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REVIEW

The functional roles of exosomal long non-coding RNAs in cancer

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Abstract

Exosomes are extracellular membranous vesicles that are secreted by various cell types. Exosomes have become indispensable facilitators in the exchange of information between cells. More importantly, exosomes perform a crucial role in a variety of diseases including cancers. Long non-coding RNAs (lncRNAs) are over 200 nucleotides long transcripts that exhibit no or limited protein-coding potentials. LncRNAs are an emerging group of regulatory RNAs and can be selectively packaged into exosomes. Exosomal lncRNAs play a central role in carcinogenesis and cancer progression by modulating tumor growth, metastasis, angiogenesis and chemoresistance. Moreover, exosomal lncRNAs function as messengers in cell-to-cell communication, and thus remodel the tumor microenvironment. Their function relevance in cancer biology hints at the possibility of employing exosomal lncRNAs as promising, non-invasive biomarkers for further cancer therapy. In this review, we provide an overview of current research on the functional roles of exosomal lncRNAs in cancer and discuss their potential clinical applications as diagnostic biomarkers and therapeutic targets for cancers.

Keywords Exosomes · Extracellular vesicles · Exosome biogenesis · Long non-coding RNA · Cancer pathogenesis · Cancer diagnosis · Cancer therapy

Background

Exosomes are extracellular vesicles ranging from 30 to 100 nm in diameter [1]. These nano-sized vesicles are generated within multivesicular endosomes and are released by cells through the fusion of these compartments with the plasma membrane [2]. They are important components in cell-to-cell communication by delivering intracellular components such as DNAs, RNAs and proteins [3]. Exosomes can be released by various types of cells, including immune cells and tumor cells [4, 5]. Tumor cells secrete more exosomes than normal cells [6]. Secreted exosomes can be taken up by nearby or remote cells [7, 8]. Exosomes have become a focus of research in the past decade. Remarkably, tumor-derived exosomes play an important role in tumorigenesis and tumor progression. For instance, gastric cancer (GC)-derived exosomes promoted tumor cell proliferation by activating phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways [9]. Primary hepatocellular carcinoma (HCC)-derived exosomes modulated adhesion of circulating HCC cells by delivering SMAD family member 3 (SMAD3), thus facilitating tumor metastasis [10]. Head and neck squamous cell carcinoma (HNSCC)-derived exosomes could promote angiogenesis by reprogramming recipient endothelial cells [11]. In addition, exosomes are found to be present in all kinds of body fluids such as saliva, blood and urine [12–14]. The accessibility of exosomes in almost all body fluids demonstrates their potential as prospective non-invasive biomarkers for different types of cancers.

Long non-coding RNAs (lncRNAs) are defined as transcripts longer than 200 nucleotides that have no or limited protein-coding capacity [15]. LncRNAs are present in either the nucleus or cytoplasm, and they can interact with DNAs, RNAs and proteins [16]. LncRNAs play a key role in gene regulation at epigenetic, transcriptional and

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post-transcriptional levels. LncRNAs are reported to exert significant functions in multiple physiological processes such as cell proliferation, apoptosis, migration and senescence [17, 18]. Increasing amounts of evidence have proved that lncRNAs are associated with the occurrence and progression of cancers by directly or indirectly interfering with gene expression [19–21]. LncRNAs can be selectively sorted into exosomes and serve as signaling messengers in intercellular communication [22]. Exosomal lncRNAs can travel to recipient cells where they transmit phenotypical changes. Exosome-derived lncRNAs are found to be involved in tumor growth, metastasis, angiogenesis and chemoresistance. Additionally, exosomal lncRNAs can reprogram cells in the tumor microenvironment, thereby contributing to tumor development. Through being enveloped into exosomes, lncRNAs can be secreted into a range of body fluids [23, 24]. LncRNAs in exosomes are protected from ribonuclease-mediated degradation and stably present in body fluids [25]. Exosomal lncRNAs may have potential as biomarkers for various types of cancers [26, 27]. Therefore, lncRNAs have gained increasing attention in the field of exosome research. In this review, we summarize the current knowledge regarding the contributions of exosomal lncRNAs to cancer progression, and also discuss their potential clinical applications as novel biomarkers and therapeutic targets in the management of cancers.

Biogenesis and characteristics of exosomes

Exosomes are phospholipid bilayer membrane vesicles of endocytic origin with a diameter of 30–100 nm [28]. Multiple cell types such as immune cells and tumor cells can secret exosomes. Exosomes function as crucial players in intercellular communication under both physiological and pathological conditions [29]. These nanovesicles can transfer bioactive molecules including DNAs, proteins, RNAs and ncRNAs from donor cells to recipient cells, leading to the variation in genetic and epigenetic factors and reprogramming of the recipient cells [7, 30, 31]. Exosomes are formed within the endosomal compartment [32] (Fig. 1). Early endosomes are originated from the inward budding of plasma membrane and subsequently mature into late endosomes [33]. Further invagination of the early endosomal

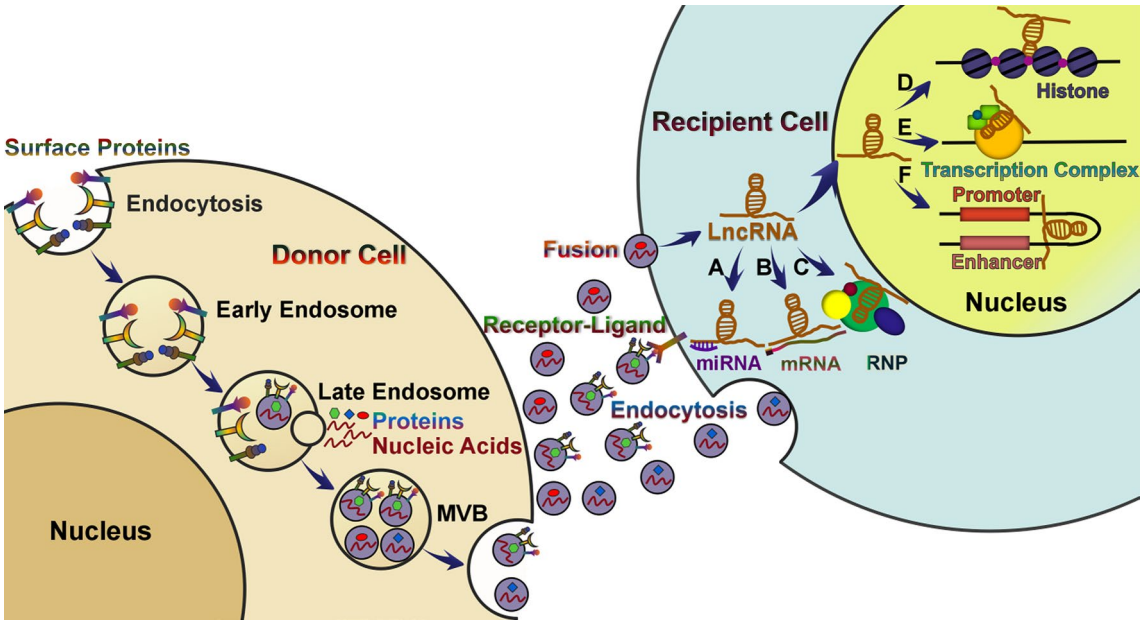

Fig. 1 Schematic illustration of exosome biogenesis and release. Exosome biogenesis begins with early endosome formation during endocytosis. The membrane proteins are internalized and delivered to early endosomes. Early endosomes are then matured into late endosomes, in which multiple intraluminal vesicles (ILVs) are generated by the inward budding of endosomal membranes. The accumulation of ILVs leads to the formation of multivesicular bodies (MVBs). Proteins and nucleic acids produced by the donor cell can be sorted to exosomes during MVB formation. Exosomes are released into the extracellular environment through the fusion of MVB with the cellular membrane. Exosomes are taken up by recipient cells through three pathways: direct fusion, receptor-mediated fusion or endocytosis. The exosomal lncRNAs are subsequently delivered to the recipient cell, thus exerting regulatory effect on various physiological processes. A LncRNAs sponge miRNAs to regulate the expression of their target genes. B LncRNAs can interact with mRNAs and recruit translation repressors to cooperatively inhibit mRNA translation. C LncRNAs serve as scaffolds for different proteins to form a ribonucleoprotein (RNP) complex, which can regulate gene expression. D LncRNAs guide epigenetic modifiers to alter the chromatin structure, histone methylation/acetylation level as well as DNA methylation level. E LncRNAs interact with the transcription complex as the guide or decoy to promote or suppress gene transcription. F LncRNAs also function as enhancers to induce gene transcription

