Advances in exosomal non-coding RNAs in cervical cancer (Review)

XINGKUI XIE[1*], HONGWEI GUAN[2*], MENG LI[3], WEI GAO[4] and KEJIA WU[5]

[1]Department of Gynecology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, P.R. China; [2]Department of Health Management Center, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei 430070, P.R. China; [3]Department of Ultrasound Imaging, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei 430060, P.R. China; [4]Medical Science Research Center, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, P.R. China; [5]Center for Reproductive Medicine, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, P.R. China

Received May 1, 2025; Accepted September 18, 2025

DOI: 10.3892/mco.2025.2899

Abstract. Exosomes, extracellular vesicles (30-150 nm in diameter) released upon the fusion of multivesicular bodies with the plasma membrane, are pivotal mediators of intercellular communication through their cargo transport. The present review aimed to provide further insight into the molecular mechanisms by which exosomal non-coding RNAs (ncRNAs), such as microRNAs, long non-coding RNAs and circular RNAs, contribute to the development of cervical cancer (CC). There are currently no US Food and Drug Administration-approved exosome products for medical use. The present review highlights the critical role of exosomal ncRNAs in the pathogenesis of CC, including tumor initiation, progression, metastasis, angiogenesis and drug resistance, and discusses their potential as novel biomarkers for diagnosis, therapeutic targets and prognostic tools for CC. However, the long-term safety and efficacy of these ncRNAs requires further confirmation by clinical trials, which is essential before exosomes can be broadly adopted in CC. Although exosomes hold significant potential in the diagnosis, therapy and prognosis of CC, several challenges remain to be addressed before their translation into therapeutic use, including the standardization of exosome isolation and storage protocols, the optimization of drug-loading efficiency, precise control over cargo release kinetics and the completion of extensive clinical trials.

Correspondence to: Dr Wei Gao, Medical Science Research Center, Zhongnan Hospital of Wuhan University, No. 169 Donghu Road, Wuhan, Hubei 430071, P.R. China
E-mail: znyycg@126.com

Professor Kejia Wu, Center for Reproductive Medicine, Zhongnan Hospital of Wuhan University, No. 169 Donghu Road, Wuhan, Hubei 430071, P.R. China
E-mail: wdzn2019@163.com

*Contributed equally

Key words: cervical cancer, exosomes, non-coding RNAs, biomarkers, tumor microenvironment

Contents

1. Introduction

Cervical cancer (CC) ranks as the fourth most prevalent malignancy among females globally, with ~569,847 new cases and 311,365 related deaths each year, according to the latest GLOBOCAN statistics (1,2). Although early-stage CC exhibits a high cure rate, the disease presents significant clinical challenges, including an increasing incidence rate, a trend towards younger onset and poor prognosis in the advanced stages of the disease. These factors underscore CC as a critical public health issue, with its elimination recognized as a global health priority. Current therapeutic strategies, such as chemotherapy combined with targeted therapy, have improved the overall survival and progression-free survival of patients with CC. However, its incidence continues to increase, particularly in cases of locally advanced disease, which is often associated with low control rates, a high metastatic potential and adverse prognostic factors. Consequently, the 5-year survival rate remains suboptimal at ~60% (3). These limitations highlight the urgent need for the identification of novel biomarkers to enhance early diagnosis, guide targeted therapies and improve prognostic assessment.

Exosomes are bilayer lipid membrane vesicles, 30-150 nm in diameter, that facilitate intercellular communication by transporting bioactive molecules, including proteins, lipids, DNA and RNA. Their lipid membranes confer stability, protecting cargo from degradation and enabling efficient delivery to recipient cells, thereby modulating diverse physiological and pathological processes (4). Ubiquitously secreted by mammalian cells, such as dendritic cells, adipocytes, endothelial cells and epithelial cells, exosomes are abundant in plasma and other bodily fluids (5). Notably,

cancer-derived exosomes are secreted at levels 10-fold higher than those from normal cells and play pivotal roles in tumor progression, including invasion, angiogenesis and chemotherapeutic resistance, via autocrine, paracrine and endocrine mechanisms (6,7). Due to their tumor-specific cargo and stability, exosomes have emerged as promising biomarkers for distinguishing malignant from non-malignant tissues (8). Among their molecular constituents, non-coding RNAs (ncRNAs), such as microRNAs (miRNAs/miRs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs), are increasingly recognized for their regulatory roles in the progression of CC. These ncRNAs represent potential diagnostic, prognostic and therapeutic targets, providing new avenues for the management of CC.

Systematic search strategy. A thorough literature search was conducted on PubMed (https://pubmed.ncbi.nlm.nih.gov/) using specific MeSH, including 'exosomes', 'cervical cancer', 'lncRNAs', 'miRNAs', 'circRNAs', 'ncRNAs', 'drug resistance', 'angiogenesis', 'EMT' and 'lymphangiogenesis'. The search was limited to studies published in various countries within the past 10 years (2015-2025). As a result, a total of 57 relevant references were identified and reviewed.

2. Exosomal miRNAs in CC

miRNAs are single-stranded non-coding RNAs (~22 nt in length) that post-transcriptionally regulate gene expression through mRNA degradation or translational inhibition, profoundly influencing cellular phenotype and function (9). A previous study demonstrated that cancer-related fibroblast-derived exosomal miR-18a-5p can regulate the transmembrane protein 170B signaling axis, stimulating the proliferation and migration, and inhibiting the apoptosis of CC cells (10). Emerging as critical regulators of tumor microenvironment homeostasis, exosomal miRNAs exhibit distinct expression profiles in the vaginal lavage fluid of patients with CC, including upregulated oncogenic miRNAs (miR-483-5p and miR-1246) and downregulated tumor suppressors (let-7d-5p and miR-20a-5p) (11). In addition, another study demonstrated that Th17 cells induced the expression of miR-142-5p in CC cells, and identified the subunits C and D of the succinate dehydrogenase complex as novel targets of miR-142-5p responsible for enhanced migration and invasion (12). These findings position exosomal miRNAs as promising molecular signatures for CC detection and monitoring.

