKT pathway<sup>47</sup>. miR-141-3p-containing exosome derived from OC cells promoted angiogenesis by activating the JAK/STAT3 and NF- $\kappa$ B signaling pathways<sup>48</sup>. The expression of miR-543 was significantly decreased in exosomes derived from OC cell lines, tissues, and patient serum, and overexpression of miR-543 resulted in the suppression of OC cell proliferation and tumor growth by targeting IGF2<sup>49</sup>.

CircRNA Foxo3 was significantly upregulated in OC cells and enhanced proliferation, migration, and invasion by targeting miR-422a/PLP2 axis<sup>50</sup>. Circ-PIP5K1A was highly expressed in chemoresistant OC cells. Knockdown of Circ-PIP5K1A constrained the proliferation, migration, and invasion as well as increased apoptosis and chemosensitivity in OC cells by targeting miR-942-5p/NFIB<sup>51</sup>. This phenomenon was also found in circ\_0007841/miR532-5p/NFIB<sup>52</sup>. CircRNA051239 expression was increased in tissues and plasma exosomes from OC patients and could promote proliferation, migration, and invasion of OC cells *in vitro*<sup>53</sup>. Cdr1as suppressed cisplatin resistance of OC cells via miR-1270/SCAI axis<sup>54</sup>. Exosomal circFoxp1 was significantly increased in OC patients and positively regulated the expression of CEBPG and FMNL3 through miR-22 and miR-150-3p, resulting in cisplatin resistance of OC cells<sup>55</sup>. The expression of circNFIX was significantly increased in OC cells and tissues, promoting angiogenesis via miR-518a-3p/TRIM44 and downstream JAK/STAT1 signaling<sup>56</sup>. Interestingly, CAF-derived exosomal circIFNGR2 inhibited OC cell proliferation, EMT, metastasis, and tumor growth via targeting miR-378/ST5 axis<sup>57</sup>.

Long noncoding RNA (lncRNA) MALAT1 was increased in both metastatic OC cells and their secreted exosomes, which could promote angiogenesis and tumor growth. Serum exosomal MALAT1 levels were associated with poor prognosis in OC patients<sup>58</sup>. Exosomal lncRNA ATB promoted angiogenesis and tumorigenesis of OC cells via regulating miR-204-3p/TGF $\beta$ R2 axis<sup>59</sup>. Exosomal lncRNA SOX2-OT enhanced proliferation, migration, invasion, and tumor

growth of OC cells by miR-181b-5p/SCD1 (sterol CoA desaturase 1) signaling<sup>60</sup>.

Reactive oxygen species (ROS) greatly downregulated exosomal miR-155-5p from OC cells, while neutralization of ROS by N-acetyl-L-cysteine (NAC) reversed it. NAC-derived tumor exosomes were also taken up by macrophages and further inhibited tumor growth and macrophage infiltration and promoted cytotoxic T-cell (CD8+) activation *in vitro* by targeting PD-L1<sup>61</sup>. Tumor-associated macrophages (TAMs) derived exosomal miR-29a-3p promoted proliferation and immune escape of OC cells through the FOXO3-AKT/GSK3 $\beta$  axis and enhanced expression of PD-L1<sup>62</sup>. Exosomal miR-200b promoted macrophage M2 polarization while inhibiting M1 polarization through inhibiting KLF6 and further facilitated OC cell proliferation and invasion<sup>63</sup>. CD163+ TAMs from ascites promoted migration, EMT, and chemoresistance via miR-221-3p downregulated ADAMTS6 and the downstream TGF- $\beta$ 1/EGFR-AKT signaling<sup>64</sup>. Plasma cell-derived miR-330-3p significantly increased tumor growth and metastasis of OC cells by targeting JAM2<sup>65</sup>.

The tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK)-stimulated macrophages inhibited metastasis of OC cells via exosomal shuttling of microRNA, miR-7, and inhibiting the EGFR/AKT/ERK1/2 pathway<sup>66</sup>. The expression of exosomal miR-92b-3p of OC cells was low. The exosomal miR-92b-3p functions as a suppressor of tumor-associated angiogenesis via targeting SOX4. Tumor volume and angiogenesis were inhibited by the Arg-Gly-Asp peptide-engineered exosomes (RGD-SKOV3-92b/exo) from RGD-labeled SKOV3-92b cells, a stable miR-92b-3p overexpression SKOV3 cells<sup>67</sup>. Another study showed that targeted delivery of miR-484 via RGD-modified exosomes improved vascular normalization, sensitized OC cells to chemotherapy, and prolonged the survival time of tumor-bearing mice<sup>68</sup>. Furthermore, the hybrid nanoparticles, formed by membrane fusion of engineered miR497-overexpressing exosomes and liposomes modified by the target peptide RGD, in combination with the chemotherapeutic drug triptolide (TP), were effectively enriched in the tumor areas and exerted significant anticancer activity. This combination therapy decreased the PI3K/AKT/mTOR signaling pathway, boosted reactive oxygen species (ROS) generation, and upregulated the polarization of macrophages from M2 to M1 macrophages<sup>69</sup>. Similarly, miR-21-3p, miR-125b-5p, and miR-181d-5p from hypoxic exosomes derived from OC increased the M2 macrophage population and promoted proliferation, migration, and tumor growth of OC<sup>70</sup>.

