Exosomal long non-coding RNAs: Emerging players in cancer metastasis and potential diagnostic biomarkers for personalized oncology

Hui Nie, Zhujun Liao, Yutong Wang, Jianhua Zhou, Xiaoyun He, Chunlin Ou

Department of Pathology, Xiangya Hospital, Central South University, Changsha, Hunan Province, 410008, PR China
Department of Rheumatology and Immunology, Xiangya Hospital, Central South University, Changsha, Hunan Province, 410008, PR China
National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan Province, 410008, PR China

Received 15 July 2020; received in revised form 6 December 2020; accepted 12 December 2020
Available online 18 December 2020

Abstract Metastasis is a major challenge in the treatment of cancer. Exosomes are a class of small extracellular vesicles (EVs) that play critical roles in several human diseases, especially cancer, by transferring information (e.g., DNA, RNA, and protein) via cell-to-cell communication. Numerous recent studies have shown that exosomal long non-coding RNAs (lncRNAs) play crucial regulatory roles in cancer metastasis in the tumor microenvironment by altering the expression of several key signaling pathways and molecules. Due to their specificity and sensitivity, exosomal lncRNAs have potential as novel tumor markers and therapeutic targets in the treatment of cancer metastasis. In this review, we aim to summarize the roles of exosomal lncRNAs in cancer metastasis, the mechanisms underlying their roles, and their potential clinical applications.

Copyright © 2020, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Cancer metastasis is a process by which malignant tumor cells detach from the primary tumor site and are transported to secondary tissues or organs via the circulatory system; these cells then colonize and form secondary tumors in these tissues or organs. Cancer invasion and metastasis are complex, dynamic, cascade-based processes that involve various factors in the tumor microenvironment as well as epithelial-mesenchymal transition (EMT), hypoxia, angiogenesis, and other mechanisms.1,2 Cells change dramatically during these processes, and show reduced cell adhesion, cytoskeletal reconstruction, extracellular matrix degradation, and the formation of cell protrusions and pseudopods.3–5 Cancer invasion and metastasis present difficult problems in clinical treatment, affecting patient prognosis and survival, and are important causes of tumor-related deaths.6,7 Therefore, exploring the molecular mechanism of cancer metastasis and identifying cancer metastasis-related markers are essential for developing novel treatments.

Exosomes are small extracellular vesicles (EVs; 30–150 nm in diameter) that are produced by almost all cell types and are released in all bodily fluids, including urine, sputum, and plasma.12 Exosomes play critical roles in several human diseases, especially cancer. Recent studies have shown that long non-coding RNAs (lncRNAs) can be encapsulated by exosomes formed by the secreting cells, are transferred to recipient cells, and can regulate cancer progression and metastasis.13 Exosomal lncRNAs can regulate the tumor microenvironment by influencing the expression of a variety of key signaling pathways and molecular and play important regulatory roles in cancer metastasis. Moreover, due to their specificity and sensitivity, exosomal lncRNAs released into tumor microenvironments are potential tumor markers.14 In this review, we aim to provide inspiration for novel research in the development of markers and therapeutic targets for cancer metastasis by summarizing the studies reporting the role of exosomal lncRNAs in cancer metastasis.

Origin of exosomes

EVs are small membranous vesicles that are released from cells into the extracellular matrix. EVs can be divided into two categories: microvesicles and exosomes.15 Microvesicles are generated directly from the plasma membrane,16 whereas exosomes are produced by invagination of the endosomal membrane, which buds inward to form multivesicular bodies (MVBs).17 During this process, the cytoplasmic contents and transmembrane and peripheral proteins are integrated, thereby forming intraluminal vesicles (ILVs).18 The ILVs in MVBs are secreted by the cell when the MVBs fuse with the cell surface to form exosomes.19 Many studies have shown that vesicles and exosomes can carry a variety of molecules, including proteins, lipids, and nucleic acids, and show cellular specificity, as the contents in EVs among cell types. EVs play key roles in cellular communication, cell migration, and angiogenesis. Exosomes were first identified and defined by both Pan and Harding et al in 1983.20,21 Initially, exosomes were considered to be metabolic waste. However, through further research and the popularization of electron microscopy, researchers have gained a new understanding of exosomes. Studies have shown that exosomes are small EVs that have a diameter of 30–150 nm and are produced by all cell types.22 Exosomes are derived from nuclear endosomes and are released into the extracellular environment after fusion with the plasma membrane.23 EVs are widely found in all human body fluids, including saliva, breast milk, cerebrospinal fluid, ascites, urine, and semen.24 Exosomes can carry RNA, DNA, proteins, lipids, and metabolites, and thus play critical roles in the cell-to-cell transduction of materials and information.25 With precision medicine, increasing attention has been paid to achieving accurate diagnoses and the targeted treatment of various diseases. Exosomes, as a hot new research focus area, and because of their ubiquity in the body and convenience of acquisition, have been targeted for disease diagnosis and treatment and show promise for use in precision medicine.26–28

Definition and characteristics of LncRNAs

NcRNAs (non-coding RNAs) are small RNAs that are transcribed but do not encode proteins.29 Based on their length, ncRNAs can be divided into small ncRNAs and long non-coding RNAs (lncRNAs). The small ncRNA classes include microRNA (miRNA), short interfering RNA (siRNA), small nuclear RNA (snRNA), rRNA, tRNA, and piwi-interacting RNA (piRNA). The lncRNAs include long intergenic ncRNA (lincRNA), antisense RNA (asRNA), pseudogenes, and circular RNA (circRNA).30 LncRNAs were first found in eukaryotic cells. They have a length of 200–10,000 nt, lack a complete open reading frame (ORF), rarely encode short functional peptides, and are typically located in the nucleus or cytoplasm.31,32 LncRNAs play important roles in numerous basic physiological processes, including ontogenesis, tissue differentiation, reproduction, and immunity.33 Their dysfunction or abnormal expression is often associated with a variety of human diseases, including cancers. Secreted exosomal lncRNAs can enter receptor cells via the humoral circulation and have been shown to be related to multiple phenotypes associated with cancer progression, including formation of the tumor microenvironment, angiogenesis, malignant proliferation, invasion, and metastasis.34–37 Recent studies have shown that lncRNAs can be encapsulated and released into the tumor microenvironment, and exosomes released by specific cells/tissues play a vital regulatory role in cancer metastasis.38,39 Zhang et al40 reported that the exosome-associated lncRNA MALAT1 can promote the metastasis of non-small cell lung cancer (NSCLC), and the expression level of MALAT1 is closely associated with lymph node metastasis in patients with NSCLC. Moreover, owing to their specificity and sensitivity, exosomal lncRNAs released into the tumor microenvironment could be used as tumor markers.

