Expression, regulation, and function of exosome-derived miRNAs in cancer progression and therapy

Bowen Li1 | Yu Cao2 | Mingjun Sun1 | Hui Feng3

Abstract
Exosomes are a novel class of intercellular signal modulators that contain a wide range of molecules and deliver information between cells and tissues. MicroRNAs (miRNAs), a type of regulatory non-coding RNA, are often incorporated into exosomes as signaling molecules. In this review, we discuss the expression of exosomal miRNAs from diverse origins such as tumor cells, solid tumor tissue, and biological fluids in various cancers (lung, breast, colorectal, liver, stomach, and pancreatic). We address the biological functions of exosome-derived miRNAs in processes such as tumor-cell proliferation, angiogenesis, metastasis, and chemoresistance in the tumor microenvironment. In particular, we discuss three oncogenic miRNAs, miR-21, miR-141, and miR-451, which occur within exosomes, in terms of gene regulation and intercellular communication. We consider therapeutic miRNA-based nanoparticles, which are widely expressed in tumors and show promise in drug therapy. The review assesses the wide-ranging evidence for using exosomal miRNAs as tumor markers in molecular diagnosis. Further, we consider the use of nanoparticle platforms to transport miRNAs, in the targeted treatment of disease and tumors.

Keywords
exosome, micro-RNA, nanotechnology, oncomiR, tumor

Abbreviations: AUFI, AU-rich element RNA-binding protein 1; BAP31, B-cell receptor associated protein 31; CADM2, cell adhesion molecule 2; CAFs, cancer-associated fibroblasts; ccRCC, clear cell renal cell carcinoma; ceRNAs, competitive endogenous RNAs; CRC, colorectal cancer; CTA, cancer/testis antigen; DAPK1, death-associated protein kinase 1; DUSP8, dual specificity phosphatase 8; EMT, epithelial-mesenchymal transition; ERCC1, cross-complementation group 1 protein; ERS, reticulum stress; ESCC, esophageal squamous cell carcinoma; FOXA2, Forkhead box protein A2; GAB1, GRB2-associated binding protein 1; GBM, glioblastoma multiforme; GDEs, glioma-derived exosomes; HCC, hepatocellular carcinoma; HNC, head and neck cancer; KIF2A, kinesin family member 2A; LSINCT5, long stress-induced non-coding transcript 5; MDSC, myeloid-derived suppressor cell; MIAT, myocardial infarction associated transcript; miRNAs, microRNA; MMT, mesothelial-to-mesenchymal transition; NPC, nasopharyngeal carcinoma; NRP1, neuropilin-1; NSCLC, non-small-cell lung cancer; oncomiRs, oncogenic miRNAs; OSCC, oral squamous cell carcinoma; PCa, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; PPP2R2A, protein phosphatase 2 regulatory subunit B alpha; RAC1, Ras-related C3 botulinum toxin substrate 1; RASSF8, ras association domain-containing protein 8; SPRY2, sprouty 2; TET1, ten-eleven translocation 1; TEXs, tumor-derived exosomes; TRAF5/6, tumor necrosis factor receptor-associated factor 5/6; UTMD, ultrasound-targeted microbubble destruction; XIST, X-inactive specific transcript.

Bowen Li and Yu Cao contributed equally to this work.
1 | INTRODUCTION

Most cancers cause great harm to public health, because of their high mortality and poor prognosis. The GLOBOCAN 2020 database provides the latest global cancer burden. In 2020, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred worldwide. The global cancer burden is expected to be 28.4 million cases in 2040. Early detection of malignancies can improve prognosis and survival. Although biopsy is the main method to diagnose tumor progression and metastasis, more advanced and safer methods with high sensitivity and specificity are needed in cancer diagnosis. Exosomes are widespread in various body fluids, including blood and urine. Because of their heterogeneous contents, they can provide information about their cells or tissues of origin; this information can be used in disease diagnosis. In addition, they are internalized by specific cell types, thereby transmitting their contents and promoting cell communication. Exosomes can be loaded with drugs, acting as carriers and permitting novel treatment strategies. The novel use of exosomes for tumor diagnosis has attracted attention. Determining the intrinsic connections between exosomal miRNAs expression and cancer progression has substantial therapeutic and monitoring significance. Hence, this review focuses on the characteristics of exosomal miRNAs in various types of cancer, outlines the common and distinctive features of cancer-exosome-derived miRNAs, highlights miRNA-associated tumor-promoting and tumor-suppressing signals and pathways, and explores the mechanisms of exosomal miRNA involvement in tumor biology.

2 | DEFINITION, COMPOSITION, AND FUNCTION OF EXOSOMES

In 1981, researchers observed that exfoliated cells from cultures of cell monolayers showed ecto-ATPase and ecto-5’-exonuclease activity. These particles, named exosomes by Johnstone et al., are small cup-shaped membranous particles (diameter 30–150 nm) encapsulated by a lipid bilayer. They are released into extracellular spaces by cells when intracellular multivesicular bodies fuse with the cell membrane during normal physiological and pathological processes. Although many mechanisms of exosome biogenesis have been revealed, the most characteristic mechanism is via the endosomal sorting complex required for transport (ESCRT) pathway. First, ESCRT-0 recognizes ubiquitous shutters and promotes the initiation of exosome budding; ESCRT-0 then recruits ESCRT-I, which recruits ESCRT-II, which may play a key role in cargo clustering; ESCRT-III then disassembles ESCRT-0, ESCRT-I, and ESCRT-II to promote exosome budding, via Vps-4.

Exosomes exist in various biological fluids, such as urine, cerebrospinal fluid, bronchial lavage, ascites, breast milk, saliva, serum, and plasma. Various cells, including lymphocytes, macrophages, mast cells, adipocytes, and tumor cells, can secrete exosomes. Although exosome composition differs between cell types, they comprise mainly proteins, nucleic acids, and lipids. Researchers have identified 9769 proteins, 3408 mRNAs, 2838 miRNAs, and 1116 lipids within exosomes. Exosomal proteins are mainly cargo or membrane proteins, and participate in processes such as antigen presentation, membrane transport and fusion, and immune defence. Lipids, critical components of the exosome membrane, participate in many processes and stabilize exosome contents, allowing exosomes to be used as biomarkers and drug-delivery vehicles.

Exosomes can be modulated by donor cells and exchange or transmit information to recipient cells in healthy tissue. Under pathological conditions, however, exosomes can influence disease progression. For example, they promote angiogenesis in hepatocellular carcinoma (HCC) and lung cancer and promote metastasis. Cancer-cell-derived exosomes transmit 14-3-3ζ from HCC cells to T cells, thereby inhibiting the anti-tumor function of tumor-infiltrating T cells. KrasG12D-targeting iExosomes, exosomes with short interfering RNAs or short hairpin RNA, can significantly reduce oncogenic Kras G12D mRNA levels and suppress KrasG12D-expressing human pancreatic orthotopic tumors; they can also inhibit tumor metastasis and increase overall survival. Moreover, exosomes can influence human immune responses: for instance, premetastatic tumor-derived exosomes induce a patrolling monocyte-dependent innate immune response, by mediating immune surveillance, thus eliminating cancer cells in the premetastatic microenvironment.