Exosomal miR-146a released by hUCMSCs contributed to hUCMSC-derived exosome-mediated chemosensitivity of OC cells mediated by LAMC2 via the PI3K/Akt signaling pathway<sup>71</sup>. hMSC-exosomes, containing high miR-18a-5p expression, suppressed OC cell proliferation, migration, invasion, chemoresistance, and tumor growth<sup>72</sup>. OC cell-secreted exosomal piR-25783 activated the TGF- $\beta$ /SMAD2/

**Table 2. Exosomes and Their Components as Therapeutic Targets for Ovarian Cancer.**

Biomarker	Trend	Type	Source	Recipient cells	Function	Mechanisms	Application	Ref
miR-21	Increase	miRNA	CAAs, CAFs	Cancer cells	Enhance chemoresistance	APAF1	Therapeutic target	41
miR-21-5p	Increase	miRNA	Cancer cells/plasma	Cancer cells	Enhance migration, invasion, tumor formation	CDK6	Early detection in plasma/ therapeutic target	42
miR-21-5p	Increase	miRNA	Cancer cells	Cancer cells	Enhance chemoresistance	PDHA1	Therapeutic target	43
miR-429	Increase	miRNA	Cancer cells	Cancer cells	Enhance chemoresistance	CASR	Therapeutic target	44
miR-6780b-5p	Increase	miRNA	Ascites	Cancer cells	Enhance EMT and metastasis	—	Therapeutic target	45
miR-130a	Increase	miRNA	Cancer cells	Endothelial cells	Enhance angiogenesis	—	Therapeutic target	46
miR-205	Increase	miRNA	Cancer cells/ serum	Endothelial cells	Biomarker/enhance angiogenesis	PTEN-AKT	Early detection in serum/ Therapeutic target	47
miR-141-3p	Increase	miRNA	Cancer cells	Endothelial cells	Enhance angiogenesis	JAK/STAT3 and NF-κB	Therapeutic target	48
miR-543	Decrease	miRNA	Cancer cells	Cancer cells	Inhibit proliferation, tumor growth	IGF2	Therapeutic target	49
CircRNA Foxo3	Increase	CircRNA	Cancer cells	Cancer cells	Enhance proliferation, migration, invasion	miR-422a/PLP2	Therapeutic target	50
circ-PIPSK1A	Increase	CircRNA	Cancer cells	Cancer cells	Enhance proliferation, migration, invasion, chemoresistance	miR-942-5p/nuclear factor 1B (NFIB)	Therapeutic target	51
circ_0007841	Increase	CircRNA	Cancer cells	Cancer cells	Enhance proliferation, migration, invasion, chemoresistance	miR532-5p/NFIB	Therapeutic target	52
CircRNA051239	Increase	CircRNA	Cancer cells/plasma	Cancer cells	Enhance proliferation, migration, invasion	—	Therapeutic target	53
Cdrlas	Decrease	CircRNA	Cancer cells/serum	Cancer cells	Suppress chemoresistance	miR-1270/SCAI	Therapeutic target	54
Circfoxp1	Increase	CircRNA	Cancer cells/serum	Cancer cells	Enhance chemoresistance	miR-22, miR-150-3p/CEBPG, FMNL3	Therapeutic target	55
circNFIX	Increase	CircRNA	Cancer cells	Endothelial cells	Enhance angiogenesis	miR-518a-3p/TRIM44	Therapeutic target	56
circIFNGR2	Increase	LncRNA	CAFs	Cancer cells	Inhibit proliferation, EMT, metastasis, tumor growth	miR-378/ST5	Therapeutic target	57
MALAT1	Increase	LncRNA	Cancer cells/serum	Cancer cells	Enhance angiogenesis, tumor growth	MALAT1	Therapeutic target	58
LncRNA ATB	Increase	LncRNA	Cancer cells	Cancer cells/ endothelial cells	Enhance angiogenesis, tumor growth	miR-204-3p/TGFβR2	Therapeutic target	59
LncRNA SOX2-OT	Increase	LncRNA	Cancer cells	Cancer cells	Enhance proliferation, migration, invasion, tumor growth	miR-181b-5p/SCD1	Therapeutic target	60
miR-155-5p	Decrease	miRNA	Cancer cells	Macrophages	Inhibit tumor growth	PD-L1	Therapeutic target	61
miR-29a-3p	Increase	miRNA	TAMs	Cancer cells	Enhance proliferation and immune escape	FOXO3-AKT/GSK3β	Therapeutic target	62
miR-200b	Increase	miRNA	Serum	Macrophages	Enhance M2 polarization, proliferation, invasion	KLF6	Therapeutic target	63
miR-221-3p	Increase	miRNA	TAMs derived from ascites	Cancer cells	Enhance migration, EMT, chemoresistance	ADAMTS6/TGF-β1/EGFR-AKT	Therapeutic target	64
miR-330-3p	Increase	miRNA	Plasma cell	Cancer cells	Enhance tumor growth, metastasis	JAM2	Therapeutic target	65
miR-7	Increase	miRNA	TWEAK-stimulated macrophages	Cancer cells	Inhibit tumor growth, metastasis	EGFR/AKT/ERK1/2	Therapeutic target/ nanocarrier	66
miR-92b-3p	Decrease	miRNA	Peptide-engineered exosomes	Cancer cells	Inhibit tumor growth, angiogenesis	SOX4	Therapeutic target/ nanocarrier	67
miR-484	Decrease	miRNA	Peptide-engineered exosomes	Cancer cells/ endothelial cells	Inhibit tumor growth, angiogenesis, chemoresistance	—	Therapeutic target/ nanocarrier	68
miR-497	—	miRNA	Peptide-engineered exosomes	Cancer cells	Inhibit tumor growth, chemoresistance	P13K/AKT/mTOR	Therapeutic target/ nanocarrier	69
miR-21-3p, miR-125b-5p, miR-181d-5p	Increase	miRNA	Hypoxic cancer cells	Cancer cells/ macrophages	Enhance proliferation, migration, tumor growth, M2 polarization,	—	Therapeutic target/ nanocarrier	70
miR-146a	Decrease	miRNA	hUCMSC	Cancer cells	Inhibit chemoresistance	LAMC2 and PI3K/Akt	Therapeutic target/ nanocarrier	71
miR-18a-5p	Decrease	miRNA	hMSC	Cancer cells	Inhibit proliferation, migration, invasion, chemoresistance, tumor growth	—	Therapeutic target/ nanocarrier	72
piR-25783	Increase	piRNA	Cancer cells	Omental fibroblasts/ cancer cells	Enhance proliferation, migration, invasion, metastasis to omentum	TGF-β/SMAD2/SMAD3	Therapeutic target	73
miR-141	Increase	miRNA	Cancer cells	Omental fibroblasts	Activated CAFs, promoted metastasis	YAP1/GROu/CXCRs	Therapeutic target	74
miR-29c-3p	Decrease	miRNA	Omental CAFs	cancer cells	Inhibit invasion, metastasis	MMP2	Therapeutic target	75
—	—	exosome	NK cells	cancer cells	Increase cytotoxicity, chemosensitivity, activate immunosuppressive microenvironment	—	Therapeutic target	76
—	—	exosome	HGSC cells	NK cells	Downregulate NKG2d, inhibit cytotoxicity	—	Therapeutic target	77