membrane leads to the accumulation of intraluminal vesicles (ILVs) incorporating cytosolic proteins or nucleic acids [34]. Cargo loading into exosomes is modulated by multiple mechanisms. The endosomal sorting complex required for transport (ESCRT) machinery has been universally recognized as a key mechanism in cargo sorting and ILV biogenesis [35]. Moreover, ceramide plays a vital role in initiating ESCRT-independent ILV formation [36–38]. ILVs accumulate in late endosomes by constantly inward budding of endosomal membranes and cytosol sequestration, resulting in the formation of multivesicular bodies (MVBs). ILVs are released into the cell exterior through the fusion of MVBs with the plasma membrane [39]. The released ILVs are also referred to as exosomes, containing molecular constituents of their host cells [40]. MVB trafficking and fusion with the cell membrane are mediated by Rab guanosine triphosphatases (GTPases) [41]. Cytoskeletal regulatory proteins such as cortactin and coronin 1b also control the exosome secretion process [42]. The released exosomes can be taken up by recipient cells through the straight fusion process, the receptor–ligand fusion process or receptor-mediated endocytosis [43]. Exosomal cargoes consist of specific compositions that originate from donor cells [44, 45]. Exosomal components could differ owing to the selective sorting of cargoes into exosomes [46]. In addition to diverse proteins, lipids and nucleic acids, ncRNAs (e.g., sncRNAs and lncRNAs) have also been detected in exosomes [47, 48].

In recent years, exosomes and their RNA cargoes have been extensively studied since they play a vital role in the cell-to-cell communication during cancer pathogenesis. The loading of RNAs into exosomes was reported to be correlated with cellular physiopathology [22]. It is intriguing whether and how accurately exosomal RNAs could represent the transcriptomic snapshot of the physiological and pathological status of their source cells. Multiple literatures confirmed an obvious asymmetric quantitative distribution of RNAs between source cells and their exosomes [49]. Previous studies revealed that the exosome sorting machinery did exist, which actively modulated the exosomal loading of specific RNAs [50, 51]. However, the biological significance of this active process remains largely unknown. The active sorting process may be beneficial for maintaining the molecular homeostasis of RNA molecules that are functionally important, inefficient, or even harmful for cells under the physiological or pathological condition. Alternatively, RNAs could be passively incorporated into exosomes depending on the abundance of cytoplasmic RNAs. The co-occurrence of active and passive sorting processes results in a partial match between exosome and donor cell transcriptomes. Moreover, aberrantly expressed exosomal RNAs in the systemic circulation of cancer patients only partially reflect RNA dysregulations identified in corresponding cancer tissues. In some cases, the RNA expression trend in exosomes is inconsistent with the one observed in cancer tissues. Recently, Barbagallo et al. [52] found that lncRNA-UCA1 exhibited an asymmetric distribution between serum exosomes and corresponding tumor tissues. The lncRNA-UCA1 was downregulated in serum exosomes from colorectal cancer (CRC) patients compared to healthy individuals. Its expression was upregulated in CRC biopsies compared to normal adjacent tissues from CRC patients. This opposite deregulation trend might suggest that the oncogenic function of lncRNA-UCA1 was critical for CRC progression, prompting cancer cells to retain this lncRNA by reducing its secretion via exosomes. Further study showed that lncRNA-UCA1 controlled pivotal cancer-related pathways by enhancing the expression of ANLN, BIRC5, IPO7, KIF2A and KIF23. The lncRNA-UCA1 regulatory axis could be a prospective target to develop innovative RNA-based anticancer therapeutics. This divergent expression trend between exosomes and native tumors could be the assorted consequence of the asymmetric distribution of RNAs between exosomes and donor cells [49]. In addition, exosomal RNAs in the circulation of cancer patients are a mixture of molecules of different cellular origins, including cancer cells and immune cells, and they play key roles in mediating the extracellular communication during cancer progression. For these reasons, exosomal RNAs do not represent an accurate reflection of the transcriptomic landscape in cancer cells, but they might represent promising biomarkers in cancer.

It has been reported that exosomes could provide secure protection of their RNA cargoes [53]. Therefore, lncRNAs are highly stable during exosome-mediated delivery process. Exosomal lncRNAs can affect the phenotype of recipient cells by targeting specific genes or cellular pathways. It is likely that lncRNAs are selectively loaded into exosomes and serve as key signaling molecules in cell-to-cell communication. The expression level of exosomal lncRNAs differs from their donor cells. For instance, six lncRNAs (MALAT1, HOTAIR, lincRNA-p21, GAS5, TUG1 and ncRNA-CCND1) exhibited different expression levels between tumor cells and exosomes [54]. The expression level of the oncogenic TUC339 was remarkably varied within exosomes compared to that in HCC donor cells [55]. These findings implied that lncRNAs were not randomly secreted into the extracellular space through exosomes. Nevertheless, the molecular mechanism by which lncRNAs are incorporated into exosomes is not yet elucidated. RNA structure motifs and protein partners were found to be responsible for defining lncRNA subcellular localization [56]. These factors may also play an important role in the exosomal loading of lncRNAs. In addition, lncRNAs can function as scaffolds for proteins and RNAs which may be involved in their entrapment inside exosomes. More studies on the membrane proteins of the exosomes would give hints about the sorting and packaging of lncRNAs into exosomes. However, there

are still many unanswered questions regarding the encapsulation of lncRNAs into exosomes and the regulation of exosome secretion. Further research is required to elucidate the detailed mechanism underlying lncRNA sorting and exosome biogenesis.

The functional roles of exosomal lncRNAs in cancer

LncRNAs, pervasively transcribed in the mammalian genome, emerge as vital participants in various biological processes such as gene expression and chromatin modification [57, 58]. Moreover, accumulated evidence indicates that lncRNAs play an important role in the occurrence and progression of cancers [59]. Recently, the area of exosome-derived lncRNAs has rapidly developed. A growing body of evidence suggests that exosomal lncRNAs can be detected in a wide range of body fluids and their deregulation is associated with tumor growth, invasion, angiogenesis, metastasis and chemoresistance [25] (Table 1). Plus, the functional significance of exosome-derived lncRNAs in cancer biology hints at the possibility of using them as promising, non-invasive biomarkers for clinical cancer therapy.

