Noncoding RNAs of Extracellular Vesicles in Tumor Angiogenesis

Subjects: Biochemistry & Molecular Biology

Contributor: Zhaowu Ma , Lingzhi Wang , , Chen-Guang Liu

Extracellular vesicles (EVs) act as multifunctional regulators of intercellular communication and are involved in diverse tumor phenotypes, including tumor angiogenesis, which is a highly regulated multi-step process for the formation of new blood vessels that contribute to tumor proliferation. EVs induce malignant transformation of distinct cells by transferring DNAs, proteins, lipids, and RNAs, including noncoding RNAs (ncRNAs). However, the functional relevance of EV-derived ncRNAs in tumor angiogenesis remains to be elucidated.

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1. Characteristics of Extracellular Vesicles and ncRNAs

Extracellular vesicles (EVs) are extracellular structures enclosed in a lipid bilayer that can be secreted by almost all known cell types [1]. Several studies have indicated that EVs play an essential role in intercellular communication between tumor cells and the tumor microenvironment (TME). EVs are highly heterogeneous; therefore, their characterization and classification are crucial for further research to avoid generating inconclusive results. Based on their size, biogenesis, and release pathways, EVs can be broadly divided into three main subtypes: exosomes, microvesicles (MVs), and apoptotic bodies. Exosomes, also called small EVs, possess a diameter ranging from 30 to 150 nm and are derived from multivesicular endosomal pathways, which are formed by inward budding of the endosomal membrane in a process that sequesters particular proteins and lipids [2]. On the contrary, MVs are generated by regulated outward budding of the plasma membrane [3]. The mechanisms of exosomal biogenesis involve multiple factors, and the most well-known regulator is endosomal sorting complex required for transport (ESCRT) [3]. Exosomal biogenesis involves inward budding of the plasma membrane to form endosomes, leading to production of multivesicular bodies (MVBs), fusion of MVBs with the plasma membrane, and release of exosomes into the extracellular space. A core component of this mechanism is the ESCRT machinery, which consists of four protein complexes and auxiliary proteins that bind to future exosome cargoes and form intraluminal vesicles that incorporate those cargoes [4][5]. Several studies have found that exosomes can be formed despite the depletion of the ESCRT complex, which reveals an ESCRT-independent approach [6]. ESCRT-independent exosomal biogenesis is regulated by sphingolipid ceramide, which is produced from the hydrolysis of sphingomyelin by neutral sphingomyelinase 2 [2]. The contents of EVs include various nucleic acids, lipids, and proteins [7]. ncRNAs carried by EVs can regulate various physiological and pathological processes through multiple mechanisms (**Figure 1**).

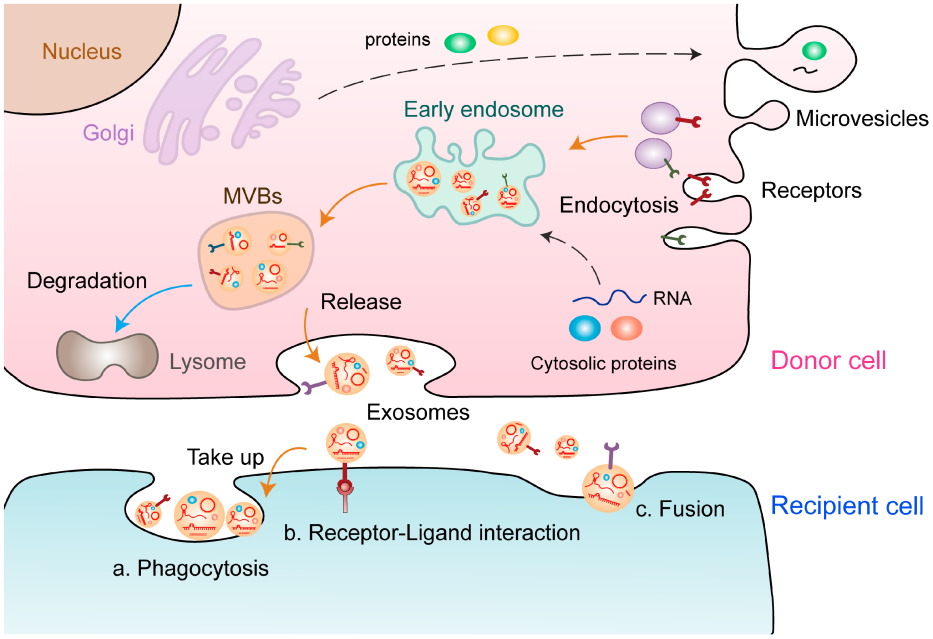

Figure 1. Formation and release of EVs. The formation of EVs involves the following processes: Proteins are transported from the Golgi apparatus or internalised from the cell surface, and nucleic acids are endocytosed and transferred to early endosomes. Early endosomes gradually mature into late endosomes and MVBs, some of which are degraded, whereas others are secreted as exosomes. These exosomes carry multiple biological components, including proteins, lipids, and nucleic acids (e.g., ncRNAs), which are delivered to the recipient cell through different ways: a. phagocytosis, b. receptor–ligand interaction, and c. direct fusion.