3 | EXOSOME-DERIVED miRNAs PARTICIPATE IN TUMOR DEVELOPMENT AND CHEMoresISTANCE

3.1 | miRNAs and oncogenic miRNAs (oncomiRs)

Genomic analyses have revealed that only 2% of RNA encodes proteins; therefore, many non-coding genome regions are transcribed into non-coding RNAs (nc-RNAs). miRNAs are a family of regulatory nc-RNAs. miRNAs are single-stranded RNAs comprising 21 to 24 nucleotides and have broad regulatory functions. In 1993, Ambros
and co-workers identified lin-4 in *Caenorhabditis elegans*; this was the first miRNA identified; further, such miRNAs did not encode a protein, but regulated other RNAs. The latest miRBase database (v. 22, March 2018) contains 38 589 entries from 271 organisms, and uncovered 2654 mature miRNAs in humans.

miRNAs participate in regulating cell development, differentiation, proliferation, cell death, and metabolism. In addition, miRNAs are related to various pathological states, such as those associated with infectious disease and carcinoma. In humans, >60% of protein-coding genes are regulated by miRNAs. Cancer-related miRNAs that influence tumorigenesis and development, functioning as tumor suppressors and oncogenes, are known as oncomiRs. OncomiRs overexpression, or low expression of tumor-suppressing miRNAs, is related to human cancers. This suggests that miRNAs influence most biological processes in humans. Based on this evidence, miRNAs are key regulators of various tumor processes and have the potential to act as specific and sensitive biomarkers for cancer.

### 3.2 Exosomal miRs as potential tumor biomarkers

Many studies have shown that exosome-derived miRNAs may be more powerful than mRNAs or proteins as cancer biomarkers because exosomal miRNAs contribute to tumorigenesis, prognosis, and responsiveness to therapy. For instance, serum exosomal miR-1247-3p levels are associated with lung metastasis in patients with HCC. Serum exosomal miR-210 originating from tumor tissue is associated with tumorigenesis in clear cell renal cell carcinoma. Circulating exosomal miR-21 levels are closely associated with HIF-1α/HIF-2α expression, T stage, and lymph node metastasis in patients with oral squamous cell carcinoma (OSCC). In a prostate cancer (PCa) metastasis model, risk-scoring based on urinary exosomal miR-21, miR-451, and miR-636 performed better than that based on preoperative prostate-specific antigens. Therefore, exosomal miRNA expression has potential indicative value in tumor diagnosis.

Research has focused on the possible relationships between exosomal miRNAs and tumor types, to discover novel tumor-specific and sensitive cancer biomarkers. For instance, miR-21 and miR-1246 are selectively enriched in exosomes and are significantly elevated in the plasma of patients with breast cancer. Circulating exosomal miR-106a-5p and miR-20b-5p, from the miR-106a-363 cluster, are consistently upregulated in breast cancer tissue. Higher serum expression of exosomal miR-19a indicates poorer colorectal cancer (CRC) prognoses.

### 3.3 Exosomal oncomiRs in tumor proliferation

Exosomal miRNAs participate in tumor proliferation and tumorigenesis. For instance, breast-cancer-secreted exosomal miR-105 is captured by cancer-associated fibroblasts (CAFs); metabolic reprogramming of stromal cells, in turn, contributes to sustained tumor growth by conditioning the shared metabolic environment. Plasma exosomal miR-19b-3p from patients with esophageal squamous cell carcinoma (ESCC) suppresses MAP2K3 expression to promote ESCC-cell proliferation. In vitro coculture of miR-155-rich or miR-21-rich exosomes promote OSCC-cell proliferation and invasion by downregulating PTEN and Bcl-6.

Exosomal miRNAs suppress tumor-cell proliferation and metastasis. CAF-derived exosomal miR-34a-5p can be transferred to OSCC cells, binding to AXL, the direct downstream target of CAF, thereby suppressing OSCC-cell proliferation and metastasis. HCC cells can internalize stellate-cell-derived exosomes loaded with miR-335-5p, leading to upregulation of miR-335-5p in cancer cells, thus inhibiting HCC growth and invasion. Likewise, it has been suggested that CAF-mediated HCC tumorigenesis is partially associated with the loss of antitumor miR-320a in CAF exosomes.

### 3.4 Exosomal oncomiRs in tumor angiogenesis

Angiogenesis, a pivotal element in the progression of malignancy, is responsible for the rapid development, early invasion, and poor prognosis of cancer. Tumor-associated exosomal miRNAs participate in tumor angiogenesis and vascular permeability. For instance, miR-23 is highly enriched in metastatic or premetastatic nasopharyngeal carcinoma (NPC) tissue; overexpression of exosomal miR-23a in NPC promotes angiogenesis by
suppression of testis-specific gene antigen (TSGA10).\(^5\)0 Similarly, tumor angiogenesis may be promoted by targeting SMAD4 and STAT6, by transferring HCC-cell-derived exosomal miR-210 into endothelial cells.\(^5\)1 The A549 lung cancer cell line delivers miR-494 into vascular endothelial cells via an exosome-mediated route, promoting angiogenesis by targeting PTEN and subsequently activating the Akt/eNOS pathway.\(^5\)2 Moreover, CRC-derived exosomal miR-25-3p alters the expression of vascular endothelial growth factor receptor 2, ZO-1, occludin, and Claudin5 in endothelial cells by targeting KLF2 and KLF4, thereby potentiating vascular permeability and angiogenesis.\(^5\)3 Colorectal-cancer-derived exosomal miR-21-5p can be delivered to endothelial cells and promote angiogenesis and vascular permeability by targeting KRIT1.\(^5\)4

### 3.5 | Exosomal oncomiRs in tumor metastasis

Metastasis, a hallmark of malignancy, results in secondary tumors, and oncogenes or biological pathways contribute to invasion by tumors.\(^5\)5 Exosomes can act as malignancy messengers to promote tumor-cell spread.\(^5\)6 For example, serum exosome-enriched miR-423-5p becomes internalized into gastric cancer cells, consequently promoting cancer growth and metastasis.\(^5\)7 Hepatoma cells deliver miR-103-rich exosomes into endothelial cells, thereby increasing vascular permeability and promoting tumor-cell migration, by repressing p120 expression.\(^5\)8 Exosomal miR-1247-3p from highly metastatic HCC cells activates \(\beta1\)-integrin-NF-kB signaling in fibroblasts, by directly targeting B4GALT3.\(^5\)9 Macrophage-derived exosomes (MDEs) mediate CRC cell migration and invasion via exosomal miR-21-5p and miR-155-5p by repressing BRG1.\(^5\)9 Gastric cancer-derived exosomal miR-21-5p induces mesothelial-to-mesenchymal transition (MMT) of peritoneal mesothelial cells and promotes peritoneal cancer metastasis by targeting SMAD7.\(^6\)0 miR-141, an epithelium-associated miRNA, mediates epithelial–mesenchymal transition (EMT) in non-small-cell lung cancer (NSCLC).\(^6\)1 miR-205-5p knockdown reduces invasion by and migration of KKU-M213 cholangiocarcinoma cells.\(^6\)2