Exosomal lncRNAs regulate tumor growth

The lncRNA *PTENP1* was remarkably decreased in bladder cancer (BC) tissues and in exosomes from plasma of BC patients [60]. Exosomal *PTENP1* was able to distinguish BC patients from healthy controls. Normal cells secreted exosomal *PTENP1* and transferred it to BC cells. Moreover, exosomal *PTENP1* promoted BC cell apoptosis, and inhibited cell invasion and migration. Likewise, exosomal *PTENP1* repressed tumor growth in vivo. In terms of mechanism, exosomal *PTENP1* enhanced the expression of phosphatase and tensin homolog (PTEN) by targeting miR-17. LncRNA MYU was dramatically upregulated in prostate cancer (PCa) tissues [61]. MYU silencing could depress PCa cell growth and migration. In contrast, MYU overexpression exhibited opposite effects. More importantly, lncRNA MYU could be transferred to adjacent cells through exosomes and promoted the proliferation and migration of the recipient cells. LncRNA MYU increased the expression of the oncogene *c-Myc* by competitively binding miR-184, and thus enhanced the growth of PCa. MYU worked as an oncogenic lncRNA in PCa partially through the miR-184/c-Myc axis. Similarly, the lncRNA PCSEAT was specifically upregulated in PCa [62]. PCSEAT knockdown led to the inhibition of PCa cell growth and motility, while PCSEAT overexpression reversed these effects. PCa cells could also transfer PCSEAT to adjacent cells through exosomes, thus enhancing cell proliferation and motility. The histone methyltransferase, polycomb group protein enhancer of zeste homolog 2 (EZH2), was reported to be involved in PCa development [63]. In terms of mechanism, PCSEAT regulated cell proliferation partially through regulation of EZH2 by competitively sponging miR-143-3p and miR-24-2-5p. Overall, PCSEAT was a potential oncogene in PCa and might hold promise as a therapeutic target for PCa.

Based on these clues, exosomal lncRNAs can target specific host factors or cellular pathways that are associated with cell proliferation. However, few studies showed the regulatory roles of exosomal lncRNAs in tumor cell growth. More investigations are demanded to comprehensively disclose the molecular mechanisms underlying the effect of exosomal lncRNAs on tumor growth. LncRNAs may possess pro- or antitumor properties. Therefore, controlling the activity of exosomal lncRNAs may represent a potential therapeutic approach for the treatment of cancers.

Exosomal lncRNAs affect tumor metastasis

MALAT1 was the first identified lncRNA that was associated with lung cancer metastasis [64–66]. Exosomal MALAT1 was found to be highly expressed in non-small cell lung cancer (NSCLC) patients [67]. Its abundance was positively correlated with tumor stage and lymphatic metastasis. Exosomal MALAT1 promoted tumor growth and migration, and inhibited cell apoptosis by regulating the expression of cyclinD1, cyclinD2 and cyclin-dependent kinase (CDK) in NSCLC cells. These findings provided novel insights into the potential of exosomal MALAT1 as a non-invasive biomarker for the diagnosis and prognosis of NSCLC. Similarly, exosomal MALAT1 was also upregulated in breast cancer tissues compared with adjacent normal tissues [68]. Moreover, breast cancer-derived exosomes accelerated cell proliferation in breast cancer by transferring MALAT1. Exosomal MALAT1 played a regulatory role in breast cancer progression and might provide a novel strategy for treating breast cancer. Hypoxic exosomes derived from BC promoted cancer cell proliferation, invasion and migration [69]. Hypoxia could enhance exosomal transfer of lncRNA-UCA1 into BC cells. Hypoxic exosomal lncRNA-UCA1 reduced the expression of E-cadherin, and upregulated vimentin and matrix metallopeptidase 9 (MMP9). The epithelial–mesenchymal transition (EMT) is known as a trigger of cancer invasion and metastasis [70]. EMT is characterized by the loss of the epithelial marker E-cadherin, and gain of mesenchymal markers, such as N-cadherin and vimentin [71]. Thus, lncRNA-UCA1 could facilitate the EMT, growth and progression of BC. These results demonstrated that hypoxic BC cells remodeled the tumor microenvironment to support tumor development through releasing the oncogenic

Table 1 The biological function of exosomal lncRNAs in cancer progression

LncRNA	Cancer type	Biological function	Mechanism	References
PTENP1	Bladder cancer	Inhibit cell proliferation, invasion and migration	Increase PTEN expression by sponging miR-17	[60]
MYU	Prostate cancer	Promote cell proliferation and migration	Increase c-Myc expression by targeting miR-184	[61]
PCSEAT	Prostate cancer	Promote cell proliferation and motility	Enhance EZH2 expression by sponging miR-143-3p and miR-24-2-5p	[62]
MALAT1	Non-small cell lung cancer; breast cancer	Promote cell proliferation and migration; inhibit cell apoptosis	Upregulate cyclinD1, cyclinD2 and CDK	[67, 68]
LncRNA-UCA1	Bladder cancer	Promote cell proliferation, migration and invasion	Downregulate E-cadherin; upregulate vimentin and MMP9	[69]
ZFAS1	Gastric cancer	Promote cell proliferation and migration	Upregulate cyclinD1, p-ERK and Bcl-2, N-cadherin, Slug and twist; downregulate Bax and E-cadherin	[72]
NONHSAT105177	Pancreatic ductal adenocarcinoma	Suppress cell proliferation, migration and EMT	Restrain snail, slug, vimentin, N-cadherin and β-catenin	[73]
Lnc-Sox2ot	Pancreatic ductal adenocarcinoma	Promote cell invasion and metastasis	Regulate Sox2 expression by acting as a ceRNA of the miR-200 family	[74]
Linc-ROR	Thyroid cancer	Induce EMT and promote cell invasion	ND	[75]
FAL1	Hepatocellular carcinoma	Promote cell proliferation and metastasis	Upregulate ZEB1 and AFP by competitively sponging miR-1236	[76]
Lnc-MMP2-2	Lung cancer	Promote cell invasion and migration	Upregulate MMP2	[77]
HULC	Pancreatic cancer	Enhance cell invasion and migration	Upregulate snail and vimentin; downregulate E-cadherin	[78]
91H	Colorectal cancer	Promote cell migration and invasiveness	Upregulate HNRNPK expression	[79]
LncRNA-CAF	Oral squamous cell carcinoma	Promote cell invasiveness	Induce the expression of α-SMA, vimentin and N-cadherin by upregulating IL-33	[83]
H19	Colorectal cancer	Enhance cell stemness and oxaliplatin resistance	Activate the β-catenin pathway by sponging miR-141	[85]
lncRUNX2-AS1	Multiple myeloma	Inhibit osteogenic potential of MSCs	Suppress RNUX2 expression	[92]
ENST00000444164	Epithelial ovarian cancer	Promote the migration of endothelial cells	Upregulate NF-κB phosphorylation	[94]
ENST0000043768	Epithelial ovarian cancer	Promote the migration of endothelial cells	Upregulate NF-κB phosphorylation	[94]
TUC339	Hepatocellular carcinoma	Facilitate tumor cell growth and adhesion; promote macrophage activation	Regulate cytokine receptor signaling pathways and CXCR chemokine receptor binding pathways	[55, 95]
Linc-CCAT2	Glioma	Promote angiogenesis	Upregulate VEGFA, TGF-β and Bcl-2; downregulate Bax and caspase-3	[98]
Linc-POU3F3	Glioma	Promote angiogenesis	Upregulate bFGF, bFGFR and Angio	[99]
H19	Hepatocellular carcinoma	Promote angiogenesis	Upregulate VEGFR1, VEGF and ICAM1	[101]
LncRNA-UCA1	Breast cancer	Confer tamoxifen resistance	Inhibit caspase-3 activation	[103]
LncRNA-SNHG14	Breast cancer	Confer trastuzumab resistance	Activate the Bcl-2/Bax signaling pathway	[104]

Table 1 (continued)