Biological characteristics of exosomal lncRNAs

EVs are vesicle bodies with bilayer phospholipid membranes that are secreted by cells; carry proteins, lipids, nucleic acids, and other bioactive components; and mediate cell-to-cell communication. Based on their size, mechanisms of
biogenesis and release, and other characteristics, EVs can be classified as exosomes, microvesicles (MVs), or apoptotic bodies. Exosomes are vesicle-like bodies, approximately 30–150 nm in diameter, that are mainly released from intracellular endosomes through exocytosis. They are multivesicular bodies (MVBs) formed by the inward budding of endoblasts, and their plasma membranes are generated by MVB fusion. Exosomes are secreted by almost all cells, and numerous studies have shown that they are present in all human bodily fluids, including saliva, breast milk, cerebrospinal fluid, ascites, urine, and semen. Exosomes are transported via the humoral circulation and enter target receptor cells in one of three ways: direct fusion, endocytosis, and receptor ligand binding. As exosomes carry proteins, nucleic acids, lipids, and other components, they can function as signal carriers, forming cell-to-cell communication systems that can influence cellular communication, cell migration, angiogenesis, and tumor cell growth. As a new subset of ncRNAs, lncRNAs can be classified into five categories according to their proximity to neighboring transcripts: sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intragenic lncRNAs, and intergenic lncRNAs. LncRNAs are widely involved in the regulation of various biological activities, due in part to their tissue-specific expression, and influence disease processes. LncRNAs, in the form of the initially transcribed or spliced RNAs, regulate important genes in a specific, multi-stage, spatiotemporal manner at the epigenetic, transcriptional, and post-transcriptional levels and significantly influence the processes of translation and protein modification. LncRNAs are important for basic physiological processes, such as ontogeny, development, differentiation, reproduction, and immunity. Therefore, dysfunction or abnormal expression of lncRNAs is often associated with human diseases, including cancer.

Recent studies have shown that lncRNAs can be packaged into exosomes to extracellular communication with local or distant cells (Fig. 1). Several exosomal lncRNAs have been shown to be closely related to various diseases, including diabetes, rheumatoid arthritis, osteoporosis and cancer (Table 1). Metastasis is an important cause of cancer-related death, and many studies have shown that exosomal lncRNAs participate in the complex process of metastasis. Tumor cells can modify their microenvironment by transporting lncRNAs, which can significantly influence tumour development and drug resistance. For example, exosomal delivery of the lncRNA RPPH1 can promote M2 polarization of macrophages and colorectal cancer (CRC) metastasis. However, the specific mechanism of exosomal lncRNA-mediated cancer metastasis is largely unknown. Therefore, a systematic understanding of the roles of various exosomal lncRNAs in cancer metastasis may identify useful diagnostic and prognostic biomarkers as well as therapeutic targets for malignant tumors.

Mechanisms of exosomal lncRNAs in cancer metastasis

An increasing number of studies have shown that exosomal lncRNAs can sponge miRNAs to regulate target gene expression and can bind proteins to affect their phosphorylation or ubiquitination, thereby regulating their expression and/or activity (Fig. 1). This can affect signaling pathways that are closely related to cancer metastasis as well as the expression and function of cancer metastasis-related molecules, leading to cancer metastasis.

Exosomal lncRNAs regulate cancer metastasis by modulating signaling pathways

Cancer metastasis is a complex process that involves changes in the tumor microenvironment as well as multiple molecular and signaling pathways. Previous studies have revealed that exosomal lncRNAs are involved in many signaling pathways related to cancer metastasis, including the Wnt/β-catenin, TGF-β/Smad, STAT3, and VEGFA/VEGFR2 signaling pathways (Fig. 2).

Studies have found that key molecules in the Wnt/β-catenin signaling pathway are altered in cancer metastasis, which can lead to the abnormal activation of this signaling pathway, inducing cancer metastasis. The Wnt/β-catenin signaling pathway has been shown to be modulated by vitamin D, which can inhibit the progression of skin cancer by altering the expression of lncRNAs. These lncRNAs can be packaged into exosomes and transported via the bloodstream or urine to target cells and can affect the target cells by modulating the Wnt/β-catenin pathway. Exosomal lncRNAs can serve as biomarkers for skin cancer. Zhang et al. reported that lncRNAs, such as LINC01281 and LINC02154, have protective and/or harmful effects in laryngeal cancer. Further studies revealed that the mechanism by which these lncRNAs affect the prognosis of laryngeal cancer may involve exosomes, the Notch signaling pathway, voltage-gated calcium channels, and the Wnt signaling pathway. The exosomal lncRNA TIRY was shown to be secreted by cancer-related fibroblasts, and TIRY can sponge miR-14 to regulate the Wnt/β-catenin signaling pathway and enhance the metastasis of oral squamous cell carcinoma.

Interestingly, transforming growth factor (TGF)-β-induced exosomes can regulate the migration and invasion of lung cancer cells. Wu et al. found that TGF-β pre-treatment can increase the vascular permeability of human lung adenocarcinoma A549 cells, thereby promoting distant metastasis through the blood. TGF-β-induced exosomes were also shown to act as carriers of intercellular communication molecules, thus regulating lung cancer metastasis and vascular permeability. TGF-β promotes enhancer activity and increases the expression of matrix metalloproteinase (MMP)2, and TGF-β-mediated exosomes have become new therapeutic targets and predictive markers of lung cancer metastasis. Overexpression of Inc-MMP2-2 can up-regulate the expression of vimentin and N-cadherin in lung cancer cells, while down-regulating the expression of E-cadherin. This increases protein levels at tight junctions between vascular endothelial cells and increases vascular permeability, which promotes lung cancer metastasis. In non-small cell lung cancer cells, studies have shown that the lncRNA MALAT1 in serum-derived exosomes can affect the proliferation and migration of cancer cells. Investigation of the functional mechanism showed that MALAT1 promotes the metastasis of lung
cancer cells by promoting the binding of TGF-β to related receptors in the cell membrane and activating downstream proteins in EMT-related signaling pathways.\textsuperscript{40}