### 3.6 | Exosomal oncomiRs in tumor chemoresistance

Accumulating evidence indicates that exosomes can facilitate chemoresistance within the tumor microenvironment. For instance, MDEs transmit miR-365 selectively to pancreatic ductal adenocarcinoma (PDAC) cells, hence inducing gemcitabine resistance in PDAC cells.\(^6\)3 M2 macrophages mediate cisplatin resistance by delivering exosomal miR-21 to gastric cancer cells.\(^6\)4 miR-223-enriched exosomes released from macrophages are transferred to epithelial ovarian cancer (EOC) cells, hastening induction of chemoresistance in EOC cells.\(^6\)5 Paclitaxel-resistant ovarian cancer exosomes contain higher levels of miR-1246 than their paclitaxel-sensitive counterparts, and anti-miR1246 treatment significantly sensitizes ovarian cancer cells to paclitaxel.\(^6\)6 CAFs carrying exosomal miR-196 confer cisplatin resistance in head and neck cancer (HNC) by targeting CDKN1B and INGS.\(^6\)7

In contrast, some exomiRs are emerging as novel therapeutic targets with anti-tumor effects. For example, temozolomide (TMZ)-resistant glioblastoma multiforme (GBM) cells transmit chemoresistance to recipient TMZ-sensitive cells in an exosomal miR-151a loss-dependent manner.\(^6\)8 ExomiR-122 derived from adipose tissue mesenchymal stem cells (AMSCs) can be used as an effective messenger to mediate communication between AMSCs and HCC cells, to render cancer cells sensitive to chemotherapeutic agents, by impacting miR-122 target gene expression in HCC cells.\(^6\)9 MiR-128-3p delivery via exosomes mediates the increased chemosensitivity of oxaliplatin-resistant CRC\(^7\)0 (Figure 1).

### 4 | ONCOMIR-21/141/451

#### 4.1 | miR-21

miR-21, one of the first miRNAs detected in the human genome, is located on chromosome 17q23.1.\(^7\)1,\(^7\)2 Functional experiments showing that it is an oncomiR have revealed that its overexpression is associated with oncogenesis in many forms of cancer.\(^7\)3 The primary mechanism of miR-21-mediated oncogenesis involves inhibiting the expression of various downstream target genes, such as PTEN\(^7\)4–\(^7\)6 and programmed cell death 4 (PDCD4), via direct binding to the 3′-UTR of target transcripts.\(^7\)7 Recent studies have confirmed that novel genes, including sprouty 2,\(^7\)8 ten-eleven translocation 1,\(^7\)9 protein phosphatase 2 regulatory subunit B alpha,\(^8\)0 cell adhesion molecule 2,\(^8\)1 dual specificity phosphatase 8,\(^8\)2 and Ras association domain-containing protein 8, are targeted by miR-21 in various tumors and participate in tumorigenesis.

It is possible that miR-21 abundance is regulated by lncRNAs that competitively bind miRNAs as competitive endogenous RNAs, thereby affecting the regulation of downstream target genes. For instance, forced expression of the lncRNA MEG3 (maternally expressed gene) reverses miR-21-mediated activation of the PI3K/Akt pathway in breast cancer cells.\(^8\)3 Likewise, LINC00312 regulates CRC-cell malignancy by binding to PTEN-targeting miR-21.\(^8\)4
miR-21 overexpression inhibits PTEN and reverses the effect of IncRNA growth arrest-specific 5, resulting in increased proliferation, migration, invasion, and EMT of OSCC cells via the PI3K/Akt pathway.\textsuperscript{85}

Conversely, miR-21 levels are upregulated by onco-genes such as KRAS\textsuperscript{86} and CBX7,\textsuperscript{87} leading to tumor onset and development. KRAS transactivates miR-21 and miR-30c via downstream activation and recruitment of ELK1 to the proximal promoters of miRNAs.\textsuperscript{86} CBX7, a constituent of polycomb repressive complex 1, upregulates miR-21 by activating the AKT-NF-κB pathway, thereby contributing to the CBX7-mediated stem cell-like characteristics of gastric cancer cells.\textsuperscript{87} miR-21 levels were increased by EGF, thereby promoting EGF-induced PDAC cell proliferation.\textsuperscript{78}

It has been validated that exosomal miR-21 influences tumor-cell proliferation, migration, and invasion. For instance, miR-21-enriched exosomes enhance PTENp1-promoter methylation by targeting TETs, thus inhibiting PTENp1 and PTEN expression, thereby promoting HCC cell growth.\textsuperscript{88} Exosomal miR-21-5p induces peritoneal mesothelial cell MMT and promotes peritoneal tumor metastasis, thereby targeting SMAD7 and thus activating the transforming growth factor-beta/Smad pathway.\textsuperscript{60} The EMT transcription factor Snail induces miR-21 expression in human HNC cells, leading to the secretion of miR-21-abundant TEXs to promote the M2 polarization of tumor-associated macrophages.\textsuperscript{89} Moreover, a hypoxic microenvironment may cause OSCC to generate miR-21-rich exosomes that are delivered to normoxic cells to promote pro-metastatic behavior.\textsuperscript{34} Likewise, hypoxia induces glioma-derived exosomes (GDEs) to express miR-10a and miR-21, to mediate GDE-induced myeloid-derived suppressor cell expansion and activation, by targeting RAR-related orphan receptor alpha and PTEN.\textsuperscript{76} Further, an acidic microenvironment induces exosomal miR-21 and miR-10b expression, thus facilitating HCC-cell proliferation, migration, and invasion both in vivo and in vitro\textsuperscript{90} (Figure 2). To the best of our knowledge, no tumor-suppression effects have been identified for miR-21.

