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REVIEW ARTICLE

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

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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.

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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.[3–9] Cancer invasion and metastasis present difficult problems in clinical treatment, affecting patient prognosis and survival, and are important causes of tumor-related deaths.[10,11] 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 (snoRNA), 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—10,0000 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 al[40] 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.[41–43] 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.[44,45] 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.[46] 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 information transmission systems that can influence cellular communication, cell migration, angiogenesis, and tumor cell growth.[47]

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.[48–53] LncRNAs are widely involved in the regulation of various biological activities, due in part to their tissue-specific expression, and influence disease processes.[54,55] 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.[56,57] 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).[58–67] 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.[68,69] For example, exosomal delivery of the lncRNA RPPH1 can promote M2 polarization of macrophages and colorectal cancer (CRC) metastasis.[70] 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,[71] TGF-β/Smad,[72] STAT3,[73] and VEGFA/VEGFR2 signaling pathways[74] (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.[75] Zhang et al[76] 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.[77]

Interestingly, transforming growth factor (TGF)-β-induced exosomes can regulate the migration and invasion of lung cancer cells. Wu et al[72] found that TGF-β pretreatment 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 lnc-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.[78] 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

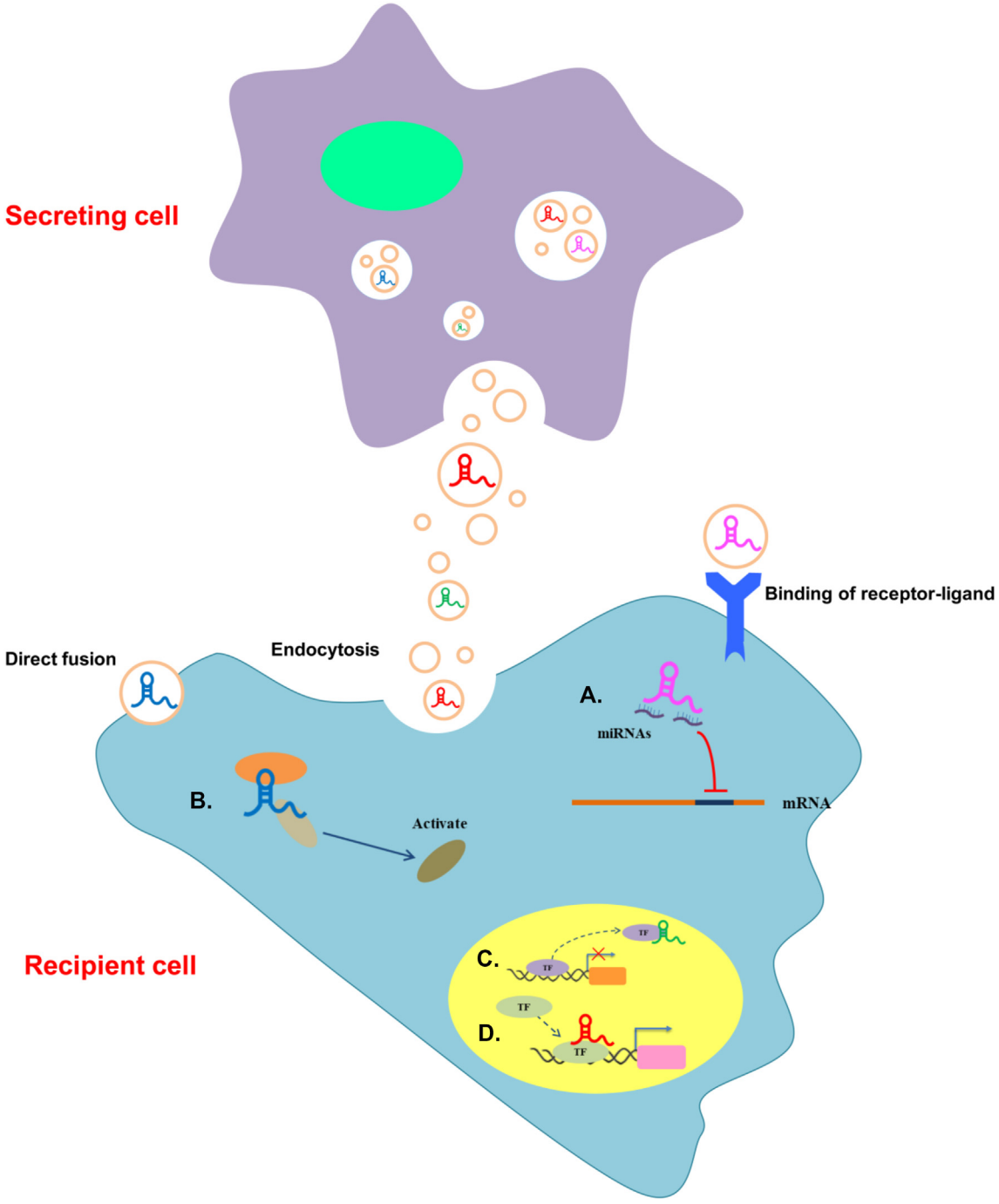

Figure 1 Exosomal long non-coding RNAs (lncRNAs) taken up by recipient cells. Exosomal lncRNAs are taken up by recipient cells via direct fusion, endocytosis, and receptor-ligand binding. Exosomal lncRNAs that enter cells can act as (**A**) competing endogenous RNAs (ceRNAs) that interact with miRNAs 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.

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.[40]

The experimental results of Li et al[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.[79] In hepatocellular carcinoma (HCC), the lncRNA HANR indirectly regulates the Eag1/VEGF axis through miR-

Table 1 Exosomal lncRNAs in human diseases.

Diseases	Exosomal lncRNAs	Secreting cells	Recipient cells	Functions	Ref.
Diabetes mellitus	H19	Mesenchymal stem cells	Fibroblasts	Inhibits fibroblast apoptosis and inflammation	58
Cholestasis		Bile duct cells	Macrophages	Promotes macrophage activation	59
Cardiovascular diseases	NEAT1	Mesenchymal stem cells	Cardiomyocytes	Protects cardiomyocytes and inhibits myocardial apoptosis	60
Myocardial infarction	KLF3-AS1		Cardiomyocytes	Inhibits apoptosis and pyroptosis in cardiomyocytes	61
Rheumatoid arthritis	HOTAIR	Monocytes	Macrophages	Affects the migration of macrophages	62