Exosomal miRNAs promote angiogenesis. Angiogenesis, the formation of new blood vessels from pre-existing vasculature, serves as a critical biological process driving tumor growth, local invasion and distant metastasis in CC (13). This process is fundamentally required for tumor progression beyond the 1 to 2-mm diffusion limit imposed. Malignant cells overcome this limitation through the robust secretion of exosomes that reprogram the tumor microenvironment to induce pathological angiogenesis (14). Given its central role in tumor progression and metastasis, angiogenesis has emerged as a promising therapeutic target for the management of advanced-stage CC (15). At the molecular level, CC-derived exosomal miRNAs orchestrate angiogenesis through multiple mechanisms: i) miR-221-3p mediates the inhibition of mitogen-activated protein kinase 10 (MAPK10). The exosomal transfer of miR-221-3p from CC cells to microvascular endothelial cells specifically targets and modulates MAPK10 activity. This interaction stimulates endothelial cell proliferation, invasion and migration, culminating in the formation of an aberrant tumor vasculature (16). ii) miR-663b-dependent vascular remodeling: CC-secreted exosomal miR-663b potently enhances tumor vascular density by suppressing vinculin expression in vascular endothelial cells. The downregulation of vinculin alters endothelial cell adhesion dynamics, thereby promoting extensive vascular network formation and significantly augmenting the angiogenic potential of CC tissues (17).

These findings illustrate the sophisticated, multi-faceted regulatory networks through which exosomal miRNAs coordinate neovascularization in CC. The diversity of these pathways highlights both the complexity of tumor angiogenesis and the potential for developing targeted anti-angiogenic therapies that disrupt specific exosomal miRNA-mediated mechanisms.

Exosomal miRNAs promote lymphangiogenesis. Lymphangiogenesis, the formation of new lymphatic vessels from pre-existing ones, plays a critical role in cancer metastasis. Tumor cells often exploit lymphatic vessels to enter the circulatory system, facilitating their spread to distant organs and aggravating disease progression (18). In a number of types of cancer, lymphatic metastasis occurs at an early stage and serves as a major route for cancer cell dissemination, with lymphangiogenesis being a key driver of this process. For instance, exosomal miR-1468-5p from CC cells promotes lymphangiogenesis and upregulates programmed death-ligand 1 expression in lymphatic vessels. This occurs through the suppression of homeobox containing 1 (HMBOX1)-suppressor of cytokine signaling 1 (SOCS1) transcription and the activation of the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway, which impairs $CD8^+$ T-cell immunity, enabling immune evasion and metastatic spread (19). Similarly, exosomes from cervical squamous cell carcinoma (CSCC) enhance human lymphatic endothelial cell (HLEC) migration and tube formation *in vitro*. Among their cargo, miR-221-3p is highly enriched and delivered to HLECs, where it downregulates vasohibin 1, further stimulating lymphangiogenesis and lymphatic metastasis (20). Given its functional role, miR-221-3p may serve as both a therapeutic target and a diagnostic biomarker for metastatic CSCC.

Exosomal miRNAs regulate drug resistance. Drug resistance represents a major therapeutic challenge in cancer management, with complex underlying mechanisms. Current research has identified three primary exosome-mediated drug resistance pathways in cancers: Antibody-based drug neutralization, drug efflux and miRNA transfer via exosomes. Notably, miRNA-mediated drug resistance is directly or indirectly associated with multidrug resistance protein 1 expression (21). The selective packaging of miRNAs into exosomes from drug-resistant cells can induce P-glycoprotein overexpression, thereby enhancing the multidrug resistance phenotype in cancer cells (22). Zhu *et al* (23) demonstrated that miR-651

expression was significantly downregulated in the circulation of patients with CC and in cisplatin-resistant HeLa cells (HeLa/DDP) compared with their cisplatin-sensitive counterparts (HeLa/S). Functional analyses revealed that miR-651 overexpression reduced cisplatin resistance and proliferation, while promoting the apoptosis of HeLa cells. Mechanistically, exosomal miR-651 from CC cells has been shown to directly target autophagy-related 3 (ATG3) to suppress cisplatin resistance. Furthermore, miR-106a/b has been implicated in the exosome-mediated modulation of cisplatin sensitivity in HeLa cells (24).

In addition, the study by Li *et al* (25) demonstrated that HIV-positive T cell-derived exosomal miR-155-5p promoted IL-6 and IL-8 secretion via AT-rich interaction domain 2 (ARID2) targeting and the subsequent activation of the ERCC excision repair 5, endonuclease (ERCC5)-NF-κB pathway, thereby accelerating epithelial-mesenchymal transition (EMT) and enhancing cervical cancer invasiveness. In CSCC, tumor-derived exosomal miR-223 induced IL-6 secretion from monocytes/macrophages *in vitro*, creating a positive feedback loop through STAT3 activation in CSCC cells (26). Moreover, highly metastatic HeLa cells transferred miR-29 via exosomes to low-metastatic C-33A cells, thereby enhancing their metastatic potential (27).

In summary, exosomal miRNAs play pivotal roles in the progression of CC by regulating angiogenesis, lymphangiogenesis, drug resistance and metastasis. These findings highlight their potential as biomarkers for early diagnosis, targets for precision therapy and indicators for prognosis assessment in the management of CC.

3. Exosomal lncRNAs in CC

lncRNAs are ncRNAs with a length of >200 nucleotides that participate in various physiological processes, including chromatin remodeling, epigenetic regulation, transcriptional and post-transcriptional regulation, as well as cell proliferation and differentiation (28). Accumulating evidence indicates that lncRNAs are dysregulated in multiple malignant tumors and modulate cancer cell phenotypes via the *cis*- and *trans*-regulation of tumor-related genes, exerting oncogenic or tumor-suppressive effects. Thus, the dysregulated expression of lncRNAs has been proposed as one of the hallmark features of malignant tumors (29). Previous studies have demonstrated that lncRNAs play critical roles in CC tumorigenesis, progression, metastasis and drug resistance, suggesting their potential as diagnostic and prognostic biomarkers for CC (30,31). Given these findings, exosomal lncRNAs, functioning as intercellular communication mediators, likely contribute to the development and progression of CC.