4.2 | miR-141

miR-141, a member of the miR-200 family and located on chromosome 12p13.31, is an epithelial-associated miRNA involved in EMT, and is dysregulated in a wide variety of cancers; specifically, it overexpressed in various
miR-141 is a direct and functionally relevant target of several tumor suppressors (MEG3, BRD7, p63α, and MIR22HG), mediating drug chemoresistance and tumor-cell proliferation. Furthermore, the lncRNA KRAL acts as a ceRNA against miR-141, effectively restoring miR-141/Keap1 mediated 5-fluorouracil resistance in HCC cell lines.

miR-141 expression is inversely associated with levels of oncogenic IncRNAs such as X-inactive specific transcript, myocardial infarction-associated transcript, and MAGI2-AS3, suppressing tumor-cell proliferation and migration in NSCLC and gastric cancer. Moreover, miR-141 suppresses PCa metastasis. In PCa cells, RNA-Seq analysis identified miR-141-regulated molecular targets including Rho GTPase family members such as CDC42, CDC42EP3, Ras-related C3 botulinum toxin substrate 1 (RAC1), and ARPC5, CD44 and EZH2.

miR-141 expression is inversely associated with levels of oncogenic IncRNAs such as X-inactive specific transcript, myocardial infarction-associated transcript, and MAGI2-AS3, suppressing tumor-cell proliferation and migration in NSCLC and gastric cancer. Moreover, miR-141 suppresses PCa metastasis. In PCa cells, RNA-Seq analysis identified miR-141-regulated molecular targets including Rho GTPase family members such as CDC42, CDC42EP3, Ras-related C3 botulinum toxin substrate 1 (RAC1), and ARPC5, CD44 and EZH2.

miR-141 expression increases due to declining expression of its target genes such as ZEB2, PDCD4, PTEN, AU-rich element RNA-binding protein 1, death-associated protein kinase 1, Keap1, DDX5, ZEB1, tumor necrosis factor receptor-associated factor 5/6, and Forkhead box protein A2. This increased miR-141 expression, in turn, alters target-protein expression in various cancers, miR-141 and its targets, including neuropilin-1 (NRP1), GRB2 associated binding protein 1, CXCL12β, TGFβ2, and GATA6, comprise a powerful and precise regulatory network that modulates angiogenesis (Figure 3).

4.3 | miR-451

miR-451a, encoded on chromosome 17q11.2, is abundant in fetal bovine serum. It is considered a valuable biomarker for cancer detection, prognosis, and treatment. miR-451 suppresses various tumor types and participates in reducing target gene expression, thereby preventing tumor-cell proliferation, apoptosis, and even chemoresistance.

Kinesin family member 2A, a microtubule depolymerase that functions in many biological processes, is an independent prognostic factor in lung squamous cell carcinoma; it has been implicated as one of 15 putative
oncogenic genes regulated by miR-451a.\textsuperscript{104} miR-451a can suppress the expression of the endoplasmic reticulum membrane protein B-cell receptor-associated protein 31, which has been identified as a novel cancer/testis antigen, by binding to its 5′-UTR and promoting CRC apoptosis by increasing endoplasmic reticulum stress (ERS).\textsuperscript{105,106} miR-451 promotes cellular drug retention in multidrug-resistant (MDR) bladder cancer cells (BIU-87/Adr) by reducing the P-gp levels in MDR cells.\textsuperscript{107} Likewise, excision repair cross-complementation group 1 protein (ERCC1) is a DNA endonuclease with variable expression in primary tumor specimens; ERCC1 positive tumors are more resistant to cisplatin treatment than ERCC1 negative tumors. miR-451 overexpression selectively enhances the chemosensitivity of ERCC1 high-expression NSCLC cells to cisplatin, by inhibiting PI3K/Akt signaling and down-regulating ERCC1 expression.\textsuperscript{108} Likewise, miR-451 overexpression directly targets tyrosine3-monoxygenase/tryptophan5-monoxygenase activation protein zeta (YWHAZ) to inhibit β-catenin expression, in turn elevating breast cancer-cell sensitivity to paclitaxel. Further, intra-tumoral injection of a miR-451 agomir induced tumor suppression in an SKBR3/PR drug-resistant xenograft model.\textsuperscript{109}

miR-451 overexpression exerted an anti-glioma effect by downregulating Rac1. Knockdown of long stress-induced non-coding transcript 5, which is overexpressed in multiple tumor types, inhibited glioma cell growth and metastasis by upregulating miR-451.\textsuperscript{110} miR-451 antagonizes angiogenesis to suppress HCC by directly targeting the interleukin 6 receptor–STAT3–vascular endothelial growth factor pathway\textsuperscript{111} (Figure 4).

5 | THERAPEUTIC RNA NANOPARTICLES

Exosomes hold great promise as endogenous nanocarriers that can deliver biological information between cells. Exosomes enriched within metalloproteinase 15 (A15 exosomes), derived from continuous protein kinase C activation in monocyte-derived macrophages, coloaded with doxorubicin hydrochloride and cholesterol-modified miRNA 159 (Cho-miR159) induced synergistic therapeutic effects in MDA-MB-231 BC cells in vitro.\textsuperscript{112} In vivo, miR159 and Dox delivery in a vesicular system effectively silenced the TCF-7 gene, producing anticancer effects without adverse effects, in triple-negative breast cancer (TNBC) therapy.\textsuperscript{112} Alarmin-painted tumor exosomes, which are used to deliver tumor-associated antigens and the HMGN 1 (N1ND) functional N-terminal domain, strengthened dendritic cell long-lasting anti-tumor immunity and tumor suppression in various syngeneic mouse models with large tumor burdens.\textsuperscript{113}

Similarly, nanoparticles have been widely used as exogenous delivery vehicles in tumor immunotherapy in vivo and in vitro. For instance, RNA nanoparticles containing an RNA aptamer binding to CD133 and anti-miR-21,
carried by a thermodynamically and chemically stable three-way junction motif, were specifically taken up by breast cancer stem cells and TNBC cells. Animal trials in TNBC have demonstrated that systemic injection of RNA nanoparticles promotes highly specific tumor targeting and high inhibition of tumor growth, without inducing cytokine secretion.

Ultrasound-targeted microbubble destruction (UTMD)—miRNA combination therapy, which uses UTMD for local delivery of nanoparticle-loaded miRNA-122 and anti-miRNA-21, alters the immune microenvironment in Hepa1-6 tumors by modulating cytokine expression, improving the response of HCC to chemotherapy by eliminating drug resistance. Triple-action nanoparticles acting via CXCR4 antagonism and miR-210/KRAS\textsuperscript{G12D} downregulation improved pancreatic cancer therapeutic effects, as revealed by delayed tumor growth, stromal depletion, reduced immunosuppression, inhibited metastasis, and prolonged survival.

In addition to nanoparticle-based delivery, an RNA micelle platform can be used to deliver anti-miRNA agents. An 8 nt LNA-modified anti-miR21 antibody can be annealed to a phi29 DNA-packaging RNA three-way junction (pRNA-3WJ) scaffold via complementation with an extended sequence. Compared to RNA nanoparticles without micelle formation, RNA micelles showed enhanced tumor-targeting ability and greater accumulation in tumors, in a mouse xenograft model. siRNAs delivered by lipid nanoparticles or other vehicles require excessively high therapeutic doses, with toxic outcomes. It has recently been shown that the pre-miR-451 backbone can facilitate the enrichment of therapeutic siRNA to the level of the most abundant miRNA in small extracellular vesicles (sEVs), thereby reducing the required delivery volume of sEVs by 100- to 10 000-fold. Therefore, integrating siRNA into the pre-miR-451 backbone offers a powerful and new approach as a delivery platform for anticancer therapy.