The experimental results of Li et al.\textsuperscript{73} revealed that the exosomal lncRNA ZFAS1 plays a key role in the migration of oesophageal squamous cell carcinoma cells by indirectly regulating the STAT3 signaling pathway. The invasion and metastasis of cancer cells are closely related to neovascularization. In gliomas, angiogenesis can be induced by tumour cells through the secretion of exosomes rich in linc-Pou3F3, and linc-Pou3F3-overexpressing glioma cell lines show increased mRNA and protein expression of VEGFA and Angio.\textsuperscript{79} In hepatocellular carcinoma (HCC), the lncRNA HANR indirectly regulates the Eag1/VEGF axis through miR-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Exosomal long non-coding RNAs (lncRNAs) taken up by recipient cells. Exosomal lncRNAs are taken up by recipient cells via direct fusion, endocytosis, and receptor-ligand binding. Exosomal lncRNAs that enter cells can act as (A) competing endogenous RNAs (ceRNAs) that interact with miRNAs and interfere with their function, (B) a scaffold that recruits and interacts with proteins and regulates their activity, (C) a decoy that interacts with transcription factors (TFs) to alter transcriptional regulation, and (D) a guide to promote gene expression by recruiting TFs to a gene promoter.}
\end{figure}
Exosomal IncRNAs regulate cancer metastasis by sponging miRNAs

Unlike mRNAs, IncRNAs are widely distributed in the nucleus and cytoplasm, and their subcellular localization is strictly related to their biological roles. LncRNAs contain many introns, which provides a molecular basis for their function as miRNA sponges. After entering target cells via the humoral circulation, exosomal lncRNAs can compete with intracellular miRNAs by binding to, and sequestering, them. LncRNAs that sponge miRNAs reverse the effects of the miRNAs on the expression of their target genes. LncRNAs and miRNAs jointly constitute the competitive endogenous RNA (ceRNA) network, which is involved in tumor proliferation, invasion, migration, and apoptosis. Numerous recent studies have revealed that lncRNAs can be packaged in exosomes and can bind to miRNAs and have significant effects on cancer metastasis (Table 2). In colorectal cancer (CRC), expression of the exosomal IncRNA UCA1 is up-regulated, and silencing of UCA1 inhibits CRC cell proliferation and reduces cell migration. UCA1 was shown to mainly sponge miR-143 and play a key regulatory role in CRC cells, and thus is a new target for CRC therapy. LncRNAs in serum exosomes and liver cancer cells were related to the prognosis of PDAC. Cao et al. reported that serum levels of the exosomal lncRNA HULC were significantly higher in HCC patients than in normal control subjects. Similarly, HULC expression levels were higher in HCC tissues than in adjacent non-cancerous tissues. Consistent with the effect of melittin treatment in pancreatic ductal adenocarcinoma (PDAC) cell lines, and its expression was significantly lower in PDAC cancer tissues than in adjacent non-cancerous tissues. Consistent with the effect of lncRNA NONHSAT105177 inhibited the proliferation, migration, and EMT of PDAC cell lines.
therapeutic target for GC patients.\textsuperscript{97} Li et al\textsuperscript{91} showed that the lncRNA FAL1 is packaged into exosomes and delivered to recipient cells and can alter target gene expression in HCC. Dual luciferase reporter assays showed that FAL1 accelerates the proliferation and metastasis of malignant cells by acting as either a ceRNA or sponge for miR-1236. In addition, FAL1 expression levels was upregulated in HCC cells and the serum exosomes of HCC patients.

Various studies have shown that chemotherapy significantly affects tumor cell metastasis, and it can increase tumor invasion and distant metastasis to some extent.\textsuperscript{102,103} Exosomal lncRNAs can modulate tumorigenesis and induce chemotherapy resistance by acting as ceRNAs. Ren et al\textsuperscript{94} showed that by transferring the exosomal lncRNA H19, carcinoma-associated fibroblasts (CAFs) can promote stemness and chemoresistance in CRC. Notably, H19 can relieve miR-141-mediated inhibition in CRC cells by ceRNA and activating the $\beta$-catenin pathway. Thus, the levels of exosomal H19 contribute to tumor development and chemotherapeutic resistance. LncRNAs have also been reported to be key regulators of trastuzumab resistance in breast cancer. For example, the exosomal lncRNA UCA1 functions as a ceRNA of miRNA-18a to induce trastuzumab resistance in breast cancer cells.\textsuperscript{104}

**Figure 2** Exosomal lncRNAs promote cancer metastasis by regulating signaling pathways. Exosomal LncRNAs promote cancer metastasis by regulating the Wnt/\(\beta\)-catenin, TGF-\(\beta\), STAT3, and VEGFA/VEGFR2 signaling pathways.

Exosomal lncRNAs regulate cancer metastasis through protein binding

After entering receptor cells, exosomal lncRNAs can exert their biological effects by binding to miRNAs. They can also modulate cancer cell migration by interacting with specific proteins. In the cytoplasm, exosomal lncRNAs can interact with proteins and affect the levels of phosphorylation and other modifications, induce degradation, and modulate their various functions, including activities related to cancer metastasis. In the nucleus, exosomal lncRNAs can play synergistic or antagonistic roles with transcription factors that regulate the expression of genes related to cancer metastasis (Fig. 1).
Numerous exosomal lncRNAs act in the cytoplasm by binding with proteins, such as exosomal lncRNA RPPH1, which was shown to be significantly up-regulated in CRC tissues. Further analysis showed that RPPH1-induced EMT of CRC cells prevents ubiquitination of β-III tubulin (TUBB3), which is important for the metastasis into CRC cells. In addition, RPPH1 was packaged by CRC cell-derived exosomes and transferred to macrophages, which further promoted the metastasis and proliferation of CRC cells by inducing M2 polarization of the macrophages. Correlation analysis showed that heterogeneous ribosomal protein K (HNRNPK) may directly interact with exosomal lncRNA 91H and participate in CRC transfer. As 91H enhances CRC metastasis by modifying the expression of HNRNPK, exosomal 91H can serve as a serum biomarker for the early detection of CRC recurrence or metastasis. Studies on the mechanisms of exosomal lncRNA-mediated tumour resistance indicated that expression levels of the lncRNA AFAP1-AS1 were higher in trastuzumab-resistant cells than in sensitive cells. The lncRNA AFAP1-AS1 was packaged into exosomes by trastuzumab-resistant cells secreted and subsequently taken up by target cells, further promoting trastuzumab resistance. Experimental data showed that exosomal AFAP1-AS1 is a promising marker for predicting trastuzumab resistance and breast cancer treatment. LncRNAs can also play a role in gene regulation by interacting with transcription factors. Chen et al. reported that the exosomal lncRNA LNMAT2 interacts directly with the heterogeneous ribonucleoprotein A2B1 (hnRNP-A2B1) and is loaded into exosomes secreted by bladder cancer (BC) cells. This exosomal LNMAT2 can be internalized by human lymphatic endothelial cells (HLECs). Through recruitment of hnRNP-A2B1 and increasing the trimethylation levels of H3K4 in the Prospero homeobox 1 (PROX1) promoter, PROX1 expression is up-regulated, leading to lymphangiogenesis and lymphatic metastasis. The bioactive lncRNA RUNX2-AS1 in myeloma (MM) cells can be packaged into exosomes and transferred to mesenchymal stem cells (MSCs), which inhibits the osteogenesis of MSCs. An in-depth study showed that RUNX2-AS1, originating from the antisense chain of Runx2, was enriched in the MSCs of MM patients. Because of their overlap, RUNX2-AS1 and RUNX2 pre-mRNA can form an RNA double helix. Transcription from this double helix inhibits the expression of RUNX2 by reducing its splicing efficiency, which reduces the osteogenic potential of MSCs.