Exosomal lncRNAs promote the proliferation and differentiation of CC cells. It has been well-established that cell proliferation and differentiation are fundamental processes in the development and progression of CC. Recent studies have demonstrated that exosomal lncRNAs promote the proliferation and differentiation of CC cells. For instance, it was previously demonstrated that the level of serum exosomal lncRNA DLX6-AS1 was significantly elevated in patients with CC compared with those with cervical intraepithelial neoplasia (CIN) or healthy controls (32). Functionally, DLX6-AS1 enhanced the proliferation, migration and EMT of CC cells by modulating the miR-16-5p/CAMP-regulated phosphoprotein 1 (ARPP19) axis or degrading fused in sarcoma protein in a xenograft mouse model (33), suggesting that the serum exosomal DLX6-AS1 may serve as a diagnostic and prognostic biomarker for CC.

Additionally, lncRNAs such as HOX transcript antisense intergenic RNA (HOTAIR) and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) have been found to be highly enriched in CC-derived exosomes isolated from cervicovaginal lavage samples, with expression levels significantly higher than those in HPV-infected patients or healthy controls (34). Mechanistically, HOTAIR and MALAT1 function as competitive endogenous RNAs (ceRNAs): HOTAIR binds to miR-214-3p to activate the Wnt/β-catenin signaling pathway, while MALAT1 sequesters miR-485-5p to upregulate MAT2A expression, thereby promoting CC cell proliferation (35,36). In a separate study, Gao *et al* (37) reported that exosomes derived from CaSki cells enhanced the self-renewal and differentiation capacities of CC stem cells, these exosomes carry lncRNA urothelial carcinoma-associated 1 (UCA1), which functions as a ceRNA for miR-122-5p to upregulate SRY-Box transcription factor 2 (SOX2) expression. Notably, silencing exosomal UCA1 or overexpressing miR-122-5p suppressed the self-renewal and differentiation of CC stem cells, subsequently inhibiting the invasion, migration and proliferation of CaSki cells. These interventions also induced cancer cell apoptosis and reduced tumor volume and weight in nude mouse models. Furthermore, lncRNA H19 was found to be upregulated in CC cell lines and detectable in extracellular vesicles from cell culture supernatants. Functional assays revealed that H19 promoted cell proliferation and multicellular tumor spheroid formation without significantly affecting apoptosis or migration, suggesting its potential as a diagnostic and therapeutic target in CC (38).

Exosomal lncRNAs promote angiogenesis. Exosomal lncRNAs have been implicated in facilitating CC metastasis through pro-angiogenic mechanisms analogous to those mediated by miRNAs. Emerging evidence suggests that CC-derived exosomal lncRNAs can modulate vascular endothelial cell behavior by either upregulating pro-angiogenic factors or sequestering anti-angiogenic miRNAs, thereby promoting tumor vascularization (39). The seminal study by Lei and Mou (40) identified the lncRNA taurine upregulated 1 (TUG1) as significantly overexpressed in both CC cells and their secreted exosomes. Mechanistically, CC-derived exosomal TUG1 was internalized by human umbilical vein-derived endothelial cells (HUVECs), where it suppressed caspase-3 activity and altered the expression of apoptosis-related proteins, ultimately enhancing endothelial cell proliferation and survival. These findings posit exosomal TUG1 as a potential diagnostic biomarker for early-stage CC.

Exosomal lncRNAs regulate drug resistance. Accumulating evidence has confirmed that tumor-derived exosomal

lncRNAs play a critical role in mediating drug resistance in cancers. In CC, the lncRNA hepatocyte nuclear factor 1 homeobox A antisense RNA 1 (HNF1A-AS1) is highly enriched in exosomes secreted by cervical cancer cells. Functionally, HNF1A-AS1 acts as a ceRNA to sponge miR-34b, thereby promoting the expression of tuftelin 1 (TUFT1). This mechanism enhances cisplatin (DDP) resistance in CC cells, concurrently promoting proliferation, conferring drug resistance and inhibiting apoptosis (41). Furthermore, recent studies have revealed that exosomal MALAT1 is markedly upregulated in DDP-resistant CC cells. The pro-resistance effect of MALAT1 can be attenuated by targeting miR-370-3p, suggesting that the exosomal MALAT1/miR-370-3p/STAT3 axis modulates DDP resistance via PI3K/Akt pathway activation (42). Thus, exosomal MALAT1 represents a potential diagnostic biomarker for patients with CC who are resistant to DDP. Another key finding demonstrated that lncRNA maternally expressed gene 3 (MEG3) expression was significantly downregulated in CC tissues compared with adjacent normal tissues. The silencing of MEG3 not only promoted CC cell proliferation and migration, but also suppressed apoptosis. Mechanistically, MEG3 enhanced DDP sensitivity by acting as a ceRNA to regulate the miR-21/PTEN axis (43). Additionally, exosomal LINC01305 was shown to contribute to chemoresistance by activating the Wnt/β-catenin signaling pathway, thereby maintaining cancer stemness through the upregulation of β-catenin, transcription factor 7 and NADH dehydrogenase subunit 2 (31). In summary, given the pivotal roles of exosomal lncRNAs in modulating the tumor microenvironment and malignant phenotypes, they emerge as promising biomarkers for CC. Their clinical applications span early screening, therapeutic decision-making, and prognostic evaluation, highlighting their translational significance.

4. Exosomal circRNAs in CC

circRNAs are a newly identified class of endogenous ncRNAs that exhibit an abundant expression in eukaryotic transcriptomes. They are characterized by their covalently closed circular structure, the absence of 5' caps and 3' poly(A) tails, and exonuclease resistance due to the lack of free termini. These features confer greater stability compared with their linear RNA counterparts (44). Functionally, circRNAs often contain miRNA response elements, enabling them to modulate gene expression at transcriptional or post-transcriptional levels through interactions with miRNAs or other RNA-binding proteins. They can function as miRNA sponges or ceRNAs to regulate diverse physiological and pathological processes, such as cancer cell proliferation, invasion and metastasis. For instance, circ_0000069 was shown to sponge miR-873-5p to de-repress tumor suppressor candidate 3, thereby promoting CC progression (45), and circ_0005576 was demonstrated to upregulate kinesin family member 20A by sequestering miR-153, which accelerated the pathogenesis of CC (46). Notably, circRNAs are enriched and stably preserved within exosomes. For example, circSLC26A4 was detected in biofluids (such as blood and urine), rendering them promising liquid biopsy biomarkers (47,48). Emerging evidence highlights dysregulated exosomal circRNA profiles in patients with CC, suggesting their clinical potential for diagnosis and therapeutic targeting.