6 | CONCLUSIONS

The detection of cancer biomarkers is significant for diagnosis and prognosis, and fluid/tissue biopsy provides a new approach. Exosomal miRNAs can be extracted from many types of body fluid. They occur in tumor cells, and participate in tumor-microenvironment reactions to promote tumor-cell growth. Serum and plasma analysis of exosomal miRNAs, therefore contributes to early disease detection and treatment monitoring. In therapy, tumor- or immune-cell-derived exosomal miRNAs may promote or suppress tumor development, causing drug resistance or promoting tumor invasiveness. Investigating serum and plasma analysis of exosomal miRNAs will facilitate early cancer diagnosis and
treatment monitoring. Exosomal miRNAs-based therapies include impairing oncomiR expression, disturbing cancer development signaling, or potentiating tumor-suppressive pathways to facilitate tumor diagnosis and therapy.

DISCLOSURES
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS
Original draft preparation, Bowen Li; Funding acquisition and draft preparation, Yu Cao; designed the outline and revised the manuscript, Mingjun Sun and Hui Feng. All authors have read and agreed to the published version of the manuscript.

ORCID
Bowen Li https://orcid.org/0000-0001-9556-5546
Yu Cao https://orcid.org/0000-0001-8282-7359
Mingjun Sun https://orcid.org/0000-0003-3676-3651
Hui Feng https://orcid.org/0000-0001-6936-1734

REFERENCES
1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Yang H, Fu H, Xu W, et al. Exosomal non-coding RNAs: a promising cancer biomarker. Clin Chem Lab Med. 2016;54(12):1871-1879. doi:10.1515/cclm-2016-0029
3. Salehi M, Sharifi M. Exosomal miRNAs as novel cancer biomarkers: challenges and opportunities. J Cell Physiol. 2018;233(9):6370-6380. doi:10.1002/jcp.26481
4. Mousavi S, Moallem R, Hassanian SM, et al. Tumor-derived exosomes: potential biomarkers and therapeutic target in the treatment of colorectal cancer. J Cell Physiol. 2019;234(8):12422-12432. doi:10.1002/jcp.28080
5. Trams EG, Lauter CJ, Norman Salem JR, et al. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles. Biochim Biophys Acta. 1981;645(1):63-70. doi:10.1016/0005-2736(81)90512-5
6. Johnstone RM, Bianchini A, Teng K. Reticulocyte maturation and exosome release: transferrin receptor containing exosomes shows multiple plasma membrane functions. Blood. 1989;74(5):1844-1851.
7. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. Nat Rev Immunol. 2002;2(8):569-579. doi:10.1038/nri855
8. Hurley JH. ESCRTs are everywhere. EMBO J. 2015;34(19):2398-2407. doi:10.15252/embj.201592484
9. Abudoureyimu M, Zhou H, Zhi Y, et al. Recent progress in the emerging role of exosome in hepatocellular carcinoma. Cell Prolif. 2019;52(2):e12541. doi:10.1111/cpr.12541
10. Kim MY, Shin H, Moon HW, et al. Urinary exosomal microRNA profiling in intermediate-risk prostate cancer. Sci Rep. 2021;11(1):7355. doi:10.1038/s41598-021-86785-z
complementarity to lin-14. Cell. 1993;75(5):843-854. doi:10.1010/160092-8674/93/00529-y

28. Kozomara A, Birgaoanu M, Griffiths-Jones S. miRBase: from microRNA sequences to function. Nucleic Acids Res. 2019;47(D1):D155-D162. doi:10.1093/nar/gky1141

29. Drury RE, O’Connor D, Pollard AJ. The clinical application of microRNAs in infectious disease. Front Immunol. 2017;8:1182. doi:10.3389/fimmu.2017.01182

30. Friedman RC, Farh K K-H, Burge CB, et al. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res. 2009;19(10):1205-1214. doi:10.1101/gr.082701.108

31. Lin S, Gregory RI. MicroRNA biogenesis pathways in cancer. Nat Rev Cancer. 2015;15(5):321-333. doi:10.1038/nrc3932

32. Fang T, Lv H, Lv G, et al. Tumor-derived exosomal miR-247-3p induces cancer-associated fibroblast activation to foster lung metastasis of liver cancer. Nat Commun. 2018;9(1):191. doi:10.1038/s41467-017-0175-z

33. Wang X, Wang T, Chen C, et al. Serum exosomal miR-210 as a potential biomarker for clear cell renal cell carcinoma. J Cell Biochem. 2018. doi:10.1002/jcb.27347

34. Li L, Li C, Wang S, et al. Exosomes derived from hypoxic oral squamous cell carcinoma cells deliver miR-21 to normoxic cells to elicit a pro-metastatic phenotype. Cancer Res. 2016;76(7):1770-1780. doi:10.1158/0008-5472.Can-15-1625

35. Shin S, Park YH, Jung S-H, et al. Urinary exosome microRNA signatures as a noninvasive prognostic biomarker for prostate cancer. NPJ Genom Med. 2021;6(1):45. doi:10.1038/s41525-021-00212-w

36. Hannafon BN, Trigoso YD, Calloway CL, et al. Plasma exosome microRNAs are indicative of breast cancer. Breast Cancer Res. 2016;18(1):90. doi:10.1186/s13058-016-0753-x

37. Li M, Zhou Y, Xia T, et al. Circulating microRNAs from the miR-106a-363 cluster on chromosome X as novel diagnostic biomarkers for breast cancer. Breast Cancer Res Treat. 2018;170(2):257-270. doi:10.1007/s10549-018-4757-3

38. Matsumura T, Sugimachi K, Iinuma H, et al. Exosomal microRNA in serum is a novel biomarker of recurrence in human colorectal cancer. Br J Cancer. 2015;113(2):275-281. doi:10.1038/bjc.2015.201

39. Lee YR, Kim G, Tak WY, et al. Circulating exosomal noncoding RNAs as prognostic biomarkers in human hepatocellular carcinoma. Int J Cancer. 2019;144(6):1444-1452. doi:10.1002/ijc.31931

40. Huang X, Yuan T, Liang M, et al. Exosomal miR-1290 and miR-375 as prognostic markers in non-small cell lung cancer. Cancer Res. 2015;75(6):201-206. doi:10.1158/0008-5472.CAN-14-2870

41. Malla B, Aebersold DM, Dal Pra A. Protocol for serum exosomal miRNAs analysis in prostate cancer patients treated with radiotherapy. J Transl Med. 2018;16(1):223. doi:10.1186/s12967-018-1592-6

42. Peng ZY, Gu RH, Yan B. Downregulation of exosome-encapsulated miR-584c-5p is associated with poor prognosis in colorectal cancer. J Cell Biochem. 2018. doi:10.1002/jcb.27291

43. Yan W, Wu X, Zhou W, et al. Cancer-cell-secreted exosomal miR-105 promotes tumour growth through the MYC-dependent metabolic reprogramming of stromal cells. Nat Cell Biol. 2018;20(5):597-609. doi:10.1038/s41556-018-0083-6