LncRNA	Cancer type	Biological function	Mechanism	References
LncRP11-838N2.4	Non-small cell lung cancer	Confer erlotinib resistance	Downregulate cleaved PARP and cleaved caspase-3	[105]
PART1	Esophageal squamous cell carcinoma	Confer gefitinib resistance	Upregulate Bcl-2 by acting as a ceRNA of miR-129	[107]
LncARSR	Renal cell carcinoma	Confer sunitinib resistance	Upregulate AXL and c-Met by targeting miR-34 and miR-449	[108]
Linc-VLDLR	Hepatocellular carcinoma	Confer sorafenib resistance	Upregulate ABC-G2	[109]
Linc-ROR	Hepatocellular carcinoma	Confer sorafenib resistance	Inhibit p53 signaling pathway	[110]
lncRNA-ATB	Hepatocellular carcinoma	Prognostic biomarker	ND	[114]
SAP30L-AS1	Prostate cancer	Diagnostic biomarker	ND	[115]
SChLAP1	Prostate cancer	Diagnostic biomarker	ND	[115]
LincRNA-p21	Prostate cancer	Diagnostic biomarker	ND	[116]
PCAT-1	Bladder cancer	Diagnostic/prognostic biomarker	ND	[117]
LINC00161	Hepatocellular carcinoma	Diagnostic biomarker	ND	[118]
LncUEGC1	Gastric cancer	Diagnostic biomarker	ND	[119]
ENSG00000258332.1	Hepatocellular carcinoma	Diagnostic/prognostic biomarker	ND	[120]
LINC00635	Hepatocellular carcinoma	Diagnostic/prognostic biomarker	ND	[120]
HOTTIP	Gastric cancer	Diagnostic/prognostic biomarker	ND	[26]
CRNDE-h	Colorectal cancer	Diagnostic/prognostic biomarker	ND	[121]
HOTAIR	Laryngeal squamous cell carcinoma	Diagnostic/prognostic biomarker	ND	[122]
Lnc-GAS5	Colorectal cancer	Diagnostic/prognostic biomarker	ND	[123]

ND not determined

lncRNA-UCA1-enriched exosomes. Additionally, the expression of lncRNA-UCA1 was increased in the exosomes derived from the serum of BC patients compared with the healthy controls. LncRNA-UCA1 might serve as a novel diagnostic biomarker for BC. The expression of lncRNA ZFAS1 was raised in GC tissues and exosomes from the serum of GC patients [72]. The elevated ZFAS1 expression was significantly associated with lymphatic metastasis and tumor–node–metastasis (TNM) stage. ZFAS1 knockdown suppressed the proliferation and migration of GC cells by inducing apoptosis, and inhibiting cell-cycle progression and EMT. On the contrary, ZFAS1 upregulation facilitated the proliferation and migration of GC cells. The mechanistic study indicated that ZFAS1 enhanced the expression of cyclinD1, phosphorylated ERK (p-ERK) and B-cell lymphoma-2 (Bcl-2), and downregulated Bcl-2-associated x protein (Bax), thus promoting tumor cell proliferation. ZFAS1 also induced the expression of N-cadherin, Slug and Twist, and suppressed the expression of E-cadherin, thereby facilitating the EMT process. Moreover, GC cells-derived exosomes could enhance cell proliferation and migration by transmitting ZFAS1, suggesting that exosomal ZFAS1 might be a potential diagnostic and prognostic biomarker for GC.

The expression of lncRNA NONHSAT105177 was lower in pancreatic ductal adenocarcinoma (PDAC) cancer tissues than in adjacent non-tumorous tissues [73]. Overexpression of NONHSAT105177 suppressed PDAC cell proliferation and migration. Moreover, NONHSAT105177 upregulation inhibited the EMT progression by reducing EMT-inducing transcription factors (Snail, Slug, vimentin, N-cadherin and β-catenin). NONHSAT105177 could be trafficked by exosomes in PDAC. These results indicated that exosomal transfer of NONHSAT105177 might play an important role in PDAC progression. In contrast, lnc-Sox2ot was highly abundant in exosomes of highly invasive PDAC cells [74]. The plasma exosomal lnc-Sox2ot expression was associated with TNM stage and overall survival (OS) rate of PDAC patients. Further study indicated that lnc-Sox2ot promoted EMT and stem cell-like properties in PDAC through regulating the expression of sex determining region Y-box 2 (Sox2) by competitively binding to the miR-200 family. Lnc-Sox2ot could be transferred from donor PDAC cells to recipient tumor cells, and thus promoted tumor invasion and metastasis. The exosomal lnc-Sox2ot played important roles in tumor progression and might be a valuable biomarker for pancreatic cancer prognosis. Thyroid cancer stem-like cell (CSC)-derived exosomes could transfer lncRNAs (MALAT1 and linc-ROR) and induced EMT in the normal thyroid cells [75]. Knockdown of linc-ROR resulted in reduced invasion of the CSC cells. CSC-derived exosomes induced EMT, and modified adjacent and distant tumor environment through the delivery of lncRNAs. Therapies directed

towards CSC-derived exosomal lncRNAs might be able to decrease the metastatic capacity of tumor cells. LncRNA FAL1 was highly expressed in HCC tissues and promoted HCC cell proliferation and metastasis [76]. Mechanistically, FAL1 could competitively sponge miR-1236 to enhance the expression of its targets, zinc finger E-box binding homeobox 1 (ZEB1) and α-fetoprotein (AFP), thus supporting HCC metastasis and progression. Exosomes from the serum of HCC patients mediated the transfer of FAL1 to HCC cells and thus enhanced the proliferation and migration of recipient HCC cells. Overall, lncRNA FAL1 played an oncogenic role in HCC and served as a novel diagnostic biomarker for HCC.

Lnc-MMP2-2 was highly upregulated in exosomes secreted from transforming growth factor-β (TGF-β)-treated lung cancer cells and might be transferred to adjacent cancer cells and endothelial cells [77]. Moreover, exosomal lnc-MMP2-2 could regulate the invasion and migration of lung cancer cells into the vasculature by enhancing the expression of MMP2. Additionally, lnc-MMP2-2 levels were confirmed to positively correlate with MMP2 expression during metastatic progression of lung cancer. These findings suggested that exosomal lnc-MMP2-2 might represent a novel therapeutic target for lung cancer treatment. TGF-β could also induce the alteration in expression of lncRNAs in pancreatic cancer cells and their derived exosomes [78]. One lncRNA, HULC, was dramatically upregulated and enriched in pancreatic cancer cell-derived exosomes. HULC could be transferred to recipient tumor cells via exosomes. Functional studies revealed that HULC promoted EMT in pancreatic cancer by upregulating Snail and vimentin and downregulating E-cadherin. Accordingly, HULC enhanced tumor cell invasion and migration. These results provided mechanistic insights into lncRNA-regulated tumor metastasis. Significantly high levels of exosomal lncRNA 91H were detected in the serum of CRC patients and cell lines [79]. Heterogeneous nuclear ribonucleoprotein K (HNRNPK), an RNA-binding protein, was reported to be highly expressed in cancers and implicated in tumor metastasis [80–82]. LncRNA 91H could significantly promote the migration and invasiveness of CRC cells by altering HNRNPK expression. Analysis of clinical values of exosomal 91H in tumor prognosis indicated that high levels of exosomal 91H were positively associated with high risk of tumor recurrence and metastasis. Therefore, exosomal 91H served as an independent prognostic factor for CRC.

Collectively, tumor-derived exosomal lncRNAs can modify the cellular physiology to support the growth and dissemination of tumor cells. The cell-to-cell communication mediated by exosomal lncRNAs may represent an important mechanism for tumor metastasis. The impact of exosomal lncRNAs in tumor metastasis has recently been the main focus of exosome research. Understanding the mechanisms by which exosomal lncRNAs regulate tumor metastasis would contribute to the development of novel therapeutic approaches for the intervention of cancer.