Exosomal circRNAs promote the EMT of CC cells. EMT is a fundamental biological process whereby epithelial cells undergo phenotypic conversion into mesenchymal cells. During this process, under stimulation by external factors, the expression of epithelial phenotypic markers is decreased, and intercellular junctions are disrupted. Conversely, mesenchymal phenotypic markers are re-expressed or upregulated, accompanied by a morphological shift from a cuboidal, polarized distribution to a spindle-shaped, randomly oriented distribution (49). As a key mechanism in cancer progression, EMT enables epithelial-derived malignant tumor cells to acquire migratory and invasive properties. Wang *et al* (50) found that the levels of hsa_circ_0009143 (circPVT1) in both plasma- and urine-derived exosomes from patients with CC were significantly elevated. Functional assays demonstrated that the overexpression of circPVT1 promoted the migration and invasion of C33A CC cells, concomitant with the upregulation of mesenchymal markers (vimentin, N-cadherin and Snail), and the downregulation of the epithelial marker, E-cadherin, all established EMT biomarkers. These findings suggest that exosomal circPVT1 may facilitate CC metastasis by activating EMT pathways.

Exosomal circRNAs promote angiogenesis. Exosomal circRNAs also contribute to multiple stages of vascular development, including intercellular crosstalk, the secretion of pro-angiogenic factors, the degradation of the vascular basement membrane, endothelial cell proliferation, tube formation, and alternative microvascular patterning such as vasculogenic mimicry (51). Previously, an *in vitro* study demonstrated that circ_0087432 is significantly upregulated in serum exosomes from patients with CC. The overexpression of exosomal circ_0087432 derived from CC cells has been shown to enhance the proliferation and migration of HUVECs (52), indicating its involvement in CC metastasis via angiogenesis. Wang *et al* (53) found that circ_0064516 was highly expressed in CC cells, and exosomes derived from CC cells carried circ_0064516 to HUVECs. circ_0064516 increased mitogen-activated protein kinase 1 (MAPK1) expression by sponging miR-6805-3p, thereby enhancing angiogenesis.

Exosomal circRNAs regulate drug resistance. Drug resistance remains a major challenge in cancer therapy. Emerging evidence suggests that the aberrant expression of exosomal circRNAs may contribute to chemoresistance. Unlike intracellular circRNAs, exosomal circRNAs appear to be selectively packaged and actively shuttled between exosomes and the cytoplasm (54). Chen *et al* (55) analyzed 46 patients with CC who received radiotherapy and chemotherapy combined with surgical resection and found that circ_0074269 expression was elevated in exosomes from DDP-resistant CC cells. Mechanistically, it may upregulate TUFT1 by sponging miR-485-5p, thereby promoting resistance to DDP in patients with CC. As demonstrated in another *in vivo* and *in vitro* study,

Table I. Summary of exosomal non-coding RNAs in cervical cancer.

Category	Specific molecule	Function	Mechanism of action	(Refs.)
miRNAs	miR-221-3p	Promotes angiogenesis	Inhibits MAPK10, stimulating endothelial cell proliferation and migration.	(16)
	miR-663b	Promotes angiogenesis	Suppresses vinculin, altering endothelial adhesion and promoting vascular network formation.	(17)
	miR-1468-5p	Promotes lymphangio-genesis and immune evasion	Suppresses HMBOX1-SOCS1, activating JAK2/STAT3 to impair CD8+ T-cell immunity.	(19)
	miR-221-3p	Promotes lymphangiogenesis	Downregulates VASH1, stimulating lymphatic endothelial cell migration and tube formation.	(20)
	miR-651	Suppresses cisplatin resistance	Directly targets ATG3 to inhibit autophagy and reduce drug resistance.	(23)
	miR-106a/b	Modulates cisplatin sensitivity	Transferred via exosomes to alter drug response in recipient cells.	(24)
	miR-155-5p	Promotes EMT and invasion	Targets ARID2, activating the ERCC5-NF-κB pathway.	(25)
	miR-223	Promotes TME inflammation	Induces IL-6 secretion from monocytes/ macrophages, creating a STAT3-mediated feedback loop.	(26)
	miR-29	Promotes metastasis	Transfer from high- to low-metastatic cells enhances their metastatic potential.	(27)
lncRNAs	DLX6-AS1	Promotes proliferation, migration, and EMT	Modulates the miR-16-5p/ARPP19 axis or degrades the FUS protein.	(32)
	HOTAIR	Promotes proliferation	Functions as a ceRNA for miR-214-3p, activating the Wnt/β-catenin pathway.	(35)
	MALAT1	Promotes proliferation	Functions as a ceRNA for miR-485-5p, upregulating MAT2A expression.	(36
	UCA1	Promotes stemness and differentiation	Functions as a ceRNA for miR-122-5p, upregulating SOX2.	(37)
	H19	Promotes proliferation	Mechanism not fully elucidated; enhances spheroid formation.	(38)
	TUG1	Promotes angiogenesis	Suppresses caspase-3 activity, enhancing endothelial cell survival and proliferation.	(40)
	HNF1A-AS1	Promotes cisplatin resistance	Functions as a ceRNA for miR-34b, upregulating TUFT1.	(41)
	MALAT1 (Resistance)	Promotes cisplatin resistance	Regulates the miR-370-3p/STAT3 axis, activating the PI3K/Akt pathway.	(42)
	MEG3	Enhances cisplatin sensitivity	Functions as a ceRNA to regulate the miR-21/ PTEN axis, suppressing proliferation.	(43)
	LINC01305	Promotes chemoresistance	Activates Wnt/β-catenin signaling to maintain cancer stemness.	(31)
circRNAs	circPVT1	Promotes EMT and metastasis	Upregulates mesenchymal markers (vimentin, N-cadherin) and downregulates E-cadherin.	(50)
	circ_0087432	Promotes angiogenesis	Enhances the proliferation and migration of HUVECs.	(52)
	circ_0064516	Promotes angiogenesis	Sponges miR-6805-3p, upregulating MAPK1.	(53)
	circ_0074269	Promotes cisplatin resistance	Sponges miR-485-5p, leading to TUFT1 upregulation.	(55)

Table I. Continued.