CAAs: cancer-associated adipocytes; EMT: epithelial–mesenchymal transition; CAFs: cancer-associated fibroblasts; TAMs: tumor-associated macrophages; hUCMSCs: human umbilical cord mesenchymal stem cells; hMSCs: human mesenchymal stem cells; NK cells: natural killer cells.



**Table 3.** Exosomes and Their Components as Biomarkers for Endometrial Cancer.

Biomarker	Trend	Type	Source	Recipient cells	Functions	Application	Ref
miR-15a-5p	Increase	miRNA	Plasma	—	Biomarker	Early detection in plasma	81
miR-142-3p, miR-146a-5p, miR-151a-5p	Increase	miRNA	Plasma	—	Biomarker	Early detection in plasma	82
miR-143-3p, miR-195-5p, miR-20b-5p, miR-204-5p, miR-423-3p, miR-484	Increase	miRNA	Serum	—	Biomarker	Early detection in serum	83
miR-200c-3p	Increase	miRNA	Urine	—	Biomarker	Early detection in urine	84
miR-93	Increase	miRNA	Plasma	—	Biomarker	Early detection in plasma	85
miR-205	Decrease	miRNA	Plasma	—	Biomarker	Early detection in plasma	85
miR-133a	Increase	miRNA	Cancer cells	Cancer cells, normal endometrial cells	Biomarker	Early detection	86
circ_0109046, circ_0002577	Increase	circRNA	Serum	—	Biomarker	Diagnosis in serum	87

SMAD3 pathway in omental fibroblasts and promoted the fibroblast-to-myofibroblast transition (FMT), resulting in the elevation of proliferative, migratory, and invasive properties as well as tumor implantation and growth in the omentum<sup>73</sup>. Exosomal miR-141 was highly secreted by OC cells and reprogrammed stromal fibroblasts into proinflammatory CAFs, facilitating metastatic colonization through activating YAP1/GRO $\alpha$ /CXCRs signaling<sup>74</sup>. miR-29c-3p was downregulated in omental CAFs-exosomes, and miR-29c-3p directly targeted MMP2 to suppress OC cell invasion and metastasis<sup>75</sup>.