Osteoporosis	MALAT1	Bone marrow mesenchymal stem cells	Osteoblasts	Reduces the inflammatory response	63
Epithelial ovarian cancer		Epithelial ovarian cancer cells	Human umbilical vein endothelial cells	Promotes angiogenesis	64
Myocardial infarction atherosclerosis	GAS5	Macrophages	Vascular endothelial cells	Regulates apoptosis of vascular endothelial cells	65
Parkinson's disease	SNCA-AS1	Peripheral blood mononuclear cells	Dopaminergic neuron	Regulates neuronal differentiation	66
Renal cell cancer	lncARSR	Sunitinib-resistant RCC cells	Sunitinib-sensitive RCC cells	Promotes sunitinib resistance of RCC cells	67

296 and promotes lymphangiogenesis in HCC cells.[74] Many signaling pathways have been shown to be related to lncRNA-mediated cancer metastasis, for example, the exosome lncRNA FMR1-AS1 can bind to toll like receptor 7 (TLR7), activate downstream TLR7–NFκB signal transduction, and promote the upregulation of c-Myc, thus inducing ESCC cell proliferation and invasion.[80] In a study of CRC invasion and metastasis, Wang et al[81] found that lncRNA-APC1-silenced CRC cells can promote angiogenesis by inhibiting exosome secretion and activating the MAPK pathway in endothelial cells In this process, exosome-secreted Wnt1 enhances the proliferation and migration of CRC cells mainly through non-classical Wnt signaling. The SKOV3-secreted lncRNA FAL1 regulates the PTEN/AKT signaling pathway to inhibit the migration of epithelial ovarian cancer cells both *in vitro* and *in vivo*.[82] Wang et al[83] reported that the exosomal lncRNA NONHSAT105177 was induced by 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 melittin treatment on NONHSAT105177, its overexpression of NONHSAT105177 inhibited the proliferation, migration, and EMT of PDAC cell lines.

Exosomal lncRNAs regulate cancer metastasis by sponging miRNAs

Unlike mRNAs, lncRNAs are widely distributed in the nucleus and cytoplasm,[84] and their subcellular localization is strictly related to their biological roles.[85,86] 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.[87,88] LncRNAs and miRNAs jointly constitute the competitive endogenous RNA (ceRNA) network, which is involved in tumor proliferation, invasion, migration, and apoptosis.[89,90] Numerous recent studies have revealed that lncRNAs can be packaged in exosomes and can bind to miRNAs and have significant effects on cancer metastasis[73,91–101] (Table 2). In colorectal cancer (CRC), expression of the exosomal lncRNA 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.[95] The exosomal lncRNA Sox2ot regulates Sox2 expression in PDAC by sponging miR-200. To regulate intracellular gene expression, exosomes are transferred from the producing cells to the recipient PDAC cells, where they promote invasion and metastasis. Exosomal lncRNA Sox2ot was also shown to be related to the prognosis of PDAC.[96] Cao et al[92] 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 tissues. HULC levels in serum exosomes and liver cancer cells were related to tumour lymph node metastasis (TNM) grade. Overexpressed lncRNA HULC promotes the growth and invasion of HCC cells, inhibiting apoptosis by regulating the HULC/miR-372-3p/Rab11a axis. *In vitro* experiments showed that down-regulation of the exosomal lncRNA SPRY4-IT1 significantly inhibited the proliferation of gastric cancer (GC) cells by inducing G1 arrest and promoting apoptosis. Other studies have shown that exosomal SPRY4-IT1 exerts biological effects through the SPRY4-IT1/miR-101-3p/AMPK axis. Researchers have suggested SPRY4-IT1 as a potential