Category	Specific molecule	Function	Mechanism of action	(Refs.)
	circ_0004488	Promotes paclitaxel resistance	Sponges miR-136, upregulating its target MEX3C.	(56)

miRNA/miR, microRNA; MAPK10, mitogen-activated protein kinase 10; HMBOX1, homeobox containing 1; SOCS1, suppressor of cytokine signaling 1; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; VASH1, vasohibin 1; ATG3, autophagy-related 3; EMT, epithelial-mesenchymal transition; ARID2, AT-rich interaction domain 2; ERCC5, ERCC excision repair 5, endonuclease; TME, tumor microenvironment; lncRNA, long non-coding RNA; ARPP19, CAMP-regulated phosphoprotein 1; FUS, fused in sarcoma; ceRNA, competing endogenous RNA; UCA1, urothelial carcinoma-associated 1; SOX2, SRY-Box transcription factor 2; TUG1, taurine upregulated 1; HNF1A-AS1, hepatocyte nuclear factor 1 homeobox A antisense RNA 1; TUFT1, tuftelin 1; MEG3, maternally expressed gene 3; circRNAs, circular RNAs; HUVECs, human umbilical vein-derived endothelial cells; MAPK1, mitogen-activated protein kinase 1; MEXC3, Mex-3 RNA-binding family member C.

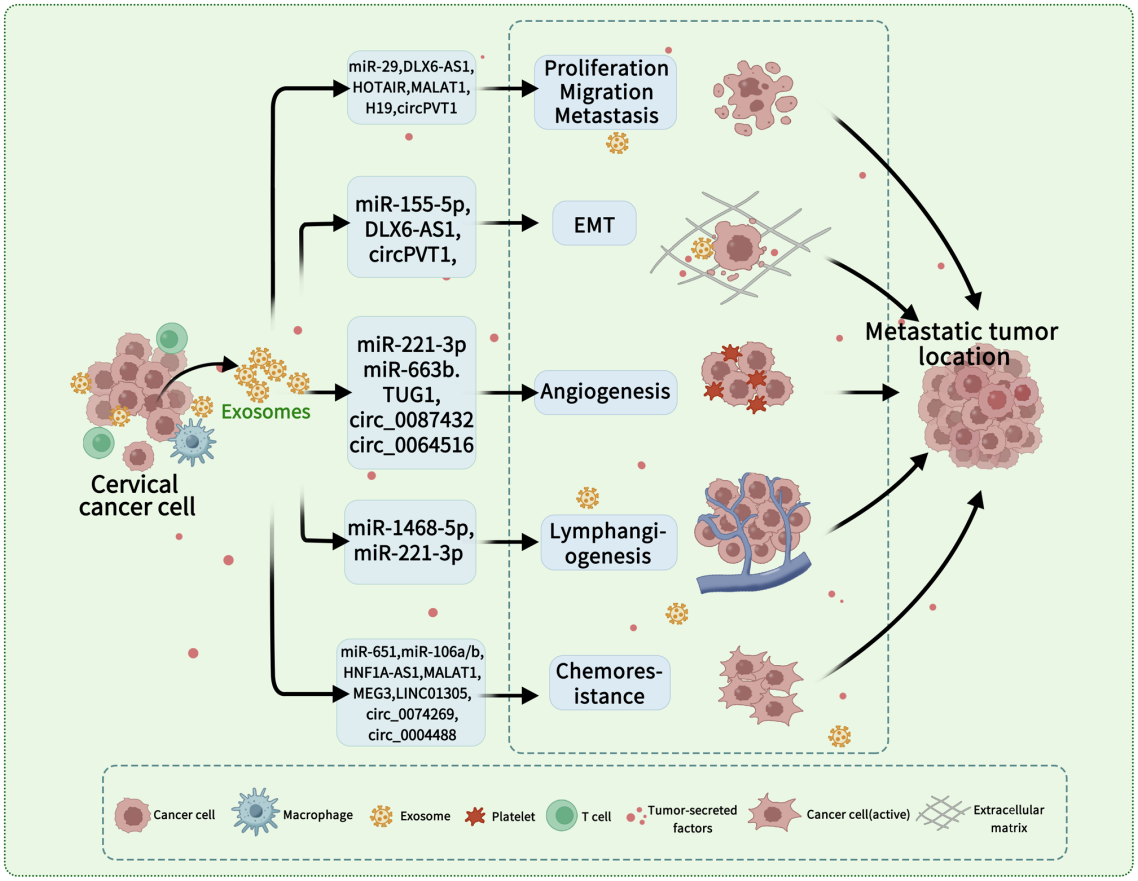

Figure 1. Summary of exosomal non-coding RNAs in cervical cancer. miRNA/miR, microRNA; HOTAIR, HOX transcript antisense intergenic RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; EMT, epithelial-mesenchymal transition; TUG1, taurine upregulated 1; HNF1A-AS1, hepatocyte nuclear factor 1 homeobox A antisense RNA 1; MEG3, maternally expressed gene 3.

circ_0004488, as a miR-136 sponge, increased the expression of Mex-3 RNA-binding family member C (MEX3C), which is a direct target gene of miR-136, ultimately increasing the resistance of CC to paclitaxel (56). These findings highlight the potential of exosomal circRNAs as biomarkers and therapeutic targets for CC. Further research is required however, to elucidate their precise mechanisms in tumor invasion and metastasis, which may provide a foundation for novel clinical interventions.