Exosomes from NK cells, which were derived from cord blood mononuclear cells (CBMC), displayed cytotoxicity against OC cells. The NK exosomes loaded with cisplatin could sensitize drug-resistant OC cells and activate NK cells from the immunosuppressive TME. However, the detailed mechanisms are unclear<sup>76</sup>. Conversely, HGSC exosomes from patients' sera downregulated NKG2D-mediated cytotoxicity in NK cells, and NKG2D expression on NK cells was upregulated after surgery, improving the NKG2D-mediated cytotoxic response<sup>77</sup>. The studies of exosomes serving as therapeutic targets on OC accumulate fast, and the results showed that exosomes and their components have great potential for treating OC.

## Exosomes in EC

The current clinical screening of EC is based on vaginal ultrasound and biopsy of endometrial tissues lacking specificity<sup>78</sup>. There are two main types of ECs. About 80% belong to type I ECs, which mostly are well differentiated with endometrioid histology and show a high level of estrogen receptor (ER). Type II ECs are poorly differentiated with serous or clear cell histology and show an 80%~90% recurrence rate within 3 years, representing a poor prognosis<sup>79</sup>. Besides, ECs can be low-grade tumors (grades 1 and 2) carrying a better prognosis or high-grade carcinomas (grades 3) carrying an intermediate prognosis<sup>80</sup>. Thus, developing powerful biomarkers and therapeutic targets is urgent, and the source from exosomes had great potential.

## The Roles of Exosomes for Diagnosis and Prognosis of EC

miR-15a-5p was consistently upregulated in plasma-derived exosomes from EC patients. Furthermore, higher exosomal miR-15a-5p expression was associated with larger tumors, p53 expression, and muscular infiltration depth (Table 3)<sup>81</sup>. Another study proved that the expression of miR-142-3p, miR-146a-5p, and miR-151a-5p was significantly overexpressed in the plasma of EC patients<sup>82</sup>. In the serum of EC patients, miR-143-3p, miR-195-5p, miR-20b-5p, miR-204-5p, miR-423-3p, and miR-484 were significantly overexpressed<sup>83</sup>. Besides, urine-derived exosomes from EC patients showed that miR-200c-3p was significantly increased<sup>84</sup>. Increased expression of plasma exosomal miR-93 was associated with smoking, grade of tumor, FIGO stage, distance organ metastases, and overall survival (OS). In contrast, decreased expression of miR-205 was associated with smoking, lymph node involvement, FIGO stage, and OS of EC patients<sup>85</sup>. FOXL2 was significantly lower in EC tissues and associated with worse OS. Conversely, miR-133a was highly expressed in EC cells and exosomes derived from EC cells and could be taken up by normal endometrial cells<sup>86</sup>. circ\_0109046 and circ\_0002577 were highly expressed in the serum of stage III EC patients, while the functions of these two circRNAs are still unclear<sup>87</sup>.

## The Therapeutic Application of Exosomes in EC

Plasma exosomal miR-26a-5p from EC patients with lymph node metastasis (LNM) showed significantly reduced and correlated with the FIGO stage (Table 4). miR-26a-5p inhibited EC cell proliferation, migration, and invasion *in vitro* and tumor growth and lymph node metastasis *in vivo*. miR-26a-5p-silenced exosomes strongly enhanced human lymphatic endothelial cells (HLECs) lymphangiogenesis and migration ability by targeting LEF1, and miR-26a-5p-overexpressed exosomes reduced tumor growth and metastasis<sup>88</sup>. Under hypoxia conditions, miRNA-21-containing exosomes derived from EC cells promoted M2-like macrophage

**Table 4. Exosomes and Their Components as Therapeutic Targets for Endometrial Cancer.**

Biomarker	Trend	Type	Source	Recipient cells	Functions	Mechanisms	Application	Ref
miR-26a-5p	Decrease	miRNA	Plasma	Cancer cells/ HLECs	Inhibit proliferation, migration, invasion, tumor growth, lymph node metastasis	LEFI	Therapeutic target/ nanocarrier	88
miR-21	Increase	miRNA	Hypoxic cancer cells	Macrophages	Enhance M2 polarization	-	Therapeutic target/ nanocarrier	89
miR-148b	Decrease	miRNA	CAFs	Cancer cells	Inhibit invasion, metastasis	DNMT1	Therapeutic target/ nanocarrier	90
miR-320a	Decrease	miRNA	CAFs	Cancer cells	Inhibit proliferation, migration, invasion	HIF1 $\alpha$ /VEGFA	Therapeutic target/ nanocarrier	91
miR-499a-5p	Decrease	miRNA	MSCs	Cancer cells/ endothelial cells	Inhibit migration, invasion, tumor growth, angiogenesis	VAV3	Therapeutic target/ nanocarrier	92
miR-503-3p	-	miRNA	hUMSCs	Cancer cells	Migration, invasion, tumor growth	MEST	Therapeutic target/ nanocarrier	93
miR302a	-	miRNA	hUMSCs	Cancer cells	Proliferation, migration, invasion	Cyclin D1/AKT	Therapeutic target/ nanocarrier	94
miR-192-5p	Decrease	miRNA	TAMs	Cancer cells	Enhance apoptosis, inhibit EMT	IRAK1/NF- $\kappa$ B	Therapeutic target/ nanocarrier	95
lncRNA DLEU1	Increase	lncRNA	Cancer cells	Cancer cells	Enhance proliferation, migration, invasion, tumor growth	miR-381-3p/E2F3	Therapeutic target	96
lncRNA NEAT1	Increase	lncRNA	Cancer cells	Cancer cells	Enhance tumor growth	miR-26a/b-5p/STAT3/YKL-40	Therapeutic target	97
circ_0001610	Increase	circRNA	M2 macrophages	Cancer cells	Enhance radiosensitivity, tumor growth	miR-139-5p/cyclin B1	Therapeutic target	98
miR-765	Decrease	miRNA	CD45RO-CD8+ T cells	Cancer cells	Inhibit EMT, invasion, tumor growth, metastasis	ER $\beta$ /PLP2/Notch	Therapeutic target/ nanocarrier	99
tRF-20-5998LO9D	Decrease	tsRNA	Cancer cells/serum	Cancer cells	Inhibit proliferation, migration, invasion, increase apoptosis	SESN2	Therapeutic target	100