### Exosomal lncRNAs as novel biomarkers and targets of cancer metastasis

Epidemiological evidence has shown that nearly 90% of cancer-related deaths can be attributed to metastasis, but only approximately 0.02% of tumor cells can form metastatic foci. Cancer metastasis is the main cause of treatment failure, as most cancer patients have advanced stage disease when clinical symptoms are observed, and their prognosis is relatively poor compared to that of patients with early tumors. Therefore, identifying cancer metastasis-related molecular targets and markers is important for cancer treatment and the prevention of cancer-related deaths.

Exosomal lncRNAs can be detected in bodily fluids, and their lncRNA contents can reveal significant information about the physiological and/or pathological changes in cancer patients. Therefore, exosomal lncRNAs have been widely studied as tumor markers in recent years.
Several clinical studies have indicated strong associations of exosomal lncRNAs with various clinical symptoms. LncRNA-APC1, which can be activated by the APC gene, is downregulated in CRC, and its decreased exosomal content was related to lymph node and/or distant metastasis, clinical stage, and poor prognosis in the advanced stages of CRC. Lee et al. showed that the exosomal lncRNA ATB was related to TNM stage and other prognostic factors in HCC, including T stage and portal vein thrombosis. Multivariate analysis showed that high expression of LncRNA-APC1 was a good independent predictor of mortality and disease progression. In CRC tissues, high expression of the lncRNA SPINT1-AS1 was related to regional lymph node metastasis, distant metastasis, and shorter recurrence-free survival (RFs). SPINT1-AS1 expression in serum exosomes from CRC patients after surgery was significantly lower than that in control subjects. Liu et al. showed that the lncRNA GAS5 was upregulated in the tissues, plasma, and exosomes of CRC patients, whereas miR-221 was downregulated. GAS5 expression was correlated with TNM stage, Dukes stage, local recurrence, distant metastasis, and miR-221 levels in tissues.

In addition to having broad prospects as biomarkers, many studies have shown that exosomal lncRNAs have significant potential as cancer treatment targets. To investigate whether exosomes can inhibit tumor growth and metastasis in the tumor microenvironment in HCC, Alzahrami et al. injected exosomes from two different stem cell populations (liver cancer stem cells (CSC) and bone marrow (BM) MSCs) into HCC model rats. Subsequent immunostaining of liver cancer markers (GST-P, AFP, and GGT) and liver enzymes (ALT, AST, and ALP) showed significantly higher staining intensity in rats injected with CSC-exosomes as well as increased numbers and areas of tumor nodules. In contrast, rats injected with MSC-exosomes showed the opposite trends, indicating that exosomes from CSCs have tumor-stimulating effects, and promote tumour growth, progression, and metastasis, while MSC exosomes have tumor-inhibiting effects. This study provided valuable insights into the effects of exosomes on the growth and progression of HCC and the potential of exosomes in tumor therapy as well as improving our understanding of HCC pathogenesis.

Table 3 Exosomal lncRNAs with potential as novel biomarkers and therapeutic targets for cancer metastasis.

| Cancers                                | Exosomal lncRNAs | Expression | Relationship with clinicopathological features | AUC    | Ref. |
|----------------------------------------|------------------|------------|-----------------------------------------------|--------|-----|
| Epithelial ovarian cancer              | MALAT1           | ↑          | Advanced cancer and lymph node metastasis     | 64     |     |
| Hepatocellular carcinoma               | ATB              | ↑          | TNM stage, T stage, and portal vein thrombosis | 112    |     |
|                                         | ENSG00000258332.1| ↑          | Lymph node metastasis, portal vein tumor embolus, TNM stage, and poor overall prognosis | 0.719  | 113 |
|                                         | LINC00635        | ↑          | Lymph node metastasis and TNM stage           | 0.750  | 113 |
| Colorectal cancer                      | HULC             | ↑          | Lymph node metastasis                         | 92     |     |
|                                         | APC1             | ↑          | Lymph node and distant metastasis             | 81     |     |
|                                         | GAS5             | ↑          | TNM stages, Dukes stages, lymph node metastasis, local recurrence, and distant metastasis | 114    |     |
|                                         | 91H              | ↑          | TNM stage                                     | 105    |     |
|                                         | CRNDE-h          | ↑          | Lymph node metastasis and distant metastasis  | 0.892  | 115 |
|                                         | UCA1             | ↑          | Tumor size, tumor stage, and metastasis status | 95     |     |
|                                         | RPPH1            | ↑          | TNM stages and poor overall prognosis         | 0.86   | 70  |
| Pancreatic ductal Adenocarcinoma        | Sox2ot           | ↑          | TNM stage                                     | 96     |     |
| Laryngeal squamous cell carcinoma       | HOTAIR           | ↑          | T stage and lymph node metastasis             | 0.727  | 116 |
| Gastric cancer                         | Inc-GNAQ-6:1     | ↓          | –                                              | 0.732  | 117 |
|                                         | ZFAS1            | ↑          | Lymph node metastasis and TNM stage           | 0.630  | 118 |
| Lung squamous cell carcinoma            | SPRY4-IT1        | ↑          | Tumor size and TNM stage                      | 97     |     |
|                                         | SOX2-OT          | ↑          | Tumor size, TNM stage, and lymph node metastasis | 0.815  | 119 |
| Non-small cell lung cancer              | MALAT-1          | ↑          | Lymph node metastasis and TNM stage           | 0.703  | 40  |
| Breast cancer                          | MALAT1           | ↑          | Cancer metastasis and TNM stage               | 120    |     |
| High-grade serous carcinoma             | ESRG             | ↑          | Poor overall prognosis                        | 121    |     |
| Bladder cancer                         | LNMAT2           | ↑          | Lymphangiogenesis and lymph node metastasis   | 107    |     |

H. Nie, Z. Liao, Y. Wang et al.
AS1- and DPP-treated group than in the DPP-treated group. This suggested that inhibition of exosomal HNF1A-AS1 can significantly inhibit tumor formation in nude mice, which provides a novel direction for future clinical research.