5. Conclusion and future prospects

Exosomes in malignant tumors have emerged as a key focus of research in recent years. These vesicles facilitate intercellular communication by transporting functional biomolecules, including ncRNAs, which play critical roles in cancer progression. Exosomal ncRNAs contribute to tumor growth, proliferation, invasion, metastasis and drug resistance by modulating key oncogenic pathways. The present

review comprehensively summarized the involvement of exosomal ncRNAs in the development of CC, particularly their regulatory effects on cell proliferation, differentiation, angiogenesis, lymphangiogenesis, EMT and chemoresistance (Table I). These mechanisms collectively promote CC initiation, progression and metastatic dissemination (Fig. 1). However, the current evidence base has significant limitations. A large amount of the supporting data is derived from *in vitro* studies and preclinical animal models, raising questions about the direct translatability of these findings to the complex human tumor microenvironment (12,23,32). For example, numerous studies rely on HeLa cell lines, while their well-documented genetic and phenotypic drift after decades of *in vitro* culture raises questions about their representativeness of native cancers (16,20,24). Findings in a single cell line cannot capture the vast heterogeneity among patients with CC. Therefore, the translational validity of these findings *in vitro* is necessarily limited at this stage. To bridge the gap between observations *in vitro* and potential clinical application, a multi-tiered validation framework is necessary. First, studies need to be conducted in a broader range of CC cell lines to assess their prevalence outside of a single cell line. Second, the association between the expression levels of key molecular markers and their clinicopathological characteristics, such as stage, grade and prognosis need to be analyzed using patient tissue samples. Finally, relevant animal models of xenograft tumors need to be established to verify the effectiveness and safety of targeted intervention in an *in vivo* environment. Furthermore, attributing specific biological effects solely to exosomal ncRNAs remains challenging due to the heterogeneity of exosome populations and the potential co-isolation of contaminating non-exosomal vesicles or free ncRNAs using common isolation techniques. The functional validation of specific exosomal ncRNAs in driving CC phenotypes often lacks rigorous genetic gain/loss-of-function experiments within the relevant cellular context.

Compared to synthetic nanoparticles, exosomes exhibit superior biocompatibility, low immunogenicity, high stability and intrinsic targeting capabilities, rendering them promising candidates for clinical applications. Nevertheless, translating this promise into reality faces substantial hurdles beyond the mentioned technical challenges. First of all, standardization is the cornerstone. The Minimal Information for Studies of Extracellular Vesicles (MISEV) 2023 guidelines launched by the International Society for Extracellular Vesicles (ISEV) provide a more comprehensive framework for research; however, their full adoption and practice still require time, which is a prerequisite for ensuring data comparability and repeatability (57). Secondly, the path to clinical transformation is a complex one. The recent rejection of Deramiocel, the first exosome mechanism therapy, by the FDA, profoundly reveals the high standards of regulatory authorities for substantive efficacy evidence (from rigorously designed controlled trials) and a robust Chemistry, Manufacturing and Controls (CMC) system, sounding the alarm for clinical development strategies across the entire field. Furthermore, the regulatory framework is evolving rapidly. Countries worldwide have clearly included exosomes in the management of advanced therapeutic drugs, laying a regulatory foundation for their development as drugs. This also implies higher technical thresholds and quality requirements. Finally, a critical concern is the potential for tumor-derived exosomes themselves to exert pro-tumorigenic effects; using them as therapeutic carriers requires meticulous engineering to eliminate residual oncogenic cargo and ensure safety. The scalability and cost-effectiveness of producing clinical-grade exosomes at sufficient quantities and purity for widespread therapeutic use are also major unresolved issues. Additionally, the immunogenicity of exosomes, while generally low, can vary significantly, depending on the source cell type and isolation method, necessitating careful evaluation for each application. However, several additional challenges need to be addressed before their translation into therapeutic use, including the standardization of exosome isolation and storage protocols, optimization of drug-loading efficiency and precise control over cargo release kinetics. Furthermore, the current understanding of exosome biogenesis, particularly the spatiotemporal regulation of exosomal cargo sorting, molecular transport mechanisms and definitive exosome markers, remains limited. Crucially, current knowledge of the *in vivo* biodistribution, pharmacokinetics and long-term fate of administered therapeutic exosomes in humans remains limited, posing significant barriers to clinical trial design and regulatory approval.

In conclusion, future studies are required to focus on elucidating these aspects while also prioritizing the development of robust methods to track exosome delivery and function *in vivo*, and to rigorously assess the safety profile of engineered exosomes in relevant models, to harness the full therapeutic potential of exosomes in oncology. Further research is warranted to provide a more in-depth understanding of the *in vivo* and molecular mechanisms of exosomes in scientific research. Technically, it is of utmost significance to develop efficient and controllable engineering transformation and large-scale production processes. The highest standards of randomized controlled trials and strict quality control norms need to be followed in clinical translation. In terms of regulations, a more detailed and scientific evaluation system needs to be established. By overcoming these challenges, the marked therapeutic potential of exosomes may prove to be beneficial to human health.

Acknowledgements

Not applicable.

Funding

The present study was supported by a grant from the National Natural Science Foundation of China (grant no. 82002760).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XX and HG conceived the study that led to the acquisition of data from the literature, and drafted the manuscript. ML