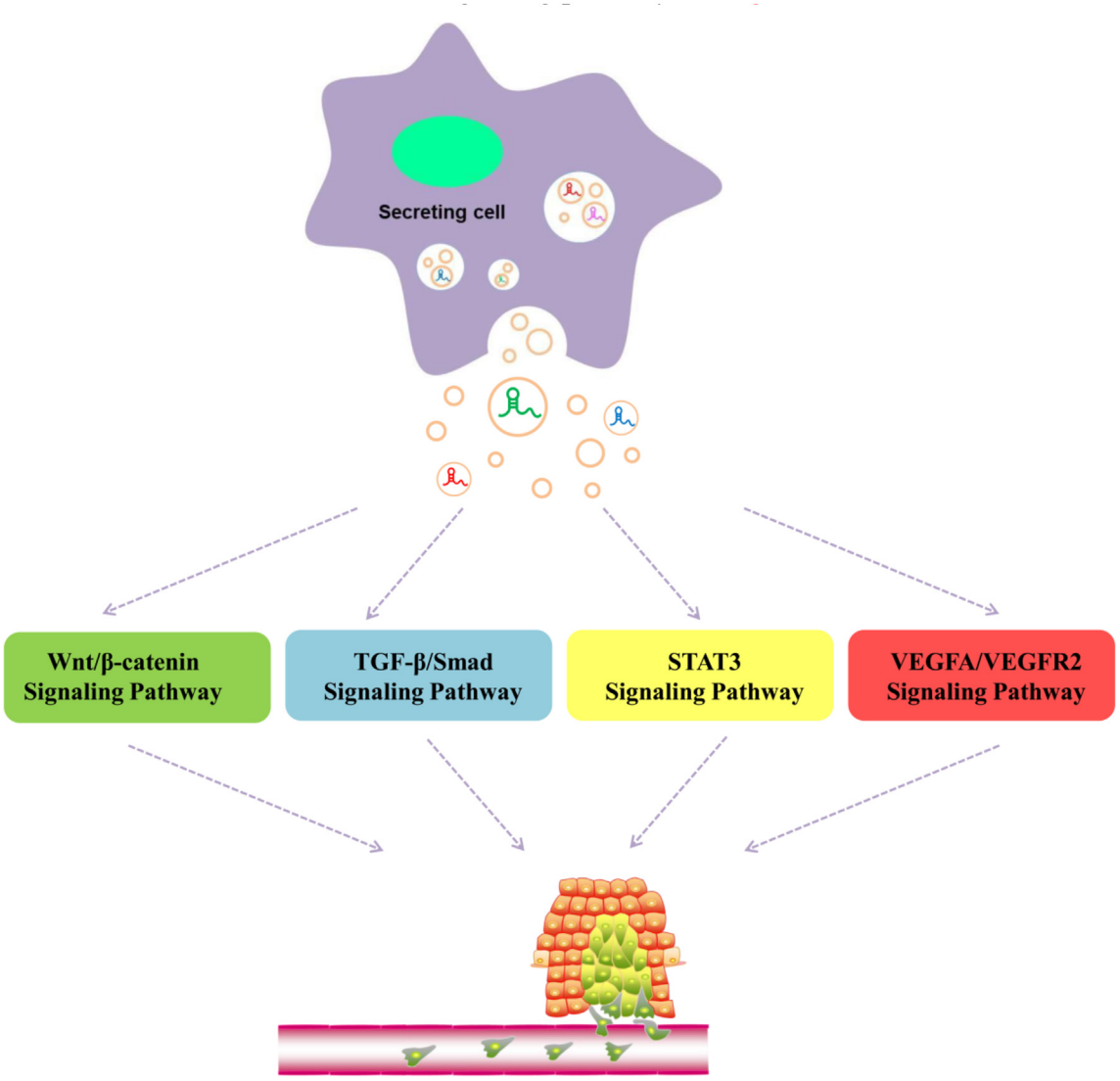

Figure 2 Exosomal lncRNAs promote cancer metastasis by regulating signaling pathways. Exosomal LncRNAs promote cancer metastasis by regulating the Wnt/β-catenin, TGF-β, STAT3, and VEGFA/VEGFR2 signaling pathways.

therapeutic target for GC patients.[97] Li et al[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.[102,103] Exosomal lncRNAs can modulate tumorigenesis and induce chemotherapy resistance by acting as ceRNAs. Ren et al[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 β-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.[104]

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).