Conclusions and future perspectives

With the development of RNA-seq and next-generation sequencing technologies, increasing numbers of exosomal IncRNAs have been identified. Compared to exosomal proteins, the extraction and detection of IncRNAs require higher specificity and sensitivity. Because exosomal IncRNAs are involved in regulating the development, metastasis, and drug resistance of various cancers, they have great potential as biological tools for the diagnosis and treatment of tumors, representing a future path in the field of oncology. However, a significant amount of work remains to translate this basic scientific research to clinical application. Recent research on regarding exosomal IncRNAs has faced a series of challenges and limitations: 1) Exosome isolation and purification methods have not been well established. To date, four main methods for the isolation and purification of EVs have been developed, namely ultra-high-speed centrifugation, filtration, precipitation, and immunocentrification. However, the existing purification methods can barely distinguish exosomes from non-vesicular components, which may affect the results of functional in vivo and in vitro experiments with exosomal IncRNAs. 2) Further investigations of exosomal IncRNAs must be performed to determine if they are specifically related to one or more diseases and to explore the underlying molecular mechanisms. 3) For the exosomal IncRNAs that may block cancer metastasis pathways, their specific roles and the corresponding mechanisms remain to be clarified. 4) Although many animal experiments have suggested the potential of exosomal IncRNAs can in the treatment of cancer metastasis, few clinical experiments have been conducted to verify the results. 5) The endogenous and exogenous factors that affect the production of exosomes have not yet been identified, which, to some extent, complicates the use of exosomal IncRNAs as clinical biological markers for cancer metastasis. The present understanding of exosomal IncRNAs is just the tip of the iceberg, and the development of novel approaches and techniques will shed new light on these processes. Exosomal IncRNAs are a promising strategy for the early detection and treatment of cancer metastasis.

Conflict of Interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Natural Science Foundation of China [grant number 81903032], the National Key Research and Development Program of China [grant number 2016YFC1201800], the China Postdoctoral Science Foundation [grant number 2020M672520], the Youth Fund of Xiangya Hospital [grant number 2018Q011], and the Mittal Innovative Entrepreneurial Project of Central South University [grant number XCX20190719].

Abbreviations

| Acronym | Description |
|---------|-------------|
| EVs     | extracellular vesicles |
| IncRNAs | long non-coding RNAs |
| EMT     | epithelial-mesenchymal transition |
| ORF     | open reading frame |
| ceRNA   | competing endogenous RNA |
| NSCLC   | non-small cell lung cancer |
| MVBs    | multivesicular bodies |
| TGF     | transforming growth factor |
| miRNAs  | microRNAs |
| MMP     | matrix metalloproteinase |
| PDAC    | pancreatic ductal adenocarcinoma |
| EOC     | epithelial ovarian cancer |
| HUVECs  | human umbilical vein endothelial cells |
| CRC     | colorectal cancer |
| HCC     | hepatocellular carcinoma |
| TNM     | tumor lymph node metastasis |
| GC      | gastric cancer |
| CAFs    | carcinoma-associated fibroblasts |
| TUBB3   | β-III tubulin |
| HNRNPK  | heterogeneous ribosomal protein K |
| BC      | bladder cancer |
| HLECs   | human lymphatic endothelial cells |
| PROX1   | Prospero homeobox 1 |
| MM      | myeloma |
| MSCs    | mesenchymal stem cells |
| RFs     | recurrence-free survival |
| OS      | overall survival |
| CSC     | cancer stem cells |
| GST-P   | glutathione S-transferase placental type |
| AFP     | alpha-fetoprotein |
| GGT     | gamma-glutamyl transpeptidase |
| ALT     | alanine aminotransferase |
| AST     | aspartic transaminase |
| ALP     | alkaline phosphatase |
| CC      | cervical cancer |

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–674.

2. Nie H, Wang Y, Liao Z, Zhou J, Ou C. The function and mechanism of circular RNAs in gastrointestinal tumours. Cell Prolif. 2020;53(7), e12815.

3. Weidle UH, Birzelle F, Kollmorgen G, Rüger R. Long non-coding RNAs and their role in metastasis. Cancer Genomics Proteomics. 2017;14(3):143–160.

4. Hu X, Sood AK, Dang CV, Zhang L. The role of long non-coding RNAs in cancer: the dark matter matters. Curr Opin Genet Dev. 2018;48:8–15.

5. Sun Z, Ou C, Liu J, et al. YAP1-induced MALAT1 promotes epithelial-mesenchymal transition and angiogenesis by sponging miR-126-5p in colorectal cancer. Oncogene. 2019;38(14):2642–2644.

6. Mason JA, Davison-Versagli CA, Leliaert AK, et al. Oncogenic Ras differentially regulates metabolism and anoikis in extracellular matrix-detached cells. Cell Death Differ. 2016;23(8):1271–1282.

7. Headley MB, Bins A, Nip A, et al. Visualization of immediate immune responses to pioneer metastatic cells in the lung. Nature. 2016;531(7595):513–517.
8. Chigusa S, Moroi T, Shoji Y. State-of-the-Art calculation of the decay rate of electroweak vacuum in the standard model. Phys Rev Lett. 2017;119(21),e211801.

9. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57–70.

10. Lee J, Abdeen AA, Wycislo KL, Fan TM, Killian KA. Interfacial geometry dictates cancer cell tumorigenicity. Nat Mater. 2016;15(8):856–862.

11. Maishi N, Ohba Y, Akiyama K, et al. Tumour endothelial cells in high metastatic tumours promote metastasis via epigenetic dysregulation of biglycan. Sci Rep. 2016;6:6,82039.