revised the language of the manuscript. WG and KW designed the outline of the review and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Raghani NR, Chorawala MR, Parekh K, Sharma A, Alsaidan OA, Alam P, Fareed M and Prajapati B: Exosomal miRNA-based theranostics in cervical cancer: Bridging diagnostics and therapy. Med Oncol 42: 193, 2025.
2. Filho AM, Laversanne M, Ferlay J, Colombet M, Piñeros M, Znaor A, Parkin DM, Soerjomataram I and Bray F: The GLOBOCAN 2022 cancer estimates: Data sources, methods, and a snapshot of the cancer burden worldwide. Int J Cancer 156: 1336-1346, 2025.
3. Mileshkin LR, Moore KN, Barnes EH, Gebski V, Narayan K, King MT, Bradshaw N, Lee YC, Diamante K, Fyles AW, *et al*: Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): An international, open-label, randomised, phase 3 trial. Lancet Oncol 24: 468-482, 2023.
4. Kalluri R and LeBleu VS: The biology, function, and biomedical applications of exosomes. Science 367: eaau6977, 2020.
5. Hao Y, Song H, Zhou Z, Chen X, Li H, Zhang Y, Wang J, Ren X and Wang X: Promotion or inhibition of extracellular vesicle release: Emerging therapeutic opportunities. J Control Release 340: 136-148, 2021.
6. Thakur A, Ke X, Chen YW, Motallebnejad P, Zhang K, Lian Q and Chen HJ: The mini player with diverse functions: Extracellular vesicles in cell biology, disease, and therapeutics. Protein Cell 13: 631-654, 2022.
7. Naderi-Meshkin H, Lai X, Amirkhah R, Vera J, Rasko JEJ and Schmitz U: Exosomal lncRNAs and cancer: Connecting the missing links. Bioinformatics 35: 352-360, 2019.
8. Ran Z, Wu S, Ma Z, Chen X, Liu J and Yang J: Advances in exosome biomarkers for cervical cancer. Cancer Med 11: 4966-4978, 2022.
9. Diener C, Keller A and Meese E: Emerging concepts of miRNA therapeutics: From cells to clinic. Trends Genet 38: 613-626, 2022.
10. Kang C, Duo Y, Zheng L, Zhao N, Wang J, Liu Z, Qiu L and Bi F: CAFs-derived exosomes promote the development of cervical cancer by regulating miR-18a-5p-TMEM170B signaling axis. Biochem Biophys Res Commun 694: 149403, 2024.
11. Nagamitsu Y, Nishi H, Sasaki T, Takaesu Y, Terauchi F and Isaka K: Profiling analysis of circulating microRNA expression in cervical cancer. Mol Clin Oncol 5: 189-194, 2016.
12. Pohlers M, Gies S, Taenzer T, Stroeder R, Theobald L, Ludwig N, Kim YJ, Bohle RM, Solomayer EF, Meese E, *et al*: Th17 cells target the metabolic miR-142-5p-succinate dehydrogenase subunit C/D (SDHC/SDHD) axis, promoting invasiveness and progression of cervical cancers. Mol Oncol 18: 2157-2178, 2024.
13. Mitra T and Elangovan S: Cervical cancer development, chemoresistance, and therapy: A snapshot of involvement of microRNA. Mol Cell Biochem 476: 4363-4385, 2021.
14. Dittmer J and Leyh B: Paracrine effects of stem cells in wound healing and cancer progression (Review). Int J Oncol 44: 1789-1798, 2014.
15. Jayson GC, Kerbel R, Ellis LM and Harris AL: Antiangiogenic therapy in oncology: Current status and future directions. Lancet 388: 518-529, 2016.
16. Zhang L, Li H, Yuan M, Li M and Zhang S: Cervical cancer cells-secreted exosomal microRNA-221-3p promotes invasion, migration and angiogenesis of microvascular endothelial cells in cervical cancer by down-regulating MAPK10 expression. Cancer Manag Res 11: 10307-10319, 2019.
17. You X, Sun W, Wang Y, Liu X, Wang A, Liu L, Han S, Sun Y, Zhang J, Guo L and Zhang Y: Cervical cancer-derived exosomal miR-663b promotes angiogenesis by inhibiting vinculin expression in vascular endothelial cells. Cancer Cell Int 21: 684, 2021.
18. Lehuédé C, Dupuy F, Rabinovitch R, Jones RG and Siegel PM: Metabolic plasticity as a determinant of tumor growth and metastasis. Cancer Res 76: 5201-5208, 2016.
19. Zhou C, Wei W, Ma J, Yang Y, Liang L, Zhang Y, Wang Z, Chen X, Huang L, Wang W and Wu S: Cancer-secreted exosomal miR-1468-5p promotes tumor immune escape via the immunosuppressive reprogramming of lymphatic vessels. Mol Ther 29: 1512-1528, 2021.
20. Zhou CF, Ma J, Huang L, Yi HY, Zhang YM, Wu XG, Yan RM, Liang L, Zhong M, Yu YH, *et al*: Cervical squamous cell carcinoma-secreted exosomal miR-221-3p promotes lymphangiogenesis and lymphatic metastasis by targeting VASH1. Oncogene 38: 1256-1268, 2019.
21. Bhattacharjee M, Ghosh A, Das S, Sarker S, Bhattacharya S, Das A, Ghosh S, Chattopadhyay S, Ghosh S and Adhikary A: systemic codelivery of thymoquinone and doxorubicin by targeted mesoporous silica nanoparticle sensitizes doxorubicin-resistant breast cancer by interfering between the MDR1/P-gp and miR 298 crosstalk. ACS Biomater Sci Eng 10: 6314-6331, 2024.
22. Havryliuk V, Wojtowicz K, Gagat M and Żuryń A: Exosome-mediated mechanisms of drug resistance in lung cancer: Molecular mechanisms and therapeutic strategies. Cell Physiol Biochem 59: 358-374, 2025.
23. Zhu X, Long L, Xiao H and He X: Cancer-derived exosomal miR-651 as a diagnostic marker restrains cisplatin resistance and directly targets ATG3 for cervical cancer. Dis Markers 2021: 1544784, 2021.
24. Raji GR, Sruthi TV, Edatt L, Haritha K, Sharath Shankar S and Sameer Kumar VB: Horizontal transfer of miR-106a/b from cisplatin resistant hepatocarcinoma cells can alter the sensitivity of cervical cancer cells to cisplatin. Cell Signal 38: 146-158, 2017.
25. Li H, Chi X, Li R, Ouyang J and Chen Y: HIV-1-infected cell-derived exosomes promote the growth and progression of cervical cancer. Int J Biol Sci 15: 2438-2447, 2019.
26. Zhang J, Jiang M, Qian L, Lin X, Song W, Gao Y and Zhou Y: The STAT3-miR-223-TGFBR3/HMGCS1 axis modulates the progression of cervical carcinoma. Mol Oncol 14: 2313-2331, 2020.
27. Cui HJ, Zhang YN and Li HT: Mechanism of exosome miRNA29 in cervical cancer metastasis. Chin J Cancer Prev Treat 25: 1365-1370, 2018.
28. Cheng T and Huang S: Roles of non-coding RNAs in cervical cancer metastasis. Front Oncol 11: 646192, 2021.
29. Eptaminitaki GC, Stellas D, Bonavida B and Baritaki S: Long non-coding RNAs (lncRNAs) signaling in cancer chemoresistance: From prediction to druggability. Drug Resist Updat 65: 100866, 2022.
30. He J, Huang B, Zhang K, Liu M and Xu T: Long non-coding RNA in cervical cancer: From biology to therapeutic opportunity. Biomed Pharmacother 127: 110209, 2020.
31. Huang X, Liu X, Du B, Liu X, Xue M, Yan Q, Wang X and Wang Q: LncRNA LINC01305 promotes cervical cancer progression through KHSRP and exosome-mediated transfer. Aging (Albany NY) 13: 19230-19242, 2021.
32. Ding XZ, Zhang SQ, Deng XL and Qiang JH: Serum exosomal lncRNA DLX6-AS1 Is a promising biomarker for prognosis prediction of cervical cancer. Technol Cancer Res Treat 20: 1533033821990060, 2021.
33. Xie F, Xie G and Sun Q: Long noncoding RNA DLX6-AS1 promotes the progression in cervical cancer by targeting miR-16-5p/ARPP19 axis. Cancer Biother Radiopharm 35: 129-136, 2020.
34. Zhang J, Liu SC, Luo XH, Tao GX, Guan M, Yuan H and Hu DK: Exosomal long noncoding RNAs are differentially expressed in the cervicovaginal lavage samples of cervical cancer patients. J Clin Lab Anal 30: 1116-1121, 2016.
35. Zhou Y, Wang Y, Lin M, Wu D and Zhao M: LncRNA HOTAIR promotes proliferation and inhibits apoptosis by sponging miR-214-3p in HPV16 positive cervical cancer cells. Cancer Cell Int 21: 400, 2021.