44. Zhang Y, Lu W, Chen Y, et al. The miR-19b-3p-MAP2K3-STAT3 feedback loop regulates cell proliferation and invasion in esophageal squamous cell carcinoma. Mol Oncol. 2021;15(5):1566-1583. doi:10.1002/1878-0261.12934

45. Chen C-M, Chu T-H, Chou C-C, et al. Exosome-derived microRNAs in oral squamous cell carcinomas impact disease prognosis. Oral Oncol. 2021;120:105402. doi:10.1016/joraloncology.2021.105402

46. Li Y-Y, Tao Y-W, Gao S, et al. Cancer-associated fibroblasts contribute to oral cancer cells proliferation and metastasis via exosome-mediated paracrine miR-34a-5p. EBioMedicine. 2018;36:209-220. doi:10.1016/j.ebiom.2018.09.006

47. Wang F, Li L, Piontek K, et al. Exosome miR-335 as a novel therapeutic strategy in hepatocellular carcinoma. Hepatology. 2018;67(3):940-954. doi:10.1002/hep.29586

48. Zhang Z, Li X, Sun W, et al. Loss of exosomal miR-320a from cancer-associated fibroblasts contributes to HCC proliferation and metastasis. Cancer Lett. 2017;397:33-42. doi:10.1016/j.canlet.2017.03.004

49. Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. Cell. 2011;146(6):873-887. doi:10.1016/j.cell.2011.08.039

50. Bao L, You BO, Shi SI, et al. Metastasis-associated miR-23a from nasopharyngeal carcinoma-derived exosomes mediates angiogenesis by repressing a novel target gene TSGA10. Oncogene. 2018;37(21):2873-2889. doi:10.1038/s41388-018-0183-6

51. Lin X-J, Fang J-H, Yang X-J, et al. Hepatocellular carcinoma cell-secreted exosomal microRNA-210 promotes angiogenesis in vitro and in vivo. Mol Ther Nucleic Acids. 2018;11:243-252. doi:10.1016/j.omtn.2018.02.014

52. Mao G, Liu Y, Fang XJ, et al. Tumor-derived microRNA-494 promotes angiogenesis in non-small cell lung cancer. Angiogenesis. 2015;18(3):373-382. doi:10.1007/s10456-015-9474-5

53. Zeng Z, Li Y, Pan Y, et al. Cancer-derived exosomal miR-25-3p promotes pre-metastatic niche formation by inducing vascular permeability and angiogenesis. Nat Commun. 2018;9(1):5395. doi:10.1038/s41467-018-07810-w

54. He Q, Ye A, Ye W, et al. Cancer-secreted exosomal miR-21-5p induces angiogenesis and vascular permeability by targeting KRIT1. Cell Death Dis. 2021;12(6):576. doi:10.1038/s41419-021-03803-8

55. Fidler IJ. The pathogenesis of cancer metastasis: the ‘seed and soil’ hypothesis revisited. Nat Rev Cancer. 2003;3(6):453-458. doi:10.1038/nrc1098

56. Kaiser J. Malignant messengers. Science. 2016;352(6282):164-166. doi:10.1126/science.352.6282.164

57. Yang H, Fu H, Wang BO, et al. Exosomal miR-423-5p targets SUSD4 to promote cancer growth and metastasis as a novel marker for gastric cancer. Mol Carcinog. 2018;57(9):1223-1236. doi:10.1002/mc.22838

58. Fang J-H, Zhang Z-J, Shang L-R, et al. Hepatoma cell-secreted exosomal microRNA-103 increases vascular permeability and promotes metastasis by targeting junction proteins. Hepatology. 2018;68(4):1459-1475. doi:10.1002/hep.29920

59. Lan J, Sun LI, Xu F, et al. M2 macrophage-derived exosomes promote cell migration and invasion in colon cancer. Cancer Res. 2019;79(1):146-158. doi:10.1158/0008-5472.CAN-18-0014

60. Li Q, Li B, Li Q, et al. Exosomal miR-21-5p derived from gastric cancer promotes peritoneal metastasis via mesothelial-to-mesenchymal transition. Cell Death Dis. 2018;9(9):854. doi:10.1038/s41419-018-0928-8
61. Zhang C, Cao J, Lv W, et al. CircRNA_100395 carried by exosomes from adipose-derived mesenchymal stem cells inhibits the malignant transformation of non-small cell lung carcinoma through the miR-141-3p-LATS2 Axis. *Front Cell Dev Biol*. 2021;9:663147. doi:10.3389/fcell.2021.663147

62. Kitdumrongthum S, Metheteatruit C, Charoensawan V, et al. Dysregulated microRNA expression profiles in cholangiocarcinoma cell-derived exosomes. *Life Sci*. 2018;210:65-75. doi:10.1016/j.lfs.2018.08.058

63. Binenbaum Y, Fridman E, Yaari Z, et al. Transfer of miRNA in macrophase-derived exosomes induces drug resistance in pancreatic adenocarcinoma. *Cancer Res*. 2018;78(18):5287-5299. doi:10.1158/0008-5472.Can-18-0124

64. Zheng P, Chen L, Yuan X, et al. Exosomal transfer of tumor-associated macrophage-derived miR-21 confers cisplatin resistance in gastric cancer cells. *J Exp Clin Cancer Res*. 2017;36(1):53. doi:10.1186/s13046-017-0528-y

65. Zhu X, Shen H, Yin X, et al. Macrophages derived exosomes deliver miR-223 to epithelial ovarian cancer cells to elicit a chemoresistant phenotype. *J Exp Clin Cancer Res*. 2019;38(1):81. doi:10.1186/s13046-019-1095-1

66. Kanlikilic P, Bayraktar R, Denizli M, et al. Exosomal microRNA miR-21 confers chemo resistance via targeting Cavi1/p-gp/M2-type macrophage axis in ovarian cancer. *ElBioMedicine*. 2018;38:100-112. doi:10.1016/j.ebiom.2018.11.004

67. Qin X, Guo H, Wang X, et al. Exosomal miR-196a derived from cancer-associated fibroblasts confers cisplatin resistance in head and neck cancer through targeting CDKN1B and ING5. *Genome Biol*. 2019;20(1):12. doi:10.1186/s13059-018-1604-0

68. Zeng A, Wei Z, Yan W, et al. Exosomal transfer of miR-151a enhances chemosensitivity to temozolomide in drug-resistant glioblastoma. *Cancer Lett*. 2018;436:10-21. doi:10.1016/j.canlet.2018.08.004

69. Lou G, Song X, Yang F, et al. Exosomes derived from miR-21-positive adipose tissue-derived MSCs increase chemosensitivity of oxaliplatin-resistant colorectal cancer cells. *Surg Oncol*. 2018;27(1):76-81. doi:10.1016/j.suronc.2017.12.004