Exosomal lncRNAs remodel the tumor microenvironment

Previously, Ding et al. [83] revealed lncRNA profiles during the transformation of cancer-associated fibroblasts (CAFs) from normal fibroblasts (NFs) in oral squamous cell carcinoma (OSCC). Among the identified lncRNAs, LncRNA-CAF was found to be significantly upregulated in CAFs. Interleukin-33 (IL-33) was primarily located in the stroma and positively co-expressed with LncRNA-CAF. Upregulated LncRNA-CAF increased the expression of CAF markers, α-smooth muscle actin (α-SMA), vimentin, and N-cadherin, in fibroblasts via IL-33. Therefore, upregulation of IL-33 could promote the activation phenotype of CAFs in OSCC, supporting the proliferation of tumor cells. Mechanistically, LncRNA-CAF could stabilize and upregulate IL-33 by preventing its degradation through the p62-dependent autophagy-lysosome pathway. Furthermore, the autophagy inducer, rapamycin, could attenuate the proliferative effect of LncRNA-CAF/IL-33 by promoting IL-33 degradation. In turn, tumor cells raised LncRNA-CAF levels in stromal fibroblasts via exosomal LncRNA-CAF to establish a pro-tumorigenic niche. These findings demonstrated that LncRNA-CAF could reprogram CAFs to support tumor growth by upregulating IL-33. Recently, a total of 52 ncRNAs were identified to be differentially distributed between CAF- and NF-derived exosomes in CRC [84]. Specifically, two lncRNAs (LINC00326 and WEE2-AS1) were found to be over represented in CAF-derived exosomes. These two lncRNAs might participate in CAFs' activation process and modulate the intercellular communication between stromal and tumor cells, affecting tumor progression. More studies should be focused on the regulatory role of these exosomal lncRNAs in the cross-talk between colon cancer cells and CAFs. LncRNA H19 was found to be highly expressed in CRCs and CAFs [85]. CAFs could promote the stemness and oxaliplatin resistance of CRCs by transferring exosomal H19. In terms of mechanism, H19 was capable of activating the β-catenin pathway by functioning as a molecular sponge of miR-141 which was reported to suppress the stemness of cancer stem cells [86]. These results suggested that CAF-derived exosomal H19 contributed to the development and oxaliplatin resistance of CRC.

Mesenchymal stem cells (MSCs) constitute a vital component of the tumor microenvironment and function in favoring tumor progression [87, 88]. Lung tumor cell-derived exosome suppressed the osteogenic and adipogenic differentiation of MSCs [89]. The lncRNA profiling

of lung tumor-derived exosome-treated MSCs was uncovered. Functional characterization indicated that deregulated lncRNAs were enriched in mRNA metabolic process and RNA binding, while pathway analysis revealed that dysregulated lncRNAs participated in oxidative phosphorylation, steroid hormone biosynthesis, and Ras signaling pathway. These results provided novel insights into the implication of exosomal lncRNAs in intercellular crosstalk between tumor cells and MSCs. Nevertheless, the functional roles of tumor-derived exosomes in MSC functionality deserve further investigations. Multiple myeloma (MM) was featured by reduced osteogenic potential of MSCs [90, 91]. Intercommunication between cancer cells and stromal cells in the tumor microenvironment was an impellent factor in tumor progression. A bioactive lncRNA RUNX2-AS1 in myeloma cells could be incorporated into exosomes and transmitted to MSCs, thereby inhibiting the osteogenesis of MSCs [92]. LncRUNX2-AS1 was upregulated in MM-MSCs and formed an RNA duplex with runt-related transcription factor 2 (RUNX2) pre-mRNA at the overlapping region. RUNX2 acts as a key regulator of MSC differentiation towards osteoblasts [93]. Thus, this RNA duplex transcriptionally inhibited RNUX2 expression by lowering the splicing efficiency, contributing to reduced osteogenic potential of MSCs. Exosomal lncRUNX2-AS1 might be a potential therapeutic target for bone lesions in MM. Collectively, myeloma cell-derived exosomal lncRUNX2-AS1 played a pivotal role in the suppression of osteogenesis by modulating the expression of RUNX2 in MSCs.

Exosomes derived from tumor-associated macrophages (TAMs) separated from epithelial ovarian cancer (EOC) could be efficiently taken up by endothelial cells [94]. TAM-derived exosomes significantly inhibited the migration of endothelial cells by targeting the miR-146b-5p/tumor necrosis factor receptor-associated factor 6 (TRAF6)/nuclear factor-κB (NF-κB)/MMP2 pathway. EOC-derived exosomes could counteract the effect of TAM-derived exosomes on endothelial cells by transferring the lncRNAs, ENST00000444164 and ENST0000043768. Mechanistically, these two lncRNAs were shown to exert a regulatory effect in the activation of NF-κB pathway. These data implied that tumor-derived exosomal lncRNAs were involved in remodeling the tumor microenvironment to support cancer progression. HCC cells-derived exosomes contained high levels of lncRNA TUC339 [55]. Exosomal TUC339 was engaged in regulating HCC cell growth and adhesion. HCC-derived exosomes could be internalized by macrophages and then transferred TUC339 to macrophages [95]. The loss-of-functional study showed that TUC339 knockdown in macrophages resulted in increased production of pro-inflammatory cytokines (IL-1β and TNF-α) and the co-stimulatory molecule (CD86), enhanced phagocytosis, and decreased cell viability. Moreover, TUC339 was verified to be required for macrophage activation. Microarray analysis together with bioinformatic prediction was conducted to investigate the transcriptome-wide impact of TUC339 in macrophages. The results indicated that 'pathways of cytokine–cytokine receptor interaction', 'C–X–C chemokine receptor (CXCR) binding', 'Toll-like receptor signaling', 'receptor for the Fc fragment of immunoglobulin G (FcγR)-mediated phagocytosis' and 'cell proliferation' were associated with TUC339 function in macrophages. These results shed light on a novel regulatory role of tumor-derived exosomal lncRNA TUC339 in macrophage within the tumor microenvironment. Intercellular transfer of TUC339 was a signaling mechanism contributing to HCC growth and spread. This study also verified that HCC cells could exert genetic impact on other cells within their local microenvironment by selectively exporting lncRNAs.

The tumor microenvironment is a good soil for tumor growth and metastasis [96]. The vital cellular components of the tumor microenvironment comprise tumor cells, stromal cells, macrophages and inflammatory cells [97]. Exosomes allow the exchange of genetic and epigenetic information between tumor cells and the tumor microenvironment. An increasing number of studies have indicated that exosomal lncRNAs can reprogram surrounding cells within the tumor microenvironment by affecting gene expression or cellular signaling pathways. By transferring to cells through exosomes, lncRNAs facilitate the formation of a microenvironment appropriate for tumor growth and metastasis. However, the roles of exosomal lncRNAs in the inherent intercellular communication networks during cancer pathogenesis remain to be further explored.