36. Tie W and Ge F: MALAT1 inhibits proliferation of HPV16-positive cervical cancer by sponging miR-485-5p to promote expression of MAT2A. DNA Cell Biol 40: 1407-1417, 2021.
37. Gao Z, Wang Q, Ji M, Guo X, Li L and Su X: Exosomal lncRNA UCA1 modulates cervical cancer stem cell self-renewal and differentiation through microRNA-122-5p/SOX2 axis. J Transl Med 19: 229, 2021.
38. Iempridee T: Long non-coding RNA H19 enhances cell proliferation and anchorage-independent growth of cervical cancer cell lines. Exp Biol Med (Maywood) 242: 184-193, 2017.
39. Zhang W, Wang Q, Yang Y, Zhou S, Zhang P and Feng T: The role of exosomal lncRNAs in cancer biology and clinical management. Exp Mol Med 53: 1669-1673, 2021.
40. Lei L and Mou Q: Exosomal taurine up-regulated 1 promotes angiogenesis and endothelial cell proliferation in cervical cancer. Cancer Biol Ther 21: 717-725, 2020.
41. Luo X, Wei J, Yang FL, Pang XX, Shi F, Wei YX, Liao BY and Wang JL: Exosomal lncRNA HNF1A-AS1 affects cisplatin resistance in cervical cancer cells through regulating microRNA-34b/TUFT1 axis. Cancer Cell Int 19: 323, 2019.
42. Hu Y, Li G, Ma Y, Luo G, Wang Q and Zhang S: Effect of exosomal lncRNA MALAT1/miR-370-3p/STAT3 positive feedback loop on PI3K/Akt pathway mediating cisplatin resistance in cervical cancer cells. J Oncol 2023: 6341011, 2023.
43. Du Y, Geng G, Zhao C, Gao T and Wei B: LncRNA MEG3 promotes cisplatin sensitivity of cervical cancer cells by regulating the miR-21/PTEN axis. BMC Cancer 22: 1145, 2022.
44. Verduci L, Strano S, Yarden Y and Blandino G: The circRNA-microRNA code: Emerging implications for cancer diagnosis and treatment. Mol Oncol 13: 669-680, 2019.
45. Zhang S, Chen Z, Sun J, An N and Xi Q: CircRNA hsa_circRNA_0000069 promotes the proliferation, migration and invasion of cervical cancer through miR-873-5p/TUSC3 axis. Cancer Cell Int 20: 287, 2020.
46. Ma H, Tian T, Liu X, Xia M, Chen C, Mai L, Xie S and Yu L: Upregulated circ_0005576 facilitates cervical cancer progression via the miR-153/KIF20A axis. Biomed Pharmacother 118: 109311, 2019.
47. Tong Y, Jia L, Li M, Li H and Wang S: Identification of exosomal circSLC26A4 as a liquid biopsy marker for cervical cancer. PLoS One 19: e0305050, 2024.
48. Preußer C, Hung LH, Schneider T, Schreiner S, Hardt M, Moebus A, Santoso S and Bindereif A: Selective release of circRNAs in platelet-derived extracellular vesicles. J Extracell Vesicles 7: 1424473, 2018.
49. Dongre A and Weinberg RA: New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol 20: 69-84, 2019.
50. Wang H, Wei M, Kang Y, Xing J and Zhao Y: Circular RNA circ_PVT1 induces epithelial-mesenchymal transition to promote metastasis of cervical cancer. Aging (Albany NY) 12: 20139-20151, 2020.
51. Zhang XP, Pei JP, Zhang CD, Yusupu M, Han MH and Dai DQ: Exosomal circRNAs: A key factor of tumor angiogenesis and therapeutic intervention. Biomed Pharmacother 156: 113921, 2022.
52. Xia H, Yang X, Chen Y, Li H and Chu GF: Effect of cervical cancer-derived exosomal hsa_circ_0087432 on the proliferation and migration of HUVECs. Med J Chin People's Liber Army 46: 327-332, 2021.
53. Wang Y, Xie Y, Wang X, Yang N, Wu Z and Zhang X: Tumor cells-derived extracellular vesicles carry circ_0064516 competitively inhibit microRNA-6805-3p and promote cervical cancer angiogenesis and tumor growth. Expert Opin Ther Targets 28: 97-112, 2024.
54. Wang Y, Liu J, Ma J, Sun T, Zhou Q, Wang W, Wang G, Wu P, Wang H, Jiang L, *et al*: Exosomal circRNAs: Biogenesis, effect and application in human diseases. Mol Cancer 18: 116, 2019.
55. Chen J, Wu S, Wang J, Sha Y and Ji Y: Hsa_circ_0074269-mediated upregulation of TUFT1 through miR-485-5p increases cisplatin resistance in cervical cancer. Reprod Sci 29: 2236-2250, 2022.
56. Yi H, Han Y, Li Q, Wang X, Xiong L and Li S: Circular RNA circ_0004488 increases cervical cancer paclitaxel resistance via the miR-136/MEX3C signaling pathway. J Oncol 2022: 5435333, 2022.
57. Welsh JA, Goberdhan DCI, O'Driscoll L, Buzas EI, Blenkiron C, Bussolati B, Cai H, Di Vizio D, Driedonks TAP, Erdbrügger U, *et al*: Minimal information for studies of extracellular vesicles (MISEV2023): From basic to advanced approaches. J Extracell Vesicles 13: e12404, 2024.