HLECs: human lymphatic endothelial cells; EMT: epithelial–mesenchymal transition.

**Table 5.** Exosomes and Their Components as Biomarkers for Cervical Cancer.

Biomarker	Trend	Type	Source	Recipient cells	Functions	Application	Ref
let-7d-3p, miR-30d-5p	Decrease	miRNA	Plasma	—	Biomarker	Early detection in plasma	104
miR-146a-5p, miR-151a-3p, miR-2110, miR-21-5p	Increase	miRNA	Plasma	—	Biomarker	Early detection in plasma	105
miR-125a-5p	Decrease	miRNA	Plasma	—	Biomarker	Early detection in plasma	106
miR-21, miR-146a	Increase	miRNA	Cervicovaginal lavage	—	Biomarker	Early detection in cervicovaginal lavage	107
HOTAIR, MALAT1	Increase	lncRNA	Cervicovaginal lavage	—	Biomarker	Early detection in cervicovaginal lavage	108
MEG3	Decrease	lncRNA	Cervicovaginal lavage	—	Biomarker	Early detection in cervicovaginal lavage	108
DLX6-AS1	Increase	lncRNA	Serum	—	Biomarker	Prognosis in serum	109
lncRNA-EXOC7	Increase	lncRNA	Serum	—	Biomarker	Prognosis in serum	110

polarization that may contribute to an immune microenvironment favoring EC progression<sup>89</sup>.

miR-148b was significantly decreased in CAFs and CAFs-derived exosomes, and exogenously transfected miR-148b CAFs-derived exosomes could suppress EC cell invasion and metastasis by targeting DNMT1<sup>90</sup>. miR-320a is poorly expressed in EC cells as well as CAFs. The direct transfer of CAF-secreted exosomal miR-320a to EC cells inhibited their proliferation, migration, and invasion by targeting HIF1 $\alpha$ -VEGFA axis<sup>91</sup>. miR-499a-5p was also downregulated in EC cells, and MSC-derived exosomes loaded with miR-499a-5p could suppress migration, invasion, tumor growth, and angiogenesis of EC cells via targeting VAV3<sup>92</sup>. Furthermore, human umbilical cord blood mesenchymal stem cells (hUMSCs)-derived exosomal miR-503-3p<sup>93</sup> and miR302a<sup>94</sup> inhibited migration, invasion, and tumor growth of EC cells by suppressing MEST, and cyclin D1-AKT axis, respectively. Upregulation of miR-192-5p in TAM-derived exosomes could significantly promote the apoptosis of EC cells and inhibit EMT via IRAK1/NF- $\kappa$ B signaling<sup>95</sup>.

lncRNA DLEU1 was highly expressed in EC cells and tissues and promoted proliferation, migration, and invasion of EC cells *in vitro* and tumor growth *in vivo* by regulating miR-381-3p-E2F3 axis<sup>96</sup>. Exosomal lncRNA NEAT1 from CAFs facilitated EC cell growth via miR-26a/b-5p-mediated STAT3/YKL-40 axis<sup>97</sup>. Exosomal circ\_0001610 derived from M2 tumor-associated macrophage reduced the radiosensitivity *in vitro* and *in vivo* by miR-139-5p-cyclin B1 axis<sup>98</sup>. miR-765 was significantly decreased in EC cells and tissues, and exosomes of CD45RO-CD8+ T cells suppressed EMT, invasion, and tumor growth, metastasis via the ER $\beta$ //PLP2/Notch axis<sup>99</sup>.

Downregulated transfer RNA-derived small RNAs (tRNA, tRF-20-S998LO9D) in both EC tissues and serum exosomes were found. Overexpression of tRF-20-S998LO9D inhibited proliferation, migration, and invasion and promoted apoptosis of EC cells via upregulating SESN2<sup>100</sup>. These results showed that exosomes and the components might serve as therapeutic targets. However, more studies are needed to elucidate the detailed mechanisms.