In the past few decades, the development of high-throughput sequencing technology has indicated that the transcription rate of the human genome generally exceeds 70%. However, <2% of the transcript is translated into proteins; most human transcriptomes are ncRNAs. Emerging studies have shown that despite being 'transcriptional junk', ncRNAs, such as miRNAs, piRNAs, circRNAs, snoRNAs, and the attractive lncRNAs, play a versatile role in manipulating gene expression [8]. miRNAs, a type of endogenous small RNA with a length of 20–24 nucleotides (nt), have many essential adjustable functions in cells. By complementarily binding to the 3'-untranslated region (UTR) of targeted mRNAs, miRNAs act as regulators of gene expression, thereby inhibiting post-transcriptional gene expression [9][10][11]. Recent studies have reported that miRNAs are selectively sorted into EVs and participate in intercellular communication in the TME [12]. In addition, EV-derived miRNAs in biofluids can be used as ideal biomarkers for various types of tumors due to their easy accessibility, high abundance, and good stability [13]. piRNAs, a type of small RNA with a length of 21–35 nt, specifically interact with PIWI protein to perform multifaceted functions in germline development and somatic tissues [14][15][16].

In addition to small RNAs, large ncRNAs also participate in gene regulation in various biological processes. lncRNAs, collectively referred to as transcripts with more than 200 nt, have limited potential to encode proteins [17]. They perform their functions through multiple molecular and cellular mechanisms, such as interacting with epigenetic factors or TFs to modulate gene transcription, sequestering miRNAs, interacting with proteins, and encoding functional small peptides [18][19][20][21]. In addition, lncRNAs can also be selectively sorted into EVs and

participate in cell-to-cell communication in the TME [22]. circRNAs, generated by a particular form of alternative splicing called back-splicing, regulate gene transcription and translation by interacting with DNAs, RNAs, and proteins [23]. Emerging studies have indicated that circRNAs participate in multiple physiological and pathological processes, including tumor angiogenesis [24][25][26].

2. EV-Derived ncRNAs: New Players in Tumor Angiogenesis

Angiogenesis is a multi-step process and has two types: sprouting and intussusceptive angiogenesis [27]. Various types of cells, including endothelial cells (ECs), tumor cells, stromal cells, and immune cells, regulate angiogenesis in the blood vessels. In addition, some regulatory and signalling molecules govern angiogenesis, including growth factors (e.g., VEGF, PDGF, FGF, and EGF) and transcription factors, such as HIFs [28][29][30]. Because angiogenesis is crucial for tumor growth and metastasis, targeting tumor-associated angiogenesis is a promising strategy for cancer treatment [31][32][33]. Currently, anti-angiogenic therapies targeting VEGF and VEGFR are used for the treatment of various tumors [34].

Several studies have indicated that EVs can be used as ncRNA carriers to play diverse roles in regulating tumor hallmarks, including angiogenesis. For example, in non-small cell lung cancer (NSCLC), RCAN1.4 has been identified as a target of miR-619-5p, and its suppression promotes angiogenesis [35]. The exosomal lncRNA FAM225A upregulates NETO2 and FOXP1 expression by sponging miR-206 to accelerate oesophageal squamous cell carcinoma (ESCC) progression and angiogenesis [36]. In addition, circSHKBP1 sponges miR-582-3p to enhance HUR expression and VEGF mRNA stability, which promotes angiogenesis and gastric tumor progression [37]. Moreover, emerging studies have indicated that EV-derived ncRNAs can regulate tumor angiogenesis by influencing a wide variety of tumor-associated molecules. The functions and mechanisms of EV-derived ncRNAs in tumor angiogenesis are summarized in **Table 1**. These studies suggest that EV-derived ncRNAs play an essential role in tumor angiogenesis. However, new technologies and animal models are required to further investigate the precise mechanisms of EV-derived ncRNAs in the regulation of tumor angiogenesis.