Exosomal lncRNAs are involved in the tumor angiogenesis

The long intergenic ncRNA CCAT2 (linc-CCAT2) was enriched in glioma cells [98]. Glioma cell-derived exosomes containing abundant linc-CCAT2 could be ingested by endothelial cells, resulting in the increased level of linc-CCAT2 in endothelial cells. Exosomal transfer of linc-CCAT2 promoted the migration, proliferation and tubular-like structure formation of endothelial cells by upregulating vascular endothelial growth factor A (VEGFA), TGF-β and Bcl-2 as well as downregulating Bax and caspase-3. In vivo study confirmed that exosomal linc-CCAT2 facilitated arteriole formation. These results confirmed that glioma cell-derived exosomes promoted angiogenesis by delivering linc-CCAT2 to endothelial cells. Another lncRNA, linc-POU3F3, was also upregulated in glioma tissues compared with adjacent normal tissues and obviously associated with the advanced tumor stage [99]. Glioma cells could transfer linc-POU3F3 to endothelial cells via exosomes. Linc-POU3F3

promoted the proliferation, migration, and tubular-like structure formation of recipient endothelial cells in vitro and arteriole formation in vivo by regulating the expression of angiogenic factors including basic fibroblast growth factor (bFGF), bFGF receptor (bFGFR), VEGFA and angiogenin (Angio). Thus, glioma cells could promote angiogenesis by releasing exosomes enriched in linc-POU3F3. $CD90^+$ liver cancer cells have been regarded as CSCs, exhibiting metastatic and aggressive phenotype [100]. LncRNA profiling indicated that H19 was enriched in $CD90^+$ HCC cells, and could be transferred to endothelial cells through exosomes [101]. Gain- and loss-of-functional studies proved that exosomal transfer of H19 stimulated angiogenesis in endothelial cells by regulating the expression of VEGF receptor 1 (VEGFR1) and VEGF. Exosomal H19 also induced the adhesion between HCC cells and endothelial cells by upregulating intercellular adhesion molecule 1 (ICAM1). Thus, lncRNA H19 was a mediator of pro-metastatic properties of HCC-derived exosomes and might be a potential therapeutic target for HCC.

Tumor angiogenesis is a complex process, typically comprising several steps: enzymatic degradation of the vessel's basement membrane, vascular endothelial cell proliferation, migration, sprouting, branching, and tube formation [102]. Tumor cells are capable of delivering lncRNAs into endothelial cells via exosomes. Exosomal lncRNAs can induce the pro-angiogenic potential of endothelial cells by elevating the expression of angiogenic factors and cell adhesion molecules. Tumor growth and metastasis rely on the establishment of tumor vasculature to offer nutrients, oxygen and other essential factors. Tumor angiogenesis is a crucial hallmark in tumor development. Investigations on its underlying mechanisms could provide novel anti-cancer therapeutics. Further studies on exosomal lncRNA-regulated tumor angiogenesis will open a novel era in tumor research, offering promising prospects to achieve improved cancer management.

Exosomal lncRNAs orchestrate tumor chemoresistance

The lncRNA-UCA1 was markedly ascended in tamoxifen-resistant breast cancer cells and their derived exosomes [103]. LncRNA-UCA1 could be transferred from tamoxifen-resistant breast cancer cells to tamoxifen-sensitive cells through exosomes. In the recipient cells, exosomal delivery of lncRNA-UCA1 conferred tamoxifen resistance to cancer cells via inhibiting apoptosis by repressing caspase-3 activation. On the contrary, lncRNA-UCA1 loss resulted in remarkable reduction of tamoxifen resistance in breast cancer cells. The lncRNA-small nucleolar RNA host gene 14 (SNHG14) was enriched in trastuzumab-resistant breast cancer cells as compared to sensitive breast cancer cells [104]. Loss-of-functional analysis indicated that lncRNA-SNHG14 knockdown might enhance trastuzumab-induced cytotoxicity. Extracellular lncRNA-SNHG14 could be incorporated into exosomes and transferred to sensitive cancer cells, hence transmitting trastuzumab resistance. Exosome-mediated transfer of lncRNA-SNHG14 might lead to trastuzumab resistance of recipient cancer cells by activating the Bcl-2/Bax signaling pathway. In addition, the expression of serum exosomal lncRNA-SNHG14 was higher in patients who showed resistance to trastuzumab treatment, in contrast to sensitive patients. Collectively, lncRNA-SNHG14 might serve as a promising therapeutic target for the intervention of breast cancer.

The lncRNA RP11-838N2.4 (lncRP11-838N2.4) was abundantly expressed in erlotinib-resistant NSCLC cells compared with normal NSCLC cells [105]. Forkhead box protein O1 (FOXO1), a transcription suppressor, negatively regulated lncRP11-838N2.4 by recruiting histone deacetylase [106]. LncRP11-838N2.4 could be transferred from erlotinib-resistant NSCLC cells to sensitive cells through exosomes, hence conferring erlotinib resistance to recipient cancer cells. Mechanistically, lncRP11-838N2.4 was capable of inhibiting erlotinib-induced cellular cytotoxicity by downregulating the levels of cleaved poly(ADP-ribose) polymerase (PARP) and cleaved caspase-3. The serum level of exosomal lncRP11-838N2.4 was increased in patients who exhibited resistance to erlotinib as compared to patients displaying sensitivity to erlotinib treatment. In summary, exosomal lncRP11-838N2.4 might be a potential therapeutic target for NSCLC patients. The expression of lncRNA PART1 was elevated in gefitinib-resistant cells as compared to parental esophageal squamous cell carcinoma (ESCC) cells [107]. Knockdown of lncRNA PART1 enhanced the gefitinib-induced cell death, while increased PART1 promoted gefitinib resistance of ESCC cells by functioning as a competing endogenous RNA (ceRNA) against miR-129 to increase Bcl-2 expression. PART1 could be packaged into exosomes and delivered into sensitive cells, hence disseminating gefitinib resistance. In addition, the high serum level of exosomal PART1 was correlated with tumor resistance to gefitinib treatment in ESCC patients. Exosome-transmitted PART1 was involved in the regulation of gefitinib responses in ESCC. LncARSR was correlated with clinically poor sunitinib response in patients with advanced renal cell carcinoma (RCC) [108]. LncARSR was upregulated in sunitinib-resistant RCC cells compared with their parental cells. LncARSR enhanced sunitinib resistance of RCC cells through competitively binding miR-34/miR-449 to facilitate the expression of the oncogenic receptor tyrosine kinases AXL and c-Met. Likewise, the level of exosomal lncARSR was dramatically higher in sunitinib-resistant

RCC cells than in parental cells. LncARSR could be transported to sensitive cells via exosomes. Exosome-transferred lncARSR conferred sunitinib resistance to recipient RCC cells and endothelial cells. Knockdown of lncARSR in vivo could restore sunitinib response in RCC. These data indicated that lncARSR could work as a potential therapeutic target to eliminate sunitinib resistance in RCC.

LincRNA-VLDLR (linc-VLDLR) was significantly upregulated in malignant HCC cells compared with non-malignant human hepatocytes, and could be selectively encapsulated in HCC cell-derived exosomes [109]. Exposure of HCC cells to anti-cancer drugs such as sorafenib and doxorubicin enhanced the expression of linc-VLDLR in HCC cells and derived exosomes. Linc-VLDLR could be delivered to recipient HCC cells via exosomes. Exosomal linc-VLDLR could promote HCC cell proliferation by inducing cell cycle progression. It also inhibited sorafenib-induced cell death partially by increasing the expression of ATP-binding cassette subfamily G member 2 (ABC-G2), a protein implicated in extracellular drug export. Linc-VLDLR was an exosome-enriched lncRNA that mediated chemotherapeutic stress response in HCC. These data revealed a novel mechanism underlying lncRNA-mediated modulation of chemotherapeutic response and resistance in cancer. The stress–responsive lncRNA, linc-ROR, was significantly upregulated in malignant HCC cells compared with non-malignant human hepatocytes [110]. Linc-ROR was also enriched in HCC cell-derived exosomes following sorafenib treatment and could be transferred to recipient cells through exosomes. Exosome-mediated delivery of linc-ROR resulted in the suppression of sorafenib-induced cell death in recipient HCC cells through repression of p53 signaling pathway. Thus, targeting the intercellular signaling mediators such as lncRNAs might be helpful to enhance tumor sensitivity to conventional chemotherapies that were used for the intervention of HCC.