12. Pegtel DM, Gould SJ. Exosomes. Annu Rev Biochem. 2019;88:487–514.

13. Li S, Li Y, Chen B, et al. exoRBase: a database of circRNA, lncRNA and mRNA in human blood exosomes. Nucleic Acids Res. 2018;46(D1):D106–D112.

14. Yousefi H, Maherennaghsh M, Molaei F, et al. Long noncoding RNAs and exosomal lncRNAs: classification, and mechanisms in breast cancer metastasis and drug resistance. Oncogene. 2020;39(5):953–974.

15. van Niel G, D’Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. 2018;19(4):213–228.

16. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013;200(4):373–383.

17. Shao H, Im H, Castro CM, Breakefield X, Weissleder R, Lee H. New technologies for analysis of extracellular vesicles. Chem Rev. 2018;118(4):1917–1950.

18. Hurley JH, Hanson PI. Membrane budding and scission by the ESCRT machinery: it’s all in the neck. Nat Rev Mol Cell Biol. 2010;11(8):556–566.

19. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol. 2014;30:255–289.

20. Harding C, Heuser J, Stahl P. Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. J Cell Biol. 1983;97(2):329–339.

21. Pan BT, Johnstone RM. Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: selective externalization of the receptor. Cell. 1983;33(3):967–976.

22. Kowal J, Tkach M, Théry C. Biogenesis and secretion of exosomes. Curr Opin Cell Biol. 2014;29:116–125.

23. Zhang H, Deng T, Ge S, et al. Exosome circRNA secreted from adipocytes promotes the growth of hepatocellular carcinoma by targeting debiquitination-related USP7. Oncogene. 2019;38(15):2844–2859.

24. Zhou R, Chen KK, Zhang J, et al. The decade of exosomal long RNA species: an emerging cancer antigen. Mol Cancer. 2018;17(1),e79.

25. Wu Y, Wang Y, Wei M, Han X, Xu T, Cui M. Advances in the study of exomnc RNA in tumors and the selection of research methods. Biomed Pharmacother. 2020;123:109716.

26. Zhang H, Zhu L, Bai M, et al. Exosomal circRNA derived from gastric tumor promotes white adipose browning by targeting the miR-133/PRDM16 pathway. Int J Cancer. 2019;144(10):2501–2515.

27. Tyner JW. Functional genomics for personalized cancer therapy. Sci Transl Med. 2014;6(243),e243fs26.

28. Weil AR. Precision medicine. Health Aff (Millwood). 2018;37(5):e687.

29. Wang Y, Nie H, He X, et al. The emerging role of super enhancer-derived noncoding RNAs in human cancer. Theranostics. 2020;10(24):11049–11062.

30. Chan JJ, Tao Y. Noncoding RNA:RNA regulatory networks in cancer. Int J Mol Sci. 2018;19(5),e13110.

31. Dempsey JL, Cui JY. Long non-coding RNAs: a novel paradigm for toxicityology. Toxicol Sci. 2017;155(1):3–21.

32. Ou C, Sun Z, He X, et al. Targeting YAP1/LINC00152/FSCN1 signaling Axis prevents the progression of colorectal cancer. Adv Sci (Weinh). 2019;7(3),e1901380.

33. Iyer MK, Niknafs YS, Malik R, et al. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet. 2015;47(3):199–208.

34. Yan Y, Xu Z, Chen X, et al. Novel function of IncRNA ADAMTS9-AS2 in promoting temozolomide resistance in glioblastoma via upregulating the FUS/MDM2 ubiquitination Axis. Front Cell Dev Biol. 2019;7,e217.

35. Sun Z, Yang S, Zhou Q, et al. Emerging role of exosome-derived long non-coding RNAs in tumor microenvironment. Mol Cancer. 2018;17(1),e82.

36. Tang Y, He Y, Zhang P, et al. LncRNAs regulate the cytoskeleton and related Rho/ROCK signaling in cancer metastasis. Mol Cancer. 2018;17(1),e77.

37. Fan C, Tang Y, Wang J, et al. Role of long non-coding RNAs in glucose metabolism in cancer. Mol Cancer. 2017;16(1),e130.

38. Fan Q, Yang L, Zhang X, et al. The emerging role of exosome-derived non-coding RNAs in cancer biology. Cancer Lett. 2018;414:107–115.

39. Wang JP, Tang YY, Fan CM, et al. The role of exosomal non-coding RNAs in cancer metastasis. Oncotarget. 2017;9(15):12487–12502.

40. Zhang R, Xia Y, Wang Z, et al. Serum long non-coding RNA MALAT-1 protected by exosomes is up-regulated and promotes cell proliferation and migration in non-small cell lung cancer. Biochim Biophys Acta. 2017;490(2):406–414.

41. EL Andaloussi S, Mäger I, Breakefield XO, Wood MJ. Extracellular vesicles: biology and emerging therapeutic opportunities. Nat Rev Drug Discov. 2013;12(5):347–357.

42. Liu S, Zhan Y, Luo J, et al. Roles of exosomes in the carcinogenesis and clinical therapy of non-small cell lung cancer. Biomed Pharmacother. 2019;111:338–346.

43. Zhang X, Sai B, Wang F, et al. Hypoxic BMSC-derived exosomal miRNAs promote metastasis of lung cancer cells via STAT3-induced EMT. Mol Cancer. 2019;18(1),e40.

44. Heijnen HF, Schiel AE, Fijnheer R, Geuze HJ, Sixma JJ. Activated platelets release two types of membrane vesicles: microvesicles by surface shedding and exosomes derived from exocytosis of multivesicular bodies and alpha-granules. Blood. 1999;94(11):3791–3799.

45. van der Pol E, Böing AN, Harrison P, Sturk A, Nieuwland R. Classification, functions, and clinical relevance of extracellular vesicles. Pharmacol Rev. 2012;64(3):676–705.

46. Zhang HG, Grizzle WE. Exosomes: a novel pathway of local and distant intercellular communication that facilitates the growth and metastasis of neoplastic lesions. Am J Pathol. 2014;184(1):28–41.

47. Vlassov AV, Magdaleno S, Setterquist R, Conrad R. Exosomes: current knowledge of their composition, biological functions, and diagnostic and therapeutic potentials. Biochim Biophys Acta. 2012;1820(7):940–948.

48. Huang G, Zhu H, Wu S, Cui M, Xu T. Long noncoding RNA can be a probable mechanism and a novel target for diagnosis and therapy in fragile X syndrome. Front Genet. 2019;10,e446.