Table 1. The emerging roles of EV-derived ncRNAs in tumor angiogenesis.

EV-Derived ncRNAs	Expression	Source Cell	Function and Mechanism	Tumor Type	Reference
miR-155	Upregulated	Tumor cell	Promotes angiogenesis via the c-MYB/VEGF axis	Gastric cancer	[38]
	Upregulated	Tumor cell	Promotes angiogenesis by inhibiting FOXO3a	Gastric cancer	[39]
miR-130a	Upregulated	Tumor cell	Activates angiogenesis by inhibiting c-MYB	Gastric cancer	[40]

EV-Derived ncRNAs	Expression	Source Cell	Function and Mechanism	Tumor Type	Reference
miR-135b	Upregulated	Tumor cell	Promotes angiogenesis by inhibiting FOXO1	Gastric cancer	[41]
	Upregulated	Tumor cell	Regulates the HIF/FIH signalling pathway	Multiple myeloma	[42]
miR-23a	Upregulated	Tumor cell	Inhibits PTEN and activates the AKT pathway	Gastric cancer	[43]
	Upregulated	Tumor cell	Increases angiogenesis by inhibiting ZO-1	Lung cancer	[44]
miR-200b-3p	Downregulated	Tumor cell	Enhances endothelial ERG expression	Hepatocellular carcinoma	[45]
miR-25-3p	Upregulated	Tumor cell	Inhibits KLF2 and KLF4, thereby elevating VEGFR2 expression	Colorectal cancer	[46]
miR-1229	Upregulated	Tumor cell	Inhibits HIPK2, thereby activating the VEGF pathway	Colorectal cancer	[47]
miR-183-5p	Upregulated	Tumor cell	Inhibits FOXO1, thereby promoting expression of VEGFA, VEGFAR2, ANG2, PIGF, MMP-2, and MMP-9	Colorectal cancer	[48]
miR-142-3p	Upregulated	Tumor cell	Inhibits TGFβR1	Lung adenocarcinoma	[49]

EV-Derived ncRNAs	Expression	Source Cell	Function and Mechanism	Tumor Type	Reference
miR-103a	Upregulated	Tumor cell	Inhibits PTEN, thereby promoting the polarization of M2 macrophages	Lung cancer	[50]
miR-126	Upregulated	MSCs	Upregulates CD34 and CXCR4, thereby promoting expression of VEGF	Lung cancer	[51]
miR-141-3p	Upregulated	Tumor cell	Inhibits SOCS5, thereby activating JAK/STAT3 and NF-κB signalling pathways	Ovarian cancer	[52]
miR-205	Upregulated	Tumor cell	Regulates the PTEN/AKT pathway	Ovarian cancer	[53]
miR-9	Downregulated	Tumor cell	Inhibits MDK, thereby regulating the PDK/AKT signalling pathway	Nasopharyngeal carcinoma	[54]
	Upregulated	Tumor cell	Promotes angiogenesis by targeting COL18A1, THBS2, PTCH1, and PHD3	Glioma	[55]
miR-23a	Upregulated	Tumor cell	Promotes angiogenesis by inhibiting TSGA10	Nasopharyngeal carcinoma	[56]
miR-210	Upregulated	Tumor cell	Enhances tube formation by inhibiting EFNA3	Leukemia	[57]

EV-Derived ncRNAs	Expression	Source Cell	Function and Mechanism	Tumor Type	Reference
	Upregulated	Tumor cell	Promotes angiogenesis by inhibiting SMAD4 and STAT6	Hepatocellular carcinoma	[58]
miR-26a	Upregulated	Tumor cell	Inhibits PTEN, thereby activating the PI3K/AKT signalling pathway	Glioma	[59]
miR-27a	Upregulated	Tumor cell	Inhibits BTG2, thereby promoting VEGF, VEGFR, MMP-2, and MMP-9 expression	Pancreatic cancer	[60]
miR-155-5p /miR-221-5p	Upregulated	M2 macrophages	Promotes angiogenesis by targeting E2F2	Pancreatic cancer	[61]
miR-21-5p	Upregulated	Tumor cell	Promotes angiogenesis by targeting TGFBI and COL4A1	Papillary carcinoma	[62]
miR-100	- -	MSCs	Regulates the mTOR/HIF-1α signalling axis	Breast cancer	[63]
miR-21	Upregulated	Tumor cell	Inhibits SPRY1, thereby promoting VEGF expression	Oesophageal squamous cell carcinoma	[64]
	Upregulated	Tumor cell	Inhibits PTEN, thereby activating PDK1/AKT signalling	Hepatocellular carcinoma	[65]

