The role of exosomal IncRNAs in cancer biology and clinical management

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Exosomes play a vital role in cell–cell communication within the cancer microenvironment. Exosomal long noncoding RNAs (IncRNAs) are important regulators in cancer development and are involved in multiple processes, including cancer cell proliferation, angiogenesis, metastasis, drug resistance, and immunomodulation. Changes in the levels of exosomal IncRNAs often appear with the occurrence and development of cancer. Therefore, exosomal IncRNAs can be used as biomarkers for cancer diagnosis and prognosis. Exosomal IncRNAs can also indicate the treatment response of patients receiving chemotherapy. Moreover, exosomal IncRNAs are potential therapeutic targets for cancer treatment. In this review, we summarize the role of exosomal IncRNAs in cancer biology as well as in clinical management. A more comprehensive and in-depth understanding of the role of exosomal IncRNAs in cancer may help us better understand the mechanism of cancer development and clinically manage cancer patients.

INTRODUCTION

Exosomes are a group of extracellular vesicles with a diameter of 30–150 nm. The release of exosomes is ubiquitous in a variety of cells in the human body. Exosomes are not simply fragments of cells; they carry abundant nucleic acids, proteins, and carbohydrates derived from their parent cells. Exosomes have been thought to be important messengers in cell–cell communication by transferring biological molecules to recipient cells, which can affect the activity and function of recipient cells.

Cancer is still the main cause of death among humans. Recently, the role of exosomes in cancer development has gained increased attention because it has provided new insight in the study and management of cancers. Cancer cells have been thought to produce more exosomes than normal cells. Cancer-derived exosomes are intentionally released by cancer cells and are important drivers of cancer cell functions. In addition, other cells in the cancer microenvironment, such as immune cells and stromal cells, are capable of releasing exosomes. Interactions between cancer cells and both immune cells and stromal cells mediated by exosomes play an essential role in cancer development.

The expression of noncoding RNAs is often found to undergo significant changes in cancer, which indicates that these noncoding RNAs are closely associated with cancer development. Noncoding RNAs, including miRNAs and long noncoding RNAs (IncRNAs), can stably exist in exosomes, and noncoding RNAs carried by exosomes are also essential for cancer regulation.

Currently, related studies mainly focus on the value of exosomal miRNAs in cancers. Exosomal IncRNAs may also play an important role in cancer development. However, the value of exosomal IncRNAs in cancers has not yet been fully revealed. Existing studies have shown that exosomal IncRNAs not only are involved in cancer progression but also can be used as biomarkers for cancer diagnosis and treatment. In this review, we highlight the latest studies to summarize the role of exosomal IncRNAs in both cancer biology and clinical management.

THE CROSSTALK PATTERN MEDIATED BY EXOSOMES IN THE CANCER MICROENVIRONMENT

The cell components in the cancer microenvironment mainly include cancer cells, immune cells, fibroblast cells, and vessel endothelial cells. Exosomes are thought to play an important role in the crosstalk among these different cells. In the cancer microenvironment, cancer cells can communicate extensively with other cells via exosomes. First, cancer cells can influence the characteristics and biological behaviors of other cancer cells by transferring exosomes. In hepatocellular carcinoma (HCC), highly metastatic cancer cells can promote epithelial–mesenchymal transition (EMT) and metastasis of low-metastatic cancer cells by transferring exosomal miR-92a-3p and regulating the PTEN/Akt pathway. In addition, cancer cells can act on immune cells by delivering exosomes. In breast cancer, cancer cell-derived exosomal IncRNA SNHG16 can upregulate the expression of CD73 on V61 Treg cells through the SNHG16/miR-16-5p/SMAD5 regulatory axis. In addition, cancer cells can interact with stromal cells with exosomes as intercellular mediators. For example, bladder cancer-derived exosomes induce the transformation of fibroblasts into cancer-associated fibroblasts through TGF-β signaling pathways. Gastric cancer (GC)-derived exosomes can deliver miR-130a into vascular endothelial cells and consequently promote angiogenesis. On