70. Koutsioumpa M, Chen H-W, O’Brien N, et al. MKAD-21 suppresses the oncogenic activity of the miR-21-3p/BCL2L12/BCL2L13 axis in bladder cancer. *Mol Cancer Ther*. 2018;17(7):1430-1440. doi:10.1158/1535-7163.Mct-17-1049

71. Li X, Chen D, Li M, et al. The CADM2/Akt pathway is involved in the inhibitory effect of miR-21-5p downregulation on proliferation and apoptosis in esophageal squamous cell carcinoma cells. *Chem Biol Interact*. 2018;288:76-82. doi:10.1016/j.cbi.2018.04.021

72. Ding T, Cui P, Zhou YA, et al. Anti-sense oligonucleotides against miR-21 inhibit the growth and metastasis of colorectal carcinoma via the DUSP8 pathway. *Mol Ther Nucleic Acids*. 2018;9:244-255. doi:10.1016/j.omtn.2018.09.004

73. Zhu M, Wang X, Gu Y, et al. MEG3 overexpression inhibits the tumorigenesis of breast cancer by downregulating miR-19-5p. *PloS One*. 2018;13:e0198468. doi:10.1186/s12943-019-0243-9

74. Shi L, Middleton J, Jeon Y-J, et al. KRAS induces lung tumorigenesis through multiple targets in human hepatocellular carcinoma. *J Cancer*. 2015;6(10):1957-1966. doi:10.1186/s12943-015-0107-2

75. Usmani A, Shoro AA, Memon Z, et al. Diagnostic, prognostic and predictive value of MicroRNA-21 in breast cancer patients, their daughters and healthy individuals. *Am J Cancer Res*. 2015;5(8):2484-2490.

76. Cai X, Hagedorn CH, Cullen BR. Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. *RNA*. 2004;10(12):1957-1966. doi:10.1261/rna.7135204

77. Selcuklu SD, Donoghue MT, Spillane C. miR-21 as a key regulator of oncogenic processes. *Biochem Soc Trans*. 2009;37(pt 4):918-925. doi:10.1042/bst0370918

78. Meng F, Henson R, Wehbe-Janek H, et al. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology*. 2007;133(2):647-658. doi:10.1053/j.gastro.2007.05.022

79. Liu C, Yu J, Yu S, et al. MicroRNA-21 acts as an oncomir through multiple targets in human hepatocellular carcinoma. *J Hepatol*. 2010;53(1):98-107. doi:10.1016/j.jhep.2010.02.021

80. Guo X, Qiu W, Liu Q, et al. Immunosuppressive effects of hypoxia-induced glioma exosomes through myeloid-derived suppressor cells via the miR-10a/Rora and miR-21/Pten Pathways. *Oncogene*. 2018;37(31):4239-4259. doi:10.1038/s41388-018-0261-9

81. Zennami K, Choi SM, Liao R, et al. PDCD4 is an androgen-repressed tumor suppressor that regulates prostate cancer growth and castration resistance. *Mol Cancer Res*. 2019;17(2):618-627. doi:10.1158/1541-7786.Mcr-18-0837

82. Zhao Q, Chen S, Zhu Z, et al. miR-21 promotes EGF-induced pancreatic cancer cell proliferation by targeting Spry2. *Cell Death Dis*. 2019;10(12):1157. doi:10.1038/s41419-018-1182-9

83. Cheng YW, Chou CJ, Yang PM. Ten-eleven translocation 1 (TET1) gene is a potential target of miR-21-5p in human colorectal cancer. *Surg Oncol*. 2018;27(1):76-81. doi:10.1016/j.suronc.2017.12.004

84. Meng F, Henson R, Wehbe-Janek H, et al. MicroRNA-21 regulates PTEN expression in oral squamous cell carcinoma by regulating the miR-21/MTOR/PTEN pathway. *Cell Death Dis*. 2019;10(11):1383. doi:10.1038/s41419-019-1549-0

85. Cao L-Q, Yang X-W, Chen Y-B, et al. Exosomal miR-21 regulates PTEN expression and apoptosis in esophageal squamous cell carcinoma cells. *Exp Cell Res*. 2018;374:365-373. doi:10.1016/j.yexcr.2018.12.014

86. Shi L, Middleton J, Jeon Y-J, et al. KRAS induces lung tumorigenesis through microRNAs modulation. *Cell Death Dis*. 2018;9(2):219. doi:10.1038/s41419-017-0243-9

87. Ni S-J, Zhao L-Q, Wang X-F, et al. CBX7 regulates stem cell-like properties of gastric cancer cells via p16 and AKT-NF-κB inhibition and miR-21 pathways. *J Hematol Oncol*. 2018;11(1):17. doi:10.1186/s13045-018-0562-z

88. Cao L-Q, Yang X-W, Chen Y-B, et al. Exosomal miR-21 regulates the TETs/PTENp1/PTEN pathway to promote hepatocellular carcinoma growth. *Mol Cancer*. 2019;18(1):148. doi:10.1186/s12943-019-1075-2

89. Hsieh CH, Tai SK, Yang MH. Snail-overexpressing cancer cells promote M2-like polarization of tumor-associated macrophages by delivering MiR-21-abundant exosomes. *Neoplasia*. 2018;20(8):775-788. doi:10.1016/j.neo.2018.06.004

90. Tian X-P, Wang C-Y, Jin X-H, et al. Acidic microenvironment up-regulates exosomal miR-21 and miR-10b in early-stage hepatocellular carcinoma to promote cancer cell proliferation and metastasis. *Theranostics*. 2019;9(7):1965-1979. doi:10.7150/thno.30958
91. Li C, Wan L, Liu Z, et al. Long non-coding RNA XIST promotes TGF-β-induced epithelial-mesenchymal transition by regulating miR-367/141-ZEB2 axis in non-small-cell lung cancer. *Cancer Lett.* 2018;418:185-195. doi:10.1016/j.canlet.2018.01.036

92. Wang H, Li H, Zhang L, et al. Overexpression of MEG3 sensitizes colorectal cancer cells to oxaliplatin through regulation of miR-141/PDCD4 axis. *Biomed Pharmacother.* 2018;106:1607-1615. doi:10.1016/j.biopha.2018.07.131

93. Liu Y, Zhao R, Wei Y, et al. BRD7 expression and c-Myc activation forms a double-negative feedback loop that controls the cell proliferation and tumor growth of nasopharyngeal carcinoma by targeting oncogenic miR-141. *J Exp Clin Cancer Res.* 2018;37(1):64. doi:10.1186/s13046-018-0734-2

94. Li X, Tian Z, Jin H, et al. Decreased c-Myc mRNA stability via the microRNA 141–3p/AUF1 axis is crucial for p63α inhibition of cyclin D1 gene transcription and bladder cancer cell tumorigenicity. *Mol Cell Biol.* 2018;38(21). doi:10.1128/MCB.00273-18