## Exosomes in CC

Human papillomavirus (HPV), especially the high-risk types, has been defined as a carcinogen, and the persistence of high-risk HPV (hr-HPV) infection is a necessary etiological cause of CC<sup>101</sup>. In low-resource countries, the simple and inexpensive way is to start with visual cytologic tests (pap smear test), and in high-resource situations, it starts with pap smear test and HPV tests to screen CC patients<sup>102</sup>. DNA methylation and epigenetic modification have gained attention as alternative methods for molecular diagnosis and prognosis in cervical neoplasia screening<sup>103</sup>. Combination tests, including HPV tests and DNA methylation tests, show great potential for improving the early detection and management of CC. However, most of the studies were limited to a country or cohort, and further research is needed to validate these biomarkers in larger national-wide or multicountry cohorts. Hence, the biomarkers, especially miRNAs, from exosomes show great potential because miRNAs may control multiple genes in one biological process rather than a single gene.

### The Roles of Exosomes for Diagnosis and Prognosis of CC

Plasma exosomal let-7d-3p and miR-30d-5p were significantly decreased in the cervical intraepithelial neoplasia II+ (CIN II+) group compared with the CIN I group of CC patients (Table 5)<sup>104</sup>. Plasma exosomal miR-146a-5p, miR-151a-3p, miR-2110, and miR-21-5p were upregulated in CC patients<sup>105</sup> while miR-125a-5p was downregulated<sup>106</sup>. Exosomal miR-21, miR-146a<sup>107</sup>, and lncRNA HOTAIR and MALAT1<sup>108</sup> levels were increased in the cervicovaginal lavage specimens of CC patients, while lncRNA MEG3 was decreased<sup>108</sup>. Besides, serum exosomal lncRNA DLX6-AS1 level was significantly increased in CC patients and positively associated with lymph node metastasis, FIGO stage, and shortened survival<sup>109</sup>. The expression of lncRNA-EXOC7 in serum and serum-derived exosomes in CC patients was elevated<sup>110</sup>.



### The Therapeutic Application of Exosomes in CC

Exosomal miR-223 promoted CC migration and tumor growth by upstream STAT3 and downstream TGFBR3 and HMGCS1 axis<sup>111</sup>. Exosomal miR-106a and 106b expressions were downregulated in cisplatin-resistant CC cells, and miR-106a/b overexpressing exosomes inhibited chemoresistance of CC cells by targeting SIRT1 (Table 6)<sup>112</sup>. TGF- $\beta$ 1 promoted the upregulation of exosomal miR-663b resulting in the enhancement of EMT and migration by targeting MGAT3<sup>113</sup>. Besides, exosomal miR-663b also promoted angiogenesis and tumor growth by targeting vinculin (VCL)<sup>114</sup>. miR-22 is frequently downregulated in various tumors, and miR-22 overexpressing exosomes deriving from HEK293 cells enhanced the radiosensitivity of CC cells by targeting MYCBP and hTERT<sup>115</sup>. miR-221-3p was highly expressed in CC tissues and cells. Exosomes derived from miR-221-3p mimic-transfected CC cells promoted invasion, migration, and angiogenesis of CC cells through downregulation of MAPK10<sup>116</sup> and lymphangiogenesis and lymphatic metastasis of HLECs by targeting VASH1<sup>117</sup>. miR-320a expression was decreased in CC tissues, and engineered miR-320a exosomes enhanced the chemoresistance and tumor growth by targeting MCL1<sup>118</sup>.

Exosomal miR-423-3p inhibited macrophage M2 polarization to suppress the tumor growth of CC cells<sup>119</sup>. miR-1323, which was transferred by CAFs-secreted exosomes, showed upregulation in CC cells, and downregulation of miR-1323 suppressed CC cell proliferation, migration, invasion, and increased cell radiosensitivity. By targeting poly(A)-binding protein nuclear 1 (PABPN1) and recruiting insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1), miR-1323 regulated the downstream protein glycogen synthase kinase 3 beta (GSK-3 $\beta$ ) and influenced Wnt/ $\beta$ -catenin signaling pathway<sup>120</sup>. miR-142-5p could be delivered from CSCC-secreted exosomes into HLECs and suppress and exhaust CD8+ T cells by induction of IDO expression via ARID2-DNMT1-IFN- $\gamma$  signaling. Serum exosomal level of miR-142-5p also positively correlated with the progression of CC patients<sup>121</sup>. miR-1468-5p promoted lymphatic PD-L1 upregulation and lymphangiogenesis by targeting homeobox containing 1 (HMBOX1) and activating the JAK2/STAT3 signaling<sup>122</sup>. Exosomal miR-155-5p derived from HIV-1 infected T cells enhanced proliferation, migration, and invasion of CC cells by ARID2-ERCC5-NF- $\kappa$ B axis<sup>123</sup>. LncRNA-HNF1A-AS1 enhances proliferation and tumor growth by targeting miR-34b/TUFT1 axis<sup>124</sup>. LncRNA UCA1 was overexpressed in CC cells, and it promoted proliferation, migration, invasion, and tumor growth of cancer stem cells (CSCs) by miR-122-5p/SOX2 axis<sup>125</sup>. LncRNA LINC01305 was increased in CC tumor tissues, and it promoted migration, invasion, and tumor growth of CC through interaction with KHSRP<sup>126</sup>.