EV-Derived ncRNAs	Expression	Source Cell	Function and Mechanism	Tumor Type	Reference
miR-181b-5p	Upregulated	Tumor cell	Inhibits PTEN and PHLPP2, thereby activating AKT signalling	Oesophageal squamous cell carcinoma	[66]
miR-9	Upregulated	Tumor cell	Inhibits S1P, thereby promoting VEGF expression	Medulloblastoma and xenoglioblastoma	[67]
miR-10a-5p	Upregulated	CAFs	Inhibits TBX5, thereby activating Hedgehog signalling	Cervical squamous cell carcinoma	[68]
miR-135b	Upregulated	Tumor cell	Enhances angiogenesis by targeting FIH-1	Multiple myeloma	[42]
miR-130b-3p	Upregulated	M2 macrophages	Regulates the miR-130b-3p/MLL3/GRHL2 signalling cascade	Gastric cancer	[69]
lncGAS5	Downregulated	Tumor cell	Inhibits angiogenesis by regulating the miR-29-3p/PTEN axis	Lung cancer	[70]
lnc-CCAT2	Upregulated	Tumor cell	Promotes VEGFA and TGF-β expression	Glioma	[71]
lnc-POU3F3	Upregulated	Tumor cell	Promotes bFGF, bFGFR, and VEGFA expression	Glioma	[72]
lncRNA RAMP2-AS1	Upregulated	Tumor cell	Promotes angiogenesis through the miR-2355-	Chondrosarcoma	[73]

EV-Derived ncRNAs	Expression	Source Cell	Function and Mechanism	Tumor Type	Reference
			5p/VEGFR2 axis		
OIP5-AS1	Upregulated	Tumor cell	Regulates angiogenesis and autophagy through miR-153/ATG5 axis	Osteosarcoma	[74]
FAM225A	Upregulated	Tumor cell	Promotes angiogenesis through the miR-206/NETO2/FOXP1 axis	Oesophageal squamous cell carcinoma	[36]
UCA1	Upregulated	Tumor cell	Promotes angiogenesis through the miR-96-5p/AMOTL2 axis	Pancreatic cancer	[75]
SNHG11	Upregulated	Tumor cell	Promotes angiogenesis through the miR-324-3p/VEGFA axis	Pancreatic cancer	[76]
SNHG1	Upregulated	Tumor cell	Promotes angiogenesis by regulating the miR-216b-5p/JAK2 axis	Breast cancer	[77]
AC073352.1	Upregulated	Tumor cell	Binds and stabilizes the YBX1 protein	Breast cancer	[78]
MALAT1	Upregulated	Tumor cell	Facilitates angiogenesis and predicts poor prognosis	Ovarian cancer	[79]
TUG1	Upregulated	Tumor cell	Promotes angiogenesis by inhibiting caspase-3 activity	Cervical cancer	[80]

EV-Derived ncRNAs	Expression	Source Cell	Function and Mechanism	Tumor Type	Reference
LINC00161	Upregulated	Tumor cell	Promotes angiogenesis and metastasis by regulating the miR-590-3p/ROCK axis	Hepatocellular carcinoma	[81]
H19	Upregulated	Cancer stem cell	Promotes VEGF production and release in ECs	Liver cancer	[82]
circSHKBP1	Upregulated	Tumor cell	Enhances VEGF mRNA stability by the miR-582-3p/HUR axis	Gastric cancer	[37]
circRNA-100,338	Upregulated	Tumor cell	Facilitates HCC metastasis by enhancing invasiveness and angiogenesis	Hepatocellular carcinoma	[83]
circCMTM3	Upregulated	Tumor cell	Promotes angiogenesis and HCC tumor growth by the miR-3619-5p/SOX9 axis	Hepatocellular carcinoma	[84]
circ_0007334	Upregulated	Tumor cell	Accelerates CRC tumor growth and angiogenesis by the miR-577/KLF12 axis	Colorectal cancer	[85]
CircFNDC3B	Downregulated	Tumor cell	Inhibits angiogenesis and CRC progression by the miR-937-5p/TIMP3 axis	Colorectal cancer	[86]

[89][90] [91][92]

Figure 2. The potential clinical application of EV-derived ncRNAs in tumor angiogenesis (**A**) EV-derived ncRNAs can be detected from patient samples and are potential diagnostic and prognostic biomarkers. (**B**) A combination of targeting EV-derived ncRNAs and using conventional anti-angiogenic agents can enhance therapeutic efficacy.