Table 2 Exosomal lncRNAs and target miRNAs related to cancer metastasis.

Cancers	Exosomal lncRNAs	Expression alteration	miRNAs	Target genes	Functions	Ref.
Hepatocellular carcinoma	FAL1	↑	miR-1236	ZEB1/AFP	Promotes proliferation and metastasis	91
	HULC	↑	miR-372-3p	Rablla	Promotes growth and invasion	92
Non-small cell lung cancer	UCA1	↑	miR-143	FOSL2	Promotes proliferation and resistance to gefitinib	93
Colorectal cancer	H19	↑	miR-141	β-catenin	Promotes stemness and chemoresistance	94
	UCA1	↑	miR-143	MYO6	Promotes metastasis	95
Esophageal cancer	ZFAS1	↑	miR-124	STAT3	Promotes proliferation, metastasis and invasion	73
Pancreatic ductal adenocarcinoma	Sox2ot	↑	miR-200	Sox2	Promotes invasion and metastasis	96
Gastric cancer	SPRY4-IT1	↑	miR-101-3p	AMPK	Promotes metastasis and invasion	97
Osteosarcoma	PVT1	↑	miR-183-5p	ERG	Promotes growth and metastasis	98
Glioma	ATB	↑	miR-204-3p	GFAP	Promotes invasion	99
Prostate cancer	MYU	↑	miR-184	c-Myc	Promotes proliferation and migration	100
	PCSEAT	↑	miR-143-3p/ miR-24-2-5p	EZH2	Promotes proliferation and migration	101

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.[70] 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.[105] 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 translation of the ERBB2 gene by binding to the AUF1 protein, without affecting mRNA levels, and finally inducing trastuzumab resistance. Experimental data showed that exosomal AFAP1-AS1 is a promising marker for predicting trastuzumab resistance and breast cancer treatment.[106] LncRNAs can also play a role in gene regulation by interacting with transcription factors. Chen et al[107] reported that the exosomal lncRNA LNMAT2 interacts directly with the heterogeneous ribonucleoprotein A2B1 (hnRNPA2B1) 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 hnRNPA2B1 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.[108]

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.[86] 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.[109] 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.[110,111] Therefore, exosomal lncRNAs have been widely studied as tumor markers in recent years[40,64,70,81,92,95–97,105,107,112–121] (Table 3).

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.[81] Lee et al[112] 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 ATB 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.[122] Serum levels of the exosomal lncRNAs ENSG00000258332.1 and LINC00635 are related to lymph node metastasis, TNM stage, and overall survival (OS). Combined detection of ENSG00000258332.1, LINC00635, and AFP has value for diagnosis and predicting the prognosis of HCC.[113] Liu et al[114] 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.[123,124] To investigate whether exosomes can inhibit tumor growth and metastasis in the tumor microenvironment in HCC, Alzahrani et al[125] 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. In cervical cancer (CC), Luo et al[126] demonstrated that exosomal HNF1A-AS1 is produced by cisplatin(DPP)-resistant cells and can promote the proliferation of CC cells and inhibit apoptosis. They further examined the effect of exosomal HNF1A-AS1 on tumor formation in nude mice, and found that tumor weight and volume were significantly lower in the exosomal HNF1A-

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
	HULC	↑	Lymph node metastasis		92
Colorectal cancer	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	lnc-GNAQ-6:1	↓	—	0.732	117
	ZFAS1	↑	Lymph node metastasis and TNM stage	0.630	118
	SPRY4-IT1	↑	Tumor size and TNM stage		97
Lung squamous cell carcinoma	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

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,[127] increasing numbers of exosomal lncRNAs have been identified. Compared to exosomal proteins, the extraction and detection of lncRNAs require higher specificity and sensitivity. Because exosomal lncRNA 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 lncRNAs 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 immunoconcentration.[15,128] 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 lncRNAs. 2) Further investigations of exosomal lncRNAs 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 lncRNAs 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 lncRNAs 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 lncRNAs as clinical biological markers for cancer metastasis. The present understanding of exosomal lncRNAs is just the tip of the iceberg, and the development of novel approaches and techniques will shed new light on these processes. Exosomal lncRNAs 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.

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Abbreviations

EVs	extracellular vesicles
lncRNAs	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

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