In summary, exosomal lncRNAs play an important role in the transmission of tumor chemoresistance properties, hence reducing the efficacy of chemotherapeutic agents. In tumor cells, lncRNAs transmitted by exosomes inhibit chemotherapy-induced cell death and promote cell survival by regulating the cellular apoptosis pathway. Chemotherapy is a mainstay treatment for a wide range of cancers [111, 112]. However, drug resistance is a predominant cause of morbidity and mortality in cancer patients and would continue to be a thorny problem in clinical cancer therapy [113]. Therefore, further studies on the roles of exosomal lncRNAs in tumor chemoresistance will lead to the development of such biomarkers as novel targets for cancer treatment. Mimics and/or antagonists for each exosomal lncRNA target could be used as an adjunct therapy to improve the effectiveness of conventional chemotherapeutic agents.

Exosomal lncRNAs may be potential cancer biomarkers

Circulating exosomal miR-21 and lncRNA-ATB were correlated with TNM stage, T stage and portal vein thrombosis in HCC [114]. High level of miR-21 and lncRNA-ATB could be independent predictors of mortality, disease progression, and low OS and progression-free survival in HCC. Circulating exosomal miR-21 and lncRNA-ATB might be novel prognostic biomarkers and therapeutic targets for HCC. Two lncRNAs, SAP30L-AS1 and SChLAP1, were remarkably upregulated in PCa-derived exosomes compared with those in total exosomes isolated from the plasma of patients [115]. SAP30L-AS1 and SChLAP1 possessed adequate diagnostic values to differentiate PCa patients from healthy controls. SAP30L-AS1 expression level was correlated with prostate-specific antigen (PSA) values and tumor invasion. SChLAP1 was effective in distinguishing between patients with benign prostatic hyperplasia (BPH) and PCa patients. These findings demonstrated that these two lncRNAs hold promise as potential diagnostic biomarkers for PCa. The serum level of exosomal lincRNA-p21 was remarkably higher in PCa than in BPH [116]. The diagnostic values of lincRNA-p21 and lincRNA-p21 in combination with PSA were assessed. As a result, the specificity of lincRNA-p21/PSA combination for predicting PCa was significantly increased compared with lincRNA-p21. Exosomal lincRNA-p21 might provide a promising biomarker for the detection of PCa.

A panel consisting of three urinary exosome (UE)-derived lncRNAs (MALAT1, PCAT-1 and SPRY4-IT1) was developed for the prediction of BC [117]. Kaplan–Meier analysis revealed that high levels of MALAT1 and PCAT-1 were associated with poor recurrence-free survival (RFS) of non-muscle-invasive BC (NMIBC). Additionally, multivariate Cox proportional hazards regression analysis showed that exosomal PCAT-1 overexpression served as an independent factor for the RFS of NMIBC prognosis. Thus, UE-derived lncRNAs had significant clinical value in the diagnosis and recurrence prediction of BC. LINC00161 was significantly enriched in the serum of HCC patients compared with patients with chronic hepatitis or healthy controls [118]. The receiver operating characteristic (ROC) analysis indicated that LINC00161 could discriminate HCC patients from healthy controls with high sensitivity and specificity. More importantly, the serum level of LINC00161 was notably correlated with serum AFP concentration and TNM stage of HCC patients. Further study indicated that the highly expressed LINC00161 in the serum of HCC patients was derived from exosomes. Collectively, circulating exosomal LINC00161 might be used as a novel biomarker for HCC.

Two lncRNAs, lncUEGC1 and lncUEGC2, were significantly upregulated in exosomes derived from early gastric

cancer (EGC) patients and GC cells [119]. LncUEGC1 could effectively discriminate EGC patients from healthy controls and those with premalignant chronic atrophic gastritis. The diagnostic accuracy of lncUEGC1 was higher than that of carcinoembryonic antigen (CEA). On the whole, exosomal lncUEGC1 might represent a promising non-invasive biomarker for EGC diagnosis. The serum levels of two exosomal lncRNAs (ENSG00000258332.1 and LINC00635) were remarkably higher in HCC patients than those in patients with liver cirrhosis (LC), chronic hepatitis B (CHB) and healthy controls [120]. Exosomal ENSG00000258332.1 and LINC00635 were able to distinguish HCC patients from CHB patients with high specificity. High levels of these two lncRNAs were related to worse OS in HCC patients. ENSG00000258332.1 and LINC00635 could be used to predict life expectancy for HCC patients. These data demonstrated that serum exosomal ENSG00000258332.1 and LINC00635 might serve as highly sensitive and non-invasive biomarkers for HCC. The expression level of serum exosomal HOTTIP was significantly higher in GC than in controls [26]. Notably, exosomal HOTTIP was superior to traditional tumor biomarkers including CEA, carbohydrate antigen 19-9 (CA 19-9) and cancer antigen 72-4 (CA 72-4) in GC diagnosis. High exosomal HOTTIP levels were associated with invasive depth, TNM stage and poor OS of GC patients. Exosomal HOTTIP might represent a novel useful biomarker for the diagnosis and prognosis of GC.

Exosomal CRNDE-h was detectable and stable in the serum of CRC patients as well as in CRC cells [121]. Exosomal CRNDE-h was upregulated in CRC patients compared to patients with colorectal benign diseases or healthy volunteers. The expression level of exosomal CRNDE-h also significantly correlated with tumor metastasis and low OS rates in CRC. Exosomal CRNDE-h in serum could effectively discriminate CRC patients from patients with colorectal benign diseases or healthy controls. The diagnostic performance of exosomal CRNDE-h was superior to the traditional tumor marker CEA. In summary, the lncRNA CRNDE-h might serve as a promising non-invasive serum-based biomarker for the diagnosis and prognosis of CRC. HOTAIR was one of the most frequently reported lncRNAs engaged in cancer progression. The expression of exosomal miR-21 and lncRNA HOTAIR was evidently higher in the serum of patients with laryngeal squamous cell carcinoma (LSCC) than those with vocal cord polyps [122]. The serum level of exosomal miR-21 and HOTAIR was tightly correlated with lymph node metastasis and clinical parameters of LSCC. Combined detection of exosomal miR-21 and HOTAIR might give better sensitivity and specificity in differentiating the patients with LSCC from patients with benign laryngeal diseases than either exosomal miR-21 or HOTAIR. The combination of exosomal miR-21 and HOTAIR might be useful as serum biomarkers for LSCC diagnosis and prognosis. The lncRNA GAS5 (lnc-GAS5) was downregulated in the tissues, plasma and exosomes from CRC patients compared with normal controls [123]. The ROC analysis showed that exosomal lnc-GAS5 was effective in differentiating CRC patients from healthy controls suggesting that exosomal lnc-GAS5 might have diagnostic value in CRC. Exosomal lnc-GAS5 expression was negatively correlated with tumor size, TNM stage, lymph node metastasis and local recurrence, and positively correlated with the 3-year OS rate in CRC patients. Multivariate analysis revealed that exosomal lnc-GAS5 expression served as an independent prognostic factor for CRC. Furthermore, lnc-GAS5 overexpression led to the inhibition of CRC cell proliferation, migration and invasion by suppressing miR-221. These results provided evidence on the role of lnc-GAS5 in the diagnosis and prognosis of CRC.

The diagnostic, prognostic and predictive values of exosomal lncRNAs in cancer have been extensively investigated. LncRNAs within exosomes are protected from RNases and may efficiently function in recipient cells. The quantity of exosomal lncRNAs is high in body fluids and could be easily evaluated in clinical practice. In addition, many lncRNAs exhibit tissue-specific expression pattern. Collectively, exosomal lncRNAs hold promise as a novel type of non-invasive biomarkers for the diagnosis and management of cancers. The potential of exosomal lncRNAs as cancer biomarkers remains to be further validated in much larger population of cancer patients.