95. Cui Z, An X, Li J, et al. LncRNA MIR22HG negatively regulates resistance to paclitaxel by regulating YWHAZ in breast cancer. *Biomed Pharmacother.* 2018;104:223-228. doi:10.1016/j.biopha.2018.05.046

96. Wu L, Pan C, Wei X, et al. lncRNA KRAL reverses 5-fluorouracil resistance in hepatocellular carcinoma cells by acting as a ceRNA against miR-141. *Cell Commun Signal.* 2018;16(1):47. doi:10.1186/s12957-018-0260-z

97. Sha M, Lin M, Wang J, et al. Long non-coding RNA MIAT promotes gastric cancer growth and metastasis through regulation of miR-141/DDX5 pathway. *J Exp Clin Cancer Res.* 2018;37(1):58. doi:10.1186/s13046-018-0725-3

98. Li D, Wang J, Zhang M, et al. LncRNA MAGI2-AS3 is regulated by BRD4 and promotes gastric cancer progression via maintaining ZEB1 overexpression by sponging miR-141/200a. *Mol Ther Nucleic Acids.* 2020;10:223-228. doi:10.1016/j.omtn.2019.11.003

99. Liu C, Liu R, Zhang D, et al. MicroRNA-141 suppresses prostate cancer stem cells and metastasis by targeting a cohort of pro-metastasis genes. *Nat Commun.* 2017;8:14270. doi:10.1038/ncomms14270

100. Huang S, Wa Q, Pan J, et al. Downregulation of miR-141-3p promotes bone metastasis via activating NF-κB signaling in prostate cancer. *J Exp Clin Cancer Res.* 2017;36(1):173. doi:10.1186/s13046-017-0645-7

101. Li J-H, Zhang Z, Du M-Z, et al. microRNA-141-3p fosters the growth, invasion, and tumorigenesis of cervical cancer cells by targeting FOXA2. *Arch Biochem Biophys.* 2018;657:23-30. doi:10.1016/j.abb.2018.09.008

102. Dong H, Weng C, Bai R, et al. The regulatory network of miR-141 in the inhibition of angiogenesis. *Angiogenesis.* 2019;22(2):251-262. doi:10.1007/s10456-018-9564-1

103. Wei Z, Batagov AO, Carter DRF, et al. Fetal bovine serum RNA interferes with the cell culture derived extracellular RNA. *Sci Rep.* 2016;6:31175. doi:10.1038/srep31175

104. Uchida A, Seki N, Mizzuno K, et al. Regulation of KIF2A by anti-tumor miR-451a inhibits cancer cell aggressiveness features in lung squamous cell carcinoma. *Cancers.* 2019;11(2):258. doi:10.3390/cancers11020258

105. Xu KE, Han B, Bai Y, et al. MiR-451a suppressing BAP31 can inhibit proliferation and increase apoptosis through inducing ER stress in colorectal cancer. *Cell Death Dis.* 2019;10(3):352. doi:10.1038/s41419-019-1403-x

106. Dani P, Yang S, Song C, et al. BAP31, a newly defined cancer/ testis antigen, regulates proliferation, migration, and invasion to promote cervical cancer progression. *Cell Death Dis.* 2018;9(8):791. doi:10.1038/s41419-018-0824-2

107. Wei S, Gao J, Zhang M, et al. Dual delivery nanoscale device for miR-451 and adriamycin co-delivery to combat multidrug resistant in bladder cancer. *Biomed Pharmacother.* 2020;122:109473. doi:10.1016/j.biopha.2019.109473

108. Liu K, Tian H, Zhang Y, et al. miR-451 selectively increases sensitivity to cisplatin in ERCC1-high non-small cell lung cancer cells. *J Cell Biochem.* 2018. doi:10.1002/jcb.26657

109. Wang W, Zhang L, Wang Y, et al. Involvement of miR-451 in resistance to paclitaxel by regulating YWHAZ in breast cancer. *Cell Death Dis.* 2017;8(10):e3071. doi:10.1038/cddis.2017.460

110. Liu B, Cao W, Ma H. Knockdown of lncRNA LSINCT5 suppresses growth and metastasis of human glioma cells via up-regulating miR-451. *Artif Cells Nanomed Biotechnol.* 2019;47(1):2507-2515. doi:10.1080/21691401.2019.1626404

111. Liu X, Zhang A, Xiang J, et al. miR-451 acts as a suppressor of angiogenesis in hepatocellular carcinoma by targeting the IL-6R-STAT3 pathway. *Onco Rep.* 2016;36(3):1385-1392. doi:10.3892/or.2016.4971

112. Gong C, Tian J, Wang Z, et al. Functional exosome-mediated co- delivery of doxorubicin and hydrophobically modified microRNA 159 for triple-negative breast cancer therapy. *J Nanobiotechnology.* 2019;17(1):93. doi:10.1186/s12951-019-0526-7

113. Zuo B, Qi H, Lu Z, et al. Alarmin-painted exosomes elicit persistent antitumor immunity in large established tumors in mice. *Nat Commun.* 2020;11(1):1790. doi:10.1038/s41467-020-15569-2

114. Yin H, Xiong G, Guo S, et al. Delivery of anti-miRNA for triple- negative breast cancer therapy using RNA nanoparticles targeting stem cell marker CD133. *Mol Ther.* 2019;27(7):1252-1261. doi:10.1016/j.mther.2019.04.018

115. Wischhusen JC, Chowdhury SM, Lee T, et al. Ultrasound-mediated delivery of miRNA-122 and anti-miRNA-21 therapeutically immuno- modulates murine hepatocellular carcinoma in vivo. *J Control Release.* 2020;321:272-284. doi:10.1016/j.jconrel.2020.01.051

116. Xie Y, Hang YU, Wang Y, et al. Stromal modulation and treatment of metastatic pancreatic cancer with local intraperitoneal triple miRNA/siRNA nanotherapy. *ACS Nano.* 2020;14(1):255-271. doi:10.1021/acs.nano.9b03978

117. Yin H, Wang H, Li Z, et al. RNA micelles for the systemic delivery of anti-miRNA for cancer targeting and inhibition without ligand. *ACS Nano.* 2019;13(1):706-717. doi:10.1021/acsnano.8b07948

118. Reshke R, Taylor JA, Savard A, et al. Reduction of the therapeutic dose of silencing RNA by packaging it in extracellular vesicles via a pre-microRNA backbone. *Nat Biomed Eng.* 2020;4(1):52-68. doi:10.1038/s41551-019-0502-4

119. Ferhan AR, Jackman JA, Park JH, et al. Nanoplasmonic sensors for detecting circulating cancer biomarkers. *Adv Drug Deliv Rev.* 2018;125:48-77. doi:10.1016/j.addr.2017.12.004

How to cite this article: Li B, Cao Y, Sun M, Feng H. Expression, regulation, and function of exosome-derived miRNAs in cancer progression and therapy. *FASEB J.* 2021;35:e21916. https://doi.org/10.1096/fj.202100294RR