49. He X, Li S, Yu B, et al. Up-regulation of LINC00467 promotes the tumorigenesis in colorectal cancer. J Cancer. 2019;10(25):6405–6413.

50. Liu C, Fu H, Liu X, et al. LINC00470 coordinates the epigenetic dysregulation of biglycan. Cell Res. 2019;29:116–125.

51. Wynn TW, Watts NB, Garlick AB, et al. Exosome-derived long non-coding RNAs in tumor microenvironment. Mol Cancer. 2018;17(1),e82.
69. Deng M, Yuan H, Liu S, Hu Z, Xiao H. Exosome-transmitted

70. Chen L, Yang W, Guo Y, et al. Exosomal lncRNA GAS5 regulates

71. Liang ZX, Liu HS, Wang FW, et al. LncRNA RPPH1 promotes

72. Wu DM, Deng SH, Liu T, Han R, Zhang T, Xu Y. TGF-beta-

73. Li Z, Qin X, Bian W, et al. Exosomal IncRNA ZFAS1 regulates

74. Bhan A, Soleimani M, Mandal SS. Long noncoding RNA and

75. Camacho CV, Choudhari R, Gadad SS. Long noncoding RNAs

76. Qiu JJ, Lin XJ, Tang XY, Zheng TT, Lin YY, Hua KQ. Exosomal

77. Li X, Liu R, Wang Y, et al. Cholangiocyte-derived exosomal

78. Mao Q, Liang XL, Zhang CL, Pang YH, Lu YX. LncRNA KLF3-AS1

79. Chen H, Xia W, Hou M. LncRNA-NEAT1 from the competing

80. Chen X, Kim D, Han J, Kim Y, Lee M, Jin EJ. PBMC and

81. Song J, Kim D, Han J, Kim Y, Lee M, Jin EJ. PBMC and

82. Song J, Kim D, Han J, Kim Y, Lee M, Jin EJ. PBMC and

83. Qiu JJ, Lin XJ, Tang XY, Zheng TT, Lin YY, Hua KQ. Exosomal

84. Chen L, Yang W, Guo Y, et al. Exosomal IncRNA GAS5 regulates

85. Elkouris M, Kouroupi G, Vourvoukeli a, et al. Long non-coding

86. Ou C, Sun Z, Li X, et al. mir-590-5p, a density-sensitive microRNA, inhibits tumorigenesis by targeting YAP1 in colorectal cancer. Mol Cancer. 2019;18(1),e22.

87. Wang FW, Cao CH, Han K, et al. APC-activated long noncoding RNA inhibits colorectal carcinoma pathogenesis through reduction of exosome production. J Clin Invest. 2019;129(2):727–743.

88. Zhang Q, Len TY, Zhang SX, Zhao QH, Yang LH. Exosomes transferring long non-coding RNA FAL1 to regulate ovarian cancer metastasis through the PTEN/AKT signaling pathway. Eur Rev Med Pharmacol Sci. 2020;24(11):43–54.

89. Wang X, Li H, Lu X, et al. Melittin-induced long non-coding RNA NONHSAT105177 inhibits proliferation and migration of pancreatic ductal adenocarcinoma. Cell Death Dis. 2018;9(10),e940.

90. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet. 2016;17(1):47–62.

91. Chen LL. Linking long noncoding RNA localization and function. Trends Biochem Sci. 2016;41(9):761–772.

92. Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. Cell. 2013;152(6):1298–1307.

93. Ou C, Sun Z, Li X, et al. The non-coding RNA landscape of plasma cell dyscrasias. Cancers (Basel). 2020;12(2),e320.

94. Wang S, Hu W, Wang Y, et al. Long non-coding RNA UCA1 promotes malignant phenotypes of renal cancer cells by modulating the miR-182-5p/DLL4 axis as a ceRNA. Mol Cancer. 2020;19(1),e18.
106. Han M, Gu Y, Lu P, et al. Exosome-mediated lncRNA AFAP1-AS1 promotes cell proliferation and migration by acting as a ceRNA of miR-1236 in hepatocellular carcinoma cells. *Life Sci*. 2018;197:122–129.

107. Cao SQ, Zheng H, Sun BC, et al. Long non-coding RNA highly up-regulated in liver cancer promotes exosome secretion. *World J Gastroenterol*. 2019;25(35):5283–5299.

108. Chen X, Wang Z, Tong F, Dong X, Wu G, Zhang R. IncRNA UCA1 promotes G0/G1 arrest resistance as a ceRNA to target FOSL2 by sponging miR-143 in non-small cell lung cancer. *Mol Ther Nucleic Acids*. 2020;19:643–653.

109. Ren J, Ding L, Zhang D, et al. Carcinoma-associated fibroblasts promote the stemness and chemoresistance of colorectal cancer by transferring exosomal IncRNA H19. *Theranostics*. 2018;8(14):3932–3948.

110. Luan Y, Li L, Luan Y, et al. Circulating IncRNA UCA1 promotes malignancy of colorectal cancer via the miR-143/MY06 Axis. *Mol Ther Nucleic Acids*. 2020;19:790–803.

111. Li Z, Jiang P, Li J, et al. Tumor-derived exosomal Inc-Sox2ot promotes EMT and stemness by acting as a ceRNA in pancreatic ductal adenocarcinoma. *Oncogene*. 2018;37(28):3822–3838.

112. Cao S, Lin L, Xia X, Wu H. IncRNA SPRY4-IT1 regulates cell proliferation and migration by sponging miR-181-3p and regulating AMPK expression in gastric cancer. *Mol Ther Nucleic Acids*. 2019;17:455–464.

113. Zhao W, Qin P, Zhang D, et al. Long non-coding RNA PVT1 encapsulated in bone marrow mesenchymal stem cell-derived exosomes promotes osteosarcoma growth and metastasis by stabilizing ERG and sponging miR-183-5p. *Aging (Albany NY)*. 2019;11(21):9581–9596.

114. Bian EB, Chen EF, Xu YD, et al. Exosomal IncRNA-ATB activates astrocytes that promote glioma cell invasion. *Int J Oncol*. 2019;54(2):713–721.

115. Wang J, Yang X, Li R, et al. Long non-coding RNA MYU promotes prostate cancer proliferation by mediating the miR-184/c-Myc axis. *Oncol Rep*. 2018;40(5):2814–2825.

116. Yang X, Wang L, Li R, et al. The long non-coding RNA PCSEAT exhibits an oncogetic property in prostate cancer and functions as a competing endogenous RNA that associates with EZH2. *Biochem Biophys Res Commun*. 2018;502(2):262–268.