EV-Derived ncRNAs	Expression	Source Cell	Function and Mechanism	Tumor Type	Reference
circGLIS3	Upregulated [94]	Tumor cell [95]	Induces endothelial cell angiogenesis by promoting Ezrin T567 phosphorylation	Glioma	[87]
[51]iRNA-823	Upregulated	Tumor cell	Promotes VEGF and IL-6 expression	Multiple myeloma	[88] [96]

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reported that exosomal ENSG00000258332.1 and LINC00635 could be used to differentiate patients with HCC from those with chronic hepatitis B with high specificity. Therefore, serum exosomal ENSG00000258332.1 and LINC00635, which are highly sensitive and can be obtained non-invasively, may be used as biomarkers for HCC [97]. Similarly, recent studies have reported serum exosomal circRNAs as novel and useful tools for the non-invasive diagnosis of cancer [98]. Exosomal circPRMT5 is highly expressed in the serum and urine of patients with bladder cancer and is closely related to tumor metastasis [99]. In addition, certain diagnostic clinical trials are currently underway. In one such trial, exosomal lncRNAs are isolated from serum samples for the diagnosis of lung cancer (NCT03830619).

A large number of studies have focused on the diagnostic, prognostic, and therapeutic significance of EV-derived ncRNAs in different tumor types. However, the specific role of EV-derived ncRNAs in angiogenesis-related diseases remains unclear. Furthermore, almost all studies have focused on cellular experiments and EV-ncRNA-associated applications in vitro; therefore, further studies are required to validate the findings for in vivo models. In addition, the potential of EV-derived ncRNAs as biomarkers remains to be further verified in multi-center, large-scale clinical trials.

3.2 EV-Derived ncRNAs as Potential Anti-Angiogenic Therapeutic Targets

Because of their negligible antigenicity, minimal cytotoxicity, and ability to bypass endocytic pathways and phagocytosis, EVs are considered ideal natural carriers for the delivery of ncRNAs [100]. In a study, engineered exosomes modified with DSPE–PEG2K–RGD loaded with miR-92b-3p produced synergistic anti-tumor and anti-angiogenesis effects with apatinib in nude mice models of abdominal tumors [101]. Another study showed that the delivery of miR-29a/c using cell-derived MVs inhibited angiogenesis in GC [102]. Furthermore, EV-derived ncRNAs have been demonstrated to be functional towards tumor hallmarks in different cell lines. Huang et al. showed that exosomes derived from HCC cells silenced with circRNA-100338 could significantly decrease the invasive ability of HCC cells. In addition, these exosomes could reduce cell proliferation, angiogenesis, permeability, vasculogenic mimicry (VM) formation ability of HUVECs, and tumor metastasis [83]. Bai et al. demonstrated that exosomal miR-135b secreted by GC cells inhibited the expression of FOXO1 protein and enhanced the growth of blood vessels in mouse models of tumor transplantation [41]. Using an NPC model, Wang et al. found that overexpressed EBV-miR-BART10-5p and hsa-miR-18a upregulated VEGF and HIF-1α in a Spry3-dependent manner and strongly promoted

angiogenesis. Moreover, in both in vitro and in vivo NPC models, treatment with iRGD-tagged exosomes enclosing antagomiR-BART10-5p and antagomiR-18a inhibited angiogenesis [103]. Therefore, exosome engineering is a promising tool in RNA-based therapeutics for cancer treatment (**Figure 2**B). Recently, RNA interference (RNAi)-based strategies, CRISPR/Cas9-mediated circRNA knockout, CRISPR/Cas13-mediated circRNA knockdown and circRNA-induced overexpressed plasmids were developed to target ncRNAs for therapeutic purposes both in vitro and in vivo [104]. In a study, the expression of pro-angiogenic factors in HUVECs was significantly reduced after miR-92a-3p was knocked down in exosomes using an miR-92a-3p inhibitor (miR-92a-3p-i) [105]. Furthermore, because EV-derived ncRNAs perform significant biological functions, specifically targeting EV-derived ncRNAs may be a promising strategy for treating many types of tumors. Currently, many studies aimed at regulating the production of EVs or blocking the uptake of EVs to achieve the goal of treating patients with cancer are underway. Using EVs as a delivery platform is a promising strategy; however, due to high costs and strict ethical regulations, the mass production of EVs is not easy to achieve to develop commercial viability.

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