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Review Article

The Role of Exosomal Long Non-Coding RNAs in Tumors and Tumour Metabolism

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Abstract

Long non-coding RNAs (lncRNAs) are RNAs that do not have protein-coding functions and are involved in a wide range of important regulatory processes through four modes of (1) signaling (2) guidance (3) structural backbone (4) decoying, which regulate gene expression at epigenetic, transcriptional and post-transcriptional levels. Exosomes are extracellular vesicles released by various cells, whose contents are protected from degradation and stabilized in the extracellular environment due to their lipid bilayer membrane structure, and which are thought to play an important role in many diseases, including tumors. The exosomes secreted by tumor cells and stromal cells contain proteins, nucleic acids, lipids, cytokines, transcription factors and other biologically active substances. With the help of exosomes, they are stably transported between cells and mediate the exchange of substances and information between cells in order to achieve intercellular communication, thus affecting the biological activities of target cells. Among them, lncRNAs are selectively sorted into exosomes, which can regulate tumor metabolism as well as tumor progression through exosomes in various ways. In this paper, the role of exosomal lncRNAs in the tumor microenvironment and tumor metabolism is reviewed, with a view to providing markers, targets and directions for clinical diagnosis, tumor therapy and tumor-related research.

Keywords

Exosomes, Long Non-Coding RNA, Tumor Microenvironment, Tumor Metabolism

1. Introduction

Non-coding RNA (ncRNA) is RNA that does not have a protein-coding function. Long non-coding RNA (lncRNA) is a subtype of ncRNAs with a length of more than 200 nucleotides [1], constituting more than 80% of ncRNA [2]. LncRNA is usually transcribed by RNA polymerase II, but in some cases, can be also transcribed by RNA polymerase III [3]. LncRNAs can generate various types of transcripts by selective splicing [4]. These transcripts generally has no protein-coding function, but some can encode short peptides [5]. LncRNAs have lower conservation level compared to other types of RNA, with only about 12% of lncRNAs found in organisms other than humans [3]. In addition, the expression

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level of LncRNAs is usually low, and the expression of lncRNAs is tissue-specific and spatio-temporal specific [6]. This indicates that their expression varies in different tissues or the same tissue in different conditions. It has been reported that lncRNAs can regulate gene expression at epigenetic, transcriptional, and post-transcriptional levels [7]. They are involved in the regulation of several important biological processes such as mRNA splicing and translation, genomic imprinting, transcriptional activation, X-chromosome inactivation, chromatin modification, transcriptional silencing and nuclear translocation. [8]. LncRNAs function through four main mechanisms: signal, guide, scaffold, and decoy. Signal refers to the lncRNA as a signal transduction molecule to participate in specific signaling pathways to regulate downstream gene transcription. Guide refers to the lncRNAs as a chaperone molecule, binding to specific proteins to form the RNA-protein complexes, localizing to a specific DNA sequence to regulate downstream transcription. Scaffold refers to the fact that a lncRNA interacts with multiple transcription factors to integrate various signaling pathways. Decoy refers to the fact that lncRNAs competitively bind to ceRNAs or proteins to block signaling pathways [5]. In recent years, the role of lncRNAs in tumorigenesis and development has attracted widespread attention. The tumor development can be influenced by affecting cell proliferation and migration [9], promoting epithelial-mesenchymal transition (EMT) [10], inducing chemoresistance [11], promoting angiogenesis [12], modulating immune system activity [13], and promoting inactivation of tumor suppressor gene [14]. There are currently 15,831 lncRNAs have been identified [5], but only about 200 have been studied in depth [15]. The functions of most lncRNAs remain unclear. Further in-depth investigation of the functions and mechanisms of more lncRNAs will be a challenging and attractive study direction. This could potentially open a new chapter in the study of the human genome.