117. Gorouzsi S, Gorgi Valokala M, Mosaffa F, Zirak MR, Zarnami P, Behravan J. Crosstalk in cancer resistance and metastasis. *Crit Rev Oncol Hematol*. 2018;132:145–153.

118. Karagiannis GS, Condeelis JS, Oktay MH. Chemotherapy-induced metastasis: mechanisms and translational opportunities. *Clin Exp Metastasis*. 2018;35(4):269–284.

119. Zou HY, Bai WD, Ye XM, Yang AG, Jia LT. Long non-coding RNA UCA1 desensitizes breast cancer cells to trastuzumab by impeding miR-18a repression of Yes-associated protein 1. *Biochem Biophys Res Commun*. 2018;496(4):1308–1313.

120. Gao T, Liu X, He B, et al. Exosomal IncRNA H19 is associated with poor development in colorectal cancer by modifying HNRNPK expression. *Cancer Cell Int*. 2018;18:e11.

121. Han M, Gu Y, Lu P, et al. Exosome-mediated IncRNA AFAP1-AS1 promotes trastuzumab resistance through binding with AUF1 and activating ERBB2 translation. *Mol Cancer*. 2020;19(1),e26.

122. Chen C, Luo Y, He W, et al. Exosomal long noncoding RNA LNMAT2 promotes lympathic metastasis in bladder cancer. *J Clin Invest*. 2020;130(1):404–421.

123. Li L, Xu H, Han H, et al. Exosome-mediated transfer of IncRUNX2-AS1 from multiple myeloma cells to MSCs contributes to osteogenesis. *Onco gene*. 2018;37(41):5508–5519.

124. Chen F, Wang N, Tan HY, Guo W, Zhang C, Feng Y. The functional roles of exosomes-derived long non-coding RNA in human cancer. *Cancer Biol Ther*. 2019;20(5):583–592.

125. Li J, Chen J, Wang S, et al. Blockage of transferred exosome-shuttled miR-494 inhibits melanoma growth and metastasis. *J Cell Physiol*. 2019;234(9):15763–15774.

126. Kahropa H, Hejazi MS, Samadi N. Exosomes: from carcinogenesis and metastasis to diagnosis and treatment of gastric cancer. *Cell Mol Life Sci*. 2019;76(9):1747–1758.

127. Lee YR, Kim G, Tak WY, et al. Circulating exosomal noncoding RNAs as prognostic biomarkers in human hepatocellular carcinoma. *Int J Cancer*. 2019;144(6):1444–1452.

128. Xu H, Chen Y, Dong X, Wang X. Serum exosomal long non-coding RNAs ENSG00000258332.1 and LINC00635 for the diagnosis and prognosis of hepatocellular carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2018;27(6):710–716.

129. Liu L, Meng T, Yang XH, et al. Prognostic and predictive value of long non-coding RNA GAS5 and microRNA-221 in colorectal cancer and their effects on colorectal cancer cell proliferation, migration, and invasion. *Cancer Biomark*. 2018;22(2):283–299.

130. Liu T, Zhang X, Gao S, et al. Exosomal long noncoding RNA CINDE-H is a novel serum-based biomarker for diagnosis and prognosis of colorectal cancer. *Oncotarget*. 2016;7(51):85551–85563.

131. Wang J, Zhou Y, Lu J, et al. Combined detection of serum exosomal miR-21 and HOTAIR as diagnostic and prognostic biomarkers for laryngeal squamous cell carcinoma. *Med Oncol*. 2014;31(9),e148.

132. Li S, Zhang M, Zhang H, et al. Exosomal long noncoding RNA Inc-GNAQ-6:1 may serve as a diagnostic marker for gastric cancer. *Clin Chim Acta*. 2020;501:252–257.

133. Pan L, Liang W, Fu M, et al. Exosomes-mediated transfer of long noncoding RNA ZFAS1 promotes gastric cancer progression. *J Cancer Res Clin Oncol*. 2017;143(6):991–1004.

134. Teng Y, Kang H, Chu Y. Identification of an exosomal long noncoding RNA SOX2-OT in plasma as a promising biomarker for lung squamous cell carcinoma. *Genet Test Mol Biomarkers*. 2019;23(4):235–240.

135. Zhang P, Zhou H, Lu K, Lu Y, Wang Y, Feng T. Exosome-mediated delivery of MALAT1 induces cell proliferation in breast cancer. *Onco Targets Ther*. 2018;11:291–299.

136. Filippov-Levy N, Cohen-Schussheim H, Tropé CG, et al. Expression and clinical role of long non-coding RNA in high-grade serous carcinoma. *Gynecol Oncol*. 2018;148(3):559–566.

137. Li C, Li W, Zhang Y, et al. Increased expression of antisense IncRNA SPINT1-AS1 predicts a poor prognosis in colorectal cancer and is negatively correlated with its sense transcript. *Onco Targets Ther*. 2018;11:3969–3978.

138. Sola C, Filliol I, Gutierrez MC, Mokrousov I, Vincent V, Rastogi N. Spoligotype database of Mycobacterium tuberculosis: biogeographic distribution of shared types and epimicrobial and phylogenetic perspectives. *Emerg Infect Dis*. 2001;7(3):390–396.

139. Zheng H, Zhan Y, Liu S, et al. The roles of tumor-derived exosomes in non-small cell lung cancer and their clinical implications. *J Exp Clin Cancer Res*. 2018;37(1),e226.

140. Alzahrani FA, El-Magd MA, Abdelfattah-Hassan A, et al. Potential effect of exosomes derived from cancer stem cells and MSCs on progression of DEN-induced HCC in rats. *Stem Cells Int*. 2018;2018,8058979.

141. Luo X, Wei J, Yang FL, et al. Exosomal IncRNA HNF1A-AS1 affects cisplatin resistance in cervical cancer cells through regulating microRNA-34b/TEFT1 axis. *Cancer Cell Int*. 2019;19,e323.

142. Wang Y, He X, Nie H, et al. Application of artificial intelligence to the diagnosis and therapy of colorectal cancer. *Am J Cancer Res*. 2020;10(1):357–3598.

143. Kowal J, Arras G, Colombo M, et al. Proteomic comparison defines novel markers to characterize heterogeneous populations of extracellular vesicle subtypes. *Proc Natl Acad Sci U S A*. 2016;113(8):E968–E977.