lncRNA PDHB-AS was significantly downregulated in CC cells, and overexpression of PDHB-AS inhibited proliferation, invasion, EMT, and chemoresistance of CC cells. PDHB-AS targeted miR-582-5p and inactivated the Wnt/ $\beta$ -catenin pathway via regulating Wnt7b and DKK1. Human keloid fibroblasts (HKFs)-derived exosomal miR-4536-5p downregulates PDHB-AS in CC cells<sup>127</sup>. LncRNA MALAT1 was highly expressed in CC tissues, exosomes, and chemoresistant cells. LncRNA MALAT1 promoted proliferation and inhibited apoptosis of CC cells by targeting miR-370-3p. While miR-370-3p was inhibited by lncRNA MALAT1, STAT3 could be re-expressed and further bind the promoter of lncRNA MALAT1, resulting in a positive feedback regulation. On the contrary, lncRNA MALAT1 promoted the chemoresistance of CC cells through STAT3/PI3K/AKT pathway<sup>128</sup>. Lnc LRRC75A-AS1 was highly expressed in exosomes derived from M2 macrophages, inducing proliferation, migration, invasion, EMT, tumor growth, and metastasis of CC cells through downregulating miR-429 and SIX1/STAT3/MMP-9 signaling<sup>129</sup>.

Circ\_0074269 was overexpressed in chemoresistant CC samples and cells. Silencing of circ\_0074269 elevated chemosensitivity, repressed chemoresistant CC cell proliferation and migration, and induced apoptosis through regulating TUFT1 expression via sponging miR-485-5p<sup>130</sup>. Circ\_0006646 expression was elevated in CC cells and exosomes of CC patients, and its knockdown suppressed CC cell proliferation, migration, invasion, tumor growth, and metastasis through regulating RRM2 expression via sponging miR-758-3p<sup>131</sup>. Paclitaxel loading into Wharton jelly-derived mesenchymal stem cells (WJ-MSCs) exosomes, serving as nanocarrier, induced apoptosis and suppressed EMT signaling of CC cells<sup>132</sup>. Since the HPV vaccines were developed, however, inexpensive tests have been needed in developing or less developed countries. Other than HPV tests, exosomes could be great targets to approach.

### Limitation

There are some limitations of exosomal biomarkers and therapeutic targets. First, only a few studies showed the results of subtypes of OC and EC, both of them have type I and type II cancers. Different cancer cell types may have different tumor etiology and studies for identifying subtype-specific exosomal biomarkers are needed. Second, all the studies of therapeutic targets were still in the exploratory stage; the real clinical applications of exosomal therapeutic targets are needed to further elucidate, such as how to specifically target cancer cells or the TME and how the biomolecules exchange between cells. Since the TME is complex, all the studies only confirm the exosomes from one cell to another or reverse it. However, the effects of exosomes may also be from one cell to more cells, which is unknown and may cause side effects.