Exosomes are disc-shaped vesicles with a diameter of 30-150nm, characterized by a lipid bilayer membrane structure that can be secreted by nearly all cells. They can be easily distinguished from other extracellular vesicles like apoptotic bodies and microvesicles through electron microscope. Due to their lipid bilayer membrane structure, exosomes encapsulate their contents, protecting them from degradation and ensuring stability in the extracellular fluid [16]. A variety of biologically active substances, including proteins, nucleic acids (such as mRNA, microRNA, and lncRNA), lipids, cytokines, and transcription factors, are encapsulated in exosomes. With the help of exosomes, these substances are stably transported between cells, mediating intercellular communication to affect the biological activities of the target cells. For example, exosomal lncRNA LNMAT2 from bladder cancer cells can be internalized by human lymphatic endothelial cells, thereby inducing lymphangiogenesis and lymphatic metastasis of bladder cancer [17]. It has been reported that the GGAG, a specific gene sequence in miRNAs, may play a role in miRNAs sorting into exosomes and regulation of their localization within exosomes [18]. Additionally, specific RNA-binding proteins, such as ELAVL1 [19] and hnRNPA2B1 [18], may be associated with the selective sorting of lncRNAs into exosomes. However, the mechanism underlying the sorting of these molecules into exosomes is still incompletely understood and requires further investigation. Exosomes are abundant in human body fluids and readily obtainable. They are highly stable, allowing for repeated detection and long-term storage for many years with frozen, refrigerated and solubilized states [20]. However, their small size and low density make them challenging to separate, adding complexity to the research of exosome. It has been found that tumor cells secrete more exosomes than homologous normal cells, potentially influencing a variety of biological processes, such as immune evasion, tissue invasion, metastasis, angiogenesis, and tumor drug resistance [21, 22]. As a new form of mediating cell-to-cell communication, exosomes have received more attention from researchers. Nonetheless, most studies have focused on mRNA and miRNA, and the study on exosomal lncRNAs is still in its preliminary stage. Therefore, further studies are needed to elucidate the functions and mechanisms of exosomal lncRNAs. This review aims to summarize the current knowledge on the roles of exosomal lncRNAs in tumors and their microenvironment, offering new biomarkers and strategies for cancer diagnosis, prognosis, and treatment, and providing a new direction for future study on exosomal lncRNAs.

2. The Role of Exosomal Long Non-Coding RNAs in Tumors and Tumour Metabolism

2.1. Regulate Tumor Cell Proliferation, Apoptosis, Migration and Invasion

Tumor cells can communicate and transmit substances and information through exosomal lncRNA to regulate tumor cell proliferation, apoptosis, migration and invasion. For example, the liver cancer cell lines HeP3B and HePG2 can activate their PI3K/AKT/mTOR signaling pathway by uptake of exosomes secreted by the liver cancer cell line HCCLM3 that highly express lncRNA H19, thereby significantly promoting the proliferation, migration and invasion of tumor cells [23]. Tumor cells and adjacent cells can also communicate and transmit subtances and information through exosomal lncRNA to regulate tumor cell proliferation, apoptosis, migration and invasion. For example, exosomal lncRNA FLJ22447 secreted by carcinoma-related fibroblasts can induce upregulation of IL-33 levels in cancer cells and prevent p62-dependent autophagy-lysosomal degradation of IL-33, thereby promoting the growth of oral squamous cell carcinoma [24]. Exosomal lncRNA HISLA derived from tumor-associated macrophages can inhibit apoptosis of breast cancer cells [25]; Exosomal lncRNA UCA1 secreted by liver

cancer cells can competitively bind to miR-216b, upregulate the expression of fibroblast growth factor receptor 1 and activate the extracellular signal-regulated kinase signaling pathway, thus preparing for the establishment of a pre-metastatic environment for the tumor and promoting the proliferation, invasion, and metastasis of hepatocellular carcinoma (HCC) [26].