Exosomal lncRNAs may represent potential therapeutic targets for cancer

Considering the important clinical impact of exosomes in cancer, the extracorporeal strategies for specifically targeting exosomes may be promising therapeutic options in the management of cancer. Notably, Aethlon Medical devised a novel device approach involving extracorporeal hemofiltration of exosomes from the entire circulatory system using an affinity plasmapheresis platform known as the Aethlon ADAPT™ (adaptive dialysis-like affinity platform technology) system [124]. The ADAPT™ system permits affinity agents (e.g, exosome-binding antibodies and lectins) to be immobilized in the outer-capillary space of plasma filtration membranes that integrate into existing dialysis machines. Accordingly, this device allows rapid extracorporeal capture and selective absorption of target factors such as exosomes from the entire circulatory system. In contrast, the blood cells and non-bound components could pass through the device. The efficacy and safety of this strategy were supported by clinical experience in hepatitis C virus-infected patients using the first ADAPT™ device, the Hemopurifier®, to decrease the

systemic load of virions having similar sizes and surface topology as cancer exosomes [125]. The ADAPT™ system might be tailored for different stages/types of cancer, since it can incorporate diverse affinity agents for efficiently capturing cancer exosomes. Although this device approach requires that patients undergo the vascular surgical procedure, ADAPT™ therapies would overcome the risks of drug interactions and toxicity posed by pharmacological approaches. Therefore, this device strategy supplies an approach for specifically targeting exosomes that should be further evaluated for its utility as a therapeutic adjunct to standard cancer treatments.

A number of lncRNAs are aberrantly expressed in cancers and are detectable in body fluids of cancer patients [126, 127]. The expression of the dysregulated lncRNAs is regarded as an indicator of the malignant degree of cancer [128]. Thus, lncRNAs are attractive therapeutic targets for the treatment of cancer. Three possible strategies to exploit exosomal lncRNAs as therapeutic targets have been proposed. Firstly, as exosomes serve as natural lncRNA carriers, they may be adapted to deliver tumor-suppressive lncRNAs. It is necessary to elucidate the detailed mechanism underlying the uptake of exosomes by cells. To successfully achieve tumor-targeted delivery of lncRNAs by exosomes, the tumor cell-specific receptor for exosomes needs to be identified. Secondly, since some lncRNAs can promote tumor development, interfering with exosomal lncRNA-mediated intercellular communication pathway may be another therapeutic strategy for cancer treatment. Deepening understanding of the mechanism underlying the sorting and loading of lncRNAs to exosomes and the internalization of exosomes by tumor cells would be helpful for the development of this novel therapeutic method that blocks the exosomal lncRNA-mediated signaling. Further work is also needed to evaluate the clinical safety of this therapeutic approach. Thirdly, apart from validating the importance of exosomal lncRNAs in cancer treatment, exosomal lncRNAs can be employed to improve the therapeutic efficacy of chemodrugs. Chemoresistance remains to be a major challenge in cancer therapy and may be improved by enhancing the response of tumor cells to chemotherapeutic agents through modulation of the cellular signaling that confers resistance. As exosomal lncRNAs can adjust tumor chemoresistance by altering cellular signaling pathways, they could increase the chemotherapeutic sensitivity of tumor cells and may even be used for combination antitumor therapy with chemotherapeutic drugs. The pathologic function and therapeutic potential of several exosome-derived lncRNAs in cancer have been evaluated in vitro and in vivo [61, 69, 129]. However, there is still a long way to go before these therapeutic approaches can be translated from bench to bedside.

Concluding remarks

Exosomes were initially considered to be responsible for cellular waste management [130, 131]. However, this perception changed due to the discovery of RNAs in exosomes [22]. Currently, exosomes are regarded as important carriers of information flow. Exosomes exert significant functions in cancer progression through the transfer of these biological contents. The possibility of using exosomes as nucleic acid or drug delivery systems for cancer therapy has drawn increasing attention owing to their stability, specificity and accessibility. Moreover, exosomes are non-immunogenic and have minimal toxic effects [132]. They are also able to cross the blood–brain barrier and easily to be handled and modified [133]. Therefore, exosomes containing therapeutic biologicals exhibit great clinical translation potential for cancer therapy.

With advances in the understanding of ncRNA function, exosome-derived ncRNAs are in the focus of intensive study. LncRNAs can bind to chromatin to promote epigenetic regulation and act as miRNA sponges to alter gene expression [134, 135]. LncRNAs also interact with RNA-binding proteins (RBPs) to fine-tune multiple cellular processes [136]. Increasing amounts of evidence demonstrate that lncRNAs serve as crucial regulators in the initiation and development of cancers. LncRNAs exhibit large potential to be developed as novel biomarkers and therapeutic targets for the prevention and treatment of cancers. LncRNAs can be secreted into the circulation through being assembled into exosomes. LncRNAs within the exosomes are protected from ribonuclease-mediated degradation and thus stably exist in body fluids. Notably, exosomal lncRNAs are confirmed to perform multifaceted functions in facilitating tumor development by controlling tumor growth, invasion, angiogenesis, and chemoresistance. Exosomal lncRNAs remodel the tumor microenvironment by serving as signaling molecules in cell-to-cell communication. Exosomal lncRNAs may represent ideal biomarkers for cancer diagnosis and therapy.

However, the study of exosomal lncRNAs is still in its infancy. Further studies are required before adopting exosomal lncRNAs into clinical practice. It is speculated that RBPs and other associated RNAs might be crucial for recognizing specific lncRNAs, protecting lncRNAs from intracellular degradation, transporting lncRNAs to exosomes or escorting lncRNAs within exosomes to recipient cells. The exact mechanisms underlying the sorting, uptake and functioning of exosomal lncRNAs are in urgent need of more investigation. A better understanding of the assortment and secretion of exosomal lncRNA would provide the theoretical basis for developing diagnostic and therapeutic approaches for cancers. Intercellular

communication mediated by exosomal lncRNAs would also provide novel insights into the complex interaction between tumor cells and host immune system, an unexplored area from this point of view. There are still some limitations in the study of exosomes. For example, a standardized procedure for harvesting and isolating exosomes has yet to be established. The present method for exosome extraction is quite time-consuming and not appropriate for routine diagnostics. Moreover, samples collected from the plasma and/or serum may also contain exosomes released by cells other than tumor cells [137]. Therefore, the purification of tumor-derived exosomes is an important issue that needs to be tackled. Endogenous controls of lncRNAs in body fluids and standard extraction methods should be ascertained. It is also very critical to standardize the analytic procedure in order to achieve high reproducibility. Accurate quantification of exosomal lncRNAs and their clinical toxicity must be determined. So far, the biological function of exosome-derived lncRNAs is not thoroughly reported. Thus, the effect of exosomal lncRNAs on cellular processes and cancer biology deserves deep explorations. One exosome-derived lncRNA may act as a tumor-suppressive lncRNA, and exosomal delivery of this lncRNA represents a promising therapeutic approach for the treatment of cancer. However, if this lncRNA is also a critical player in multiple physiological processes, deregulation of this lncRNA may cause the breakdown of cellular homeostasis, thus eliciting severe side-effects. Further studies should be targeted towards exploring the normal physiological function of exosomal lncRNAs in vivo and advancing our knowledge of the detailed mechanisms by which they regulate cancer development. In-depth understanding of exosomal lncRNAs will not only shed light on their functions in cancer pathogenesis but will open novel avenues for cancer diagnosis and therapeutics. Effective therapeutic strategies for cancer treatment using exosomes as transport vesicles for targeted delivery of lncRNAs would be expected in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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