**Table 6. Exosomes and Their Components as Therapeutic Targets for Cervical Cancer.**

Biomarker	Trend	Type	Source	Recipient cells	Functions	Mechanisms	Application	Ref
miR-223	Increase	miRNA	Cancer cells	Cancer cells	Enhance migration, tumor growth	TGFB3/HMGS1	Therapeutic target/nanocarrier	111
miR-106a, miR-106b	Decrease	miRNA	Cancer cells	Cancer cells	Inhibit chemoresistance	SIRT1	Therapeutic target/ nanocarrier	112
miR-663b	Increase	miRNA	Cancer cells	Cancer cells	Enhance EMT, migration	MGAT3	Therapeutic target	113
miR-663b	Increase	miRNA	Cancer cells	Cancer cells/endothelial cells	Enhance tumor growth, angiogenesis	VCL	Therapeutic target	114
miR-22	Decrease	miRNA	Cancer cells	Cancer cells	Inhibit radiosensitivity	MYCBP /hTERT	Therapeutic target/nanocarrier	115
miR-221-3p	Increase	miRNA	Cancer cells	Cancer cells/endothelial cells	Enhance migration, angiogenesis	MAPK10	Therapeutic target/nanocarrier	116
miR-221-3p	Increase	miRNA	Cancer cells	HLECs	Enhance lymphangiogenesis, lymphatic metastasis	VASH1	Therapeutic target/ nanocarrier	117
miR-320a	Increase	miRNA	Cancer cells	Cancer cells	Enhance chemoresistance, tumor growth	MCL1	Therapeutic target/nanocarrier	118
miR-423-3p	Increase	miRNA	Cancer cells	Cancer cells/macrophages	Enhance M2 polarization, chemoresistance, tumor growth	—	Therapeutic target	119
miR-1323	Increase	miRNA	CAFs	Cancer cells	Enhance proliferation, migration, invasion, inhibit radiosensitivity	PABPN1/IGFBP1/GSK-3 $\beta$ /Wnt/ $\beta$ -catenin	Therapeutic target	120
miR-142-5p	Increase	miRNA	Cancer cells	Cancer cells	Suppress and exhaust CD8 <sup>+</sup> T cells	IDO/ARID2-DNMT1-IFN- $\gamma$	Diagnosis/therapeutic target	121
miR-1468-5p	Increase	miRNA	Cancer cells	HLECs	Enhance lymphangiogenesis	HMBOX1/ JAK2/STAT3	Therapeutic target	122
miR-155-5p	Increase	miRNA	Cancer cells	HLECs	Enhance proliferation, migration, invasion	ARID2/ERCC5/NF- $\kappa$ B	Therapeutic target	123
lncRNA HNF1A-AS1	Increase	lncRNA	HIV-1 infected T cells	Cancer cells	Enhance proliferation, tumor growth and inhibit apoptosis	miR-34b/TUFT1	Therapeutic target	124
lncRNA UCA1	Increase	lncRNA	Cancer cells	CSCs	Enhance proliferation, migration, invasion, tumor growth	miR-122-5p/SOX2	Therapeutic target	125
lncRNA LINCO1035	Increase	lncRNA	Cancer cells	Cancer cells	Enhance migration, invasion, tumor growth	KHSRP	Therapeutic target	126
lncRNA PDHB-AS	Decrease	lncRNA	HKF/cancer cells	Cancer cells	Inhibited proliferation, invasion, EMT, and chemoresistance	miR-582-5p/Wnt/ $\beta$ -catenin	Therapeutic target	127
lncRNA MALATI	Increase	lncRNA	Cancer cells	Cancer cells	Promoted proliferation, chemoresistance, inhibited apoptosis	STAT3/PB3K/AKT	Therapeutic target	128
lnc LRRc75A-AS1	Increase	lncRNA	M2 macrophages	Cancer cells	Promoted proliferation, migration, invasion, EMT, tumor growth, metastasis	miR-429 /SIX1/STAT3/MMP-9	Therapeutic target	129
circ_0074269	Increase	circRNA	Cancer cells	Cancer cells	Increase proliferation, migration, chemoresistance, induce apoptosis	miR-485-5p/TUFT1	Therapeutic target	130
Circ_0006646	Increase	circRNA	Cancer cells	Cancer cells	Increase proliferation, migration, invasion, tumor growth, metastasis	miR-758-3p/RRM2	Therapeutic target	131
—	—	—	Paclitaxel loading	Cancer cells	Induce apoptosis, Suppress EMT signaling	—	Therapeutic target/nanocarrier	132

HLECs: human lymphatic endothelial cells; HKF: human keloid fibroblasts; WJ-MSC: Wharton jelly-derived mesenchymal stem cells; EMT: epithelial–mesenchymal transition.

Thus, studies or clinical trials are needed to elucidate the altogether effects of exosomal biomolecules from one cell to another or the other cells bidirectionally or multiple-directionally (eg, bidirectional: cancer cells  $\rightleftharpoons$  CAFs, cancer cells  $\rightleftharpoons$  immune cells, cancer cells  $\rightleftharpoons$  MSCs, or multiple-directional: cancer cells  $\rightleftharpoons$  CAFs  $\rightleftharpoons$  MSCs  $\rightleftharpoons$  immune cells) in the TME.

## Conclusion and Perspectives

Discovery of new diagnostic and prognostic biomarkers, as well as therapeutic targets, for gynecological cancers are urgent. Exosomes play pivotal roles in the pathogenesis of gynecological cancers by orchestrating the communication between cancer cells and the TME, including CAFs, MSCs, and immune cells. Exosomes, especially miRNAs, may function as positive or negative regulators of cancer development through various signaling pathways and associate with the diagnosis and prognosis. It is easy to approach because exosomes can secret into body fluid serving as liquid biopsy. Thus, exosomes have great potential as diagnostic and prognostic biomarkers for gynecological cancers.

Exosomes-derived biomolecules also could serve as therapeutic targets for precision medicine. Each miRNA, regardless of upregulation (oncomiR) or downregulation (tumor suppressor), regulates various signaling pathways contributing to cancer development. One miRNA could target multiple genes and regulate at least one biological process which makes it more efficient when taking miRNAs as therapeutic targets. Furthermore, due to the nano-size of exosomes, it could be engineered by modifying the surface molecules to increase the tissue-targeting specificity as a nanocarrier to deliver drugs or functional biomolecules. In summary, exosomes could not only be biomarkers but also therapeutic targets as well as nanocarriers.

## Author Contributions

D.-C.D. contributed to conceptualization, writing—review and editing, visualization, supervision, project administration, and funding acquisition. K.H.W. contributed to methodology, software, formal analysis, investigation, and writing—original draft preparation. Both authors contributed to validation, resources, and data curation, and have read and agreed to the published version of the manuscript.

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This article does not contain any studies with human or animal subjects.

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