2.2. Regulate Tumor Angiogenesis

Angiogenesis is a key factor for tumor cells to resist hypoxic environment and promote their proliferation, migration and invasion. Tumor angiogenesis involves the following steps: enzymatic degradation of the vessel's basement membrane, endothelial cell proliferation, migration, sprouting, branching, and tube formation. Angiogenic factors play a decisive role in the above processes. Tumor-derived exosomal lncRNA can stimulate circulating angiogenesis by increasing the expression of membrane molecules and soluble factors, promoting their own proliferation, migration and invasion [27]. For example, the exosomal lncRNA HOTAIR secreted by glioma cells stimulates angiogenesis and promotes tumor growth by increasing the expression of vascular endothelial growth factor [28]. The exosomal lncRNA MALAT1 derived from metastatic epithelial ovarian cancer promotes angiogenesis by stimulating the expression of angiogenesis related genes, such as angiopoietin and bFGF [29]. The exosomal lncRNA SNHG12 derived from breast cancer cells promotes angiogenesis in human umbilical vein endothelial cells through PBRM1 and MMP10, resulting in increased malignancy of breast cancer [30].

2.3. Regulate the Characteristics of Cancer Stem Cell

The characteristics of cancer stem cells (CSCs) refers to the fact that certain tumor cells are similar to normal stem cells with unlimited self-renewable ability, differentiation potential, high tumorigenicity, specific surface markers, and other characteristics that are conducive to tumor proliferation, migration, and invasion [31]. CSCs have been found in many types of solid tumors, such as colorectal cancer, renal cancer, and HCC [32]. Exosomal lncRNA can regulate the characteristics of CSCs and promote tumor development. For example, exosomal lncRNA H19 secreted by carcinoma-associated fibroblasts sponges for miR-141, which acts as the ceRNA, leading to the activation of the β-catenin pathway and enhancing the stemness of colorectal CSCs [33]. Exosomal lncRNA Sox2ot secreted by highly invasive pancreatic ductal adenocarcinoma cells is internalized by less invasive PDAC and competitively binds to miR-200, promoting EMT and stem cell like properties and leading to tumor invasion and metastasis [34].

2.4. Promote EMT

EMT refers to the process that cells shed their epithelial characteristics and gain mesenchymal characteristics, thereby acquiring the ability to metastasize to distant sites [35]. Its main characteristics involve decreased expression of epithelial cell markers, such as E-calmodulin and keratin, and increased expression of the mesenchymal cell marker, vimentin. Exosomal lncRNA MRPL23-AS1 can form an RNA-protein complex with EZH2, increase H3K27me3 on the E-cadherin promoter region, lead to the initiation of EMT and promote the invasion of salivary adenoid cystic carcinoma [36]. ZFAS1 upregulates cyclin D1, p-ERK, Bcl-2, N-cadherin, Slug, Snail and Twist proteins, downregulates Bax and E-cadherin to promote EMT [37]. HGC-derived lncRNA PCGEM1-riched exosomes can promote the invasion and migration of normoxic-cultured gastric cancer cells. Mechanistically, PCGEM1 preserves stability and minimizes the degradation of SNAI1, thereby inducing EMT in gastric cancer [38].

2.5. Regulate Tumor Drug Resistance

Tumor drug resistance is an important factor affecting the prognosis of tumor patients, so finding the relevant mechanisms of tumor drug resistance will be the key to conquering tumors. Drug resistance is regarded as a combined, complex, and multi-step process. Although research on drug resistance is becoming increasingly in-depth, the molecular mechanism of tumor cell desensitization is still unclear. It has been reported that exosomal lncRNA plays an important role in tumor drug resistance, providing a new direction for conquering tumor drug resistance. Exosomal lncARSR secreted by sunitinib-resistant renal cell carcinoma-resistant cells can be internalized by sensitive cells. These exosomes competitively bind to miR-34 and miR-449, leading to increased expression of AXL and c-MET and reactivation of STAT3, AKT, and ERK signaling pathways. Interestingly, activated AKT induces phosphorylation and degradation of FOXO1 or FOXO3a, resulting in transcriptional inhibition of lncARSR, forming a positive feedback loop to impart resistance to sunitinib [39]. Therefore, cancer drug desensitization cannot only target tumor cells themselves, but also consider tumor-associated stroma and microenvironment. lncRNA-SNHG14 can be packaged into exosomes and secreted by trastuzumab-resistant breast cancer cells. It promotes trastuzumab resistance by targeting the Bcl-2/Bax signaling pathway, inhibiting of the expression of apoptotic proteins, and inhibiting cell apoptosis. Exosomal lncRNA-SNHG14 in human serum possible be considered as a diagnostic biomarker for breast cancer, improving the clinical efficacy of trastuzumab treatment [40].

2.6. Promote the Inactivation of Tumor Suppressor Genes

Tumor suppressor genes can also be called anti-oncogenes. The inactivation of tumor suppressor genes plays an important

role in promoting tumor development. High-expression transcripts for liver cancer (HULC) are highly expressed in HCC tissues. The research results showed that HULC is highly expressed in HBV-related liver cancer tissues and can promote the proliferation of HCC cells by downregulating the tumor suppressor gene [41].

2.7. Regulate Immune System Activity

Tumors and the immune system are in a stalemate situation before tumorigenesis. After tumorigenesis, the immune system becomes impaired and the tumor establishes a microenvironment with immunosuppression to promote tumor progression. Exosomal lncRNA TUC339 secreted by HCC induces macrophage activation and polarization, resulting in reduced production of pro-inflammatory cytokines, reduced co-stimulatory molecule expression, and diminished phagocytosis activity [42]. Lnc-EGFR stimulates t-regulatory cell differentiation to promote immune evasion in liver cancer [43]. The exosome-mediated lncRNA ENST00000560647 in pancreatic cancer exosomes is likely to be the most critical factor in promoting dendritic cell immune evasion [44].

2.8. Regulating Tumor Metabolic Reprogramming

Metabolic reprogramming is one of the important characteristics of tumors. Metabolic reprogramming can not only provide the necessary ATP and macromolecule for the unlimited proliferation of tumor cells and maintain redox balance, but also release microenvironmental mediators under stress. This stimulates immune cells to change their own metabolic patterns, thereby jointly affecting the development of tumors in the microenvironment [45].

Metabolic reprogramming is an important hallmark of malignancy and can be regulated by the microenvironment. Exosome-shuttling is an effective way for biomolecules to be transported between different types of cells in the tumor microenvironment and plays a key role in regulating cell biology of cancer. Numerous studies have shown that lncRNA plays a vital role in the process of tumor metabolic reprogramming and is involved in regulating multiple metabolic pathways, including glucose metabolism, lipid metabolism, and glutamine metabolism. For example, the expression level of lncRNA ANRIL is increased in nasopharyngeal carcinoma. It increases glucose uptake and promotes the progression of nasopharyngeal carcinoma by activating the AKT/mTOR signaling pathway and up-regulating the expression of GLUT1 and LDHA [46]. TUG1 sponges miR-145, indirectly upregulating the expression of Sirt3 and glutamate dehydrogenase to increase glutamine metabolism, plays an important role in intrahepatic cholangiocarcinoma [47]. Exosome LINC01614 derived from cancer-associated fibroblasts in lung adenocarcinoma directly interacts with ANXA2 and p65, promoting the activation of NF-κB. This leads to the upregulation of glutamine transporters SLC38A2 and SLC7A5, ultimately enhancing glutamine influx in cancer cells [48]. HULC stimulates the accumulation of triglycerides and cholesterol in HCC cells through the miR-9/PPARA/ACSL1 signaling pathway in HCC cells, leading to lipid metabolism disorders [49]. Although research on the regulation of tumor metabolism by exosomal lncRNAs has attracted increasing attention from scholars in recent years, it have mainly focused on glucose metabolism. Studies on lipid metabolism, nucleotide metabolism, and amino acid metabolism still needs to be developed.

Table 1. *LncRNAs and Their Roles in Tumors and Tumour Metabolism.*

lncRNA	Upstream and downstream molecules of lncRNA	Functions of lncRNA	Reference
LNMAT2	PROX1	Promote lymphatic metastasis in bladder cancer through exosome-mediated transfer to HLECs, upregulating PROX1 expression and facilitating lymphangiogenesis.	[17]
H19	PI3K/AKT/mTOR signaling pathway	Activate PI3K/AKT/mTOR signaling pathway, thereby promoting the proliferation, migration and invasion of tumor cells	[23]
FLJ22447	IL-33	Induce upregulation of IL-33 levels and prevent p62-dependent autophagy-lysosomal degradation of IL-33, thereby promoting the growth of oral squamous cell carcinoma.	[24]
HISLA	HIF-1α	Block PHD2 and HIF-1α interaction, inhibit HIF-1α degradation, and promot HIF-1α stability, ultimately enhancing the survival and proliferation of breast cancer cells by creating a more hypoxic and glycolytic tumor microenvironment.	[25]
UCA1	Mir-216B, Fgfr1/Erk Signaling Pathway	Upregulate expression of fibroblast growth factor receptor 1 and activate extracellular signal-regulated kinase signaling pathway, thus preparing for the establishment of a pre-metastatic environment for tumor	[26]

lncRNA	Upstream and downstream molecules of lncRNA	Functions of lncRNA	Reference
		and promoting proliferation, invasion, and metastasis of HCC.	
HOTAIR	Trkb	Stimulate angiogenesis and promote tumor growth by increasing the expression of vascular endothelial growth factor.	[28]
MALAT1	VEGF-A, VEGF-D, ENA-78, PlGF, IL-8, angiogenin, bFGF and leptin	Promote angiogenesis by stimulating the expression of angiogenesis-related genes.	[29]
SNHG12	PBRM1, MMP10	Promote angiogenesis in human umbilical vein endothelial cells through PBRM1 and MMP10, resulting in increased malignancy of breast cancer.	[30]
H19	β-catenin pathway	Activate the β-catenin pathway and enhance the stemness of colorectal CSCs.	[33]
Sox2ot	miR-200	Internalized by less invasive PDAC and competitively binds to miR-200, promote EMT and stem cell like properties and lead to tumor invasion and metastasis.	[34]
MRPL23-AS1	H3K27me3	Increase H3K27me3 on the E-cadherin promoter region, lead to the initiation of EMT and promote the invasion of salivary adenoid cystic carcinoma.	[36]
ZFAS1	cyclin D1, p-ERK, Bcl-2, N-cadherin, Slug, Snail and Twist proteins, Bax, E-cadherin	Upregulate cyclin D1, p-ERK, Bcl-2, N-cadherin, Slug, Snail and Twist proteins and downregulate Bax and E-cadherin to promote EMT.	[37]
PCGEM1	SNAI1	Preserve stability and minimize the degradation of SNAI1, thereby inducing EMT in gastric cancer.	[38]
LncARSR	miR-34, miR-449, AXL, c-MET, STAT3, AKT, ERK, FOXO1, FOXO3a	Increase expression of AXL and c-MET, and reactivate the STAT3, AKT, and ERK signaling pathways, leading to sunitinib resistance.	[39]
SNHG14	Bcl-2/Bax	Promotes trastuzumab resistance by targeting the Bcl-2/Bax signaling pathway, inhibiting of the expression of apoptotic proteins, and inhibiting cell apoptosis.	[40]
TUC339	IL-4	Induce macrophage activation and polarization, resulting in reduced production of pro-inflammatory cytokines, reduced co-stimulatory molecule expression, and diminished phagocytosis activity.	[42]
Lnc-EGFR	EGFR/Foxp3, AP-1/NF-AT1	Stimulate t-regulatory cell differentiation to promote immune evasion in liver cancer.	[43]
ENST00000560647	TP53, KRAS, SMAD4, CDKN2A	Might play a critical role in in promoting dendritic cell immune evasion, thus might contributing to tumorigenesis and immune evasion.	[44]
ANRIL	GLUT1, LDHA, AKT/mTOR	Increase glucose uptake and promote the progression of nasopharyngeal carcinoma by activating the AKT/mTOR signaling pathway and up-regulating the expression of GLUT1 and LDHA.	[46]
TUG1	miR-145, Sirt3, Gdh	Upregulate the expression of Sirt3 and glutamate dehydrogenase to increase glutamine metabolism, plays an important role in intrahepatic cholangiocarcinoma.	[47]
LINC01614	NF-κB, SLC38A2, SLC7A5	Promote activation of NF-κB and lead to upregulation of glutamine transporters SLC38A2 and SLC7A5, ultimately enhancing glutamine influx in cancer cells.	[48]
HULC	miR-9, PPARA, ACSL1	Stimulate the accumulation of triglycerides and cholesterol in HCC cells through the miR-9/PPARA/ACSL1 signaling pathway in HCC cells, leading to lipid metabolism disorders.	[49]

3. Discussion

Research on the role of exosome-derived lncRNA in tumors and their microenvironment is developing rapidly, but at the same time, it faces many difficulties. First, the isolation and purification of exosomes remains very challenging, and there is a need to continuously propose and improve isolation techniques to increase the yield and purity of exosomes. In addition, the underlying mechanisms of how cells regulate exosome secretion, how active substances are sorted into exosomes, how do exosomes accurately transfer these actives to target cells, and how they affect their metabolism remain to be further elucidated. Moreover, exosomes, as a new form of mediating cell-to-cell communication, play an extremely important role in numerous pathophysiological processes, such as the development of immune and vaccine, biomarkers for tumor diagnosis, targeted drug delivery, etc. [50]. They are increasingly gaining attention from researchers. However, most of the studies still focus on mRNA and miRNA in exosomes, while the research on exosomal lncRNA is still in its preliminary stage and requires more attention and investment from scholars. Furthemore, there are few studies on lipid, amino acid, and nucleotide metabolism mediated by exosomal lncRNA. Further research focusing on lipid, amino acid, and nucleotide metabolism are essential for studying the promotion of tumor metabolism and progression by exosomal lncRNA. Then, exosomes are regarded as a promising biomarker for tumor diagnosis, prognosis and treatment. However, the current clinical studies have small samples sizes and poor reproducibility, and large multicenter studies are needed to improve the effectiveness of liquid biopsies. Lastly, the biological properties of exosomes and the active substances they release make them attractive targets for cancer treatment. How to use exosomes to deliver drugs to therapeutic targets? Are treatments targeting exosomes effective in tumor progression? All of the above indicate that the application of exosomes in anti-tumor therapy still has a long way to go.

4. Conclusion

Tumor cells, carcinoma-related fibroblasts, macrophages, vascular endothelial cells, lymphocytes and other various types of cells can secrete exosomes. With the help of exosomes to deliver lncRNA between cells, they mainly affect biological processes, such as tumor proliferation and migration, apoptosis, invasion and metastasis, angiogenesis, EMT, tumor drug resistance, regulation of tumor stem cell characteristics, modulation of immune system activity, promotion of oncogenes inactivation, and modulation of metabolic reprogramming in tumors.

Abbreviations

ncRNA	Non-Coding RNA
lncRNA	Long Non-Coding RNA
EMT	Epithelial-Mesenchymal Transition
HCC	hepatocellular Carcinoma
CSCs	Cancer Stem Cells
HULC	High-Expression Transcripts for Liver Cancer

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Author Contributions

Yaomin Luo: Conceptualization, Funding acquisition, Investigation, Methodology, Writing – original draft

Yanhong Liu: Formal Analysis, Investigation, Software, Visualization, Writing – original draft

Zhen Jiang: Conceptualization, Funding acquisition, Project administration, Resources, Writing – review & editing

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Data Availability Statement

Anonymized data will be available on request.

Conflicts of Interest

All authors declare no conflicts of interest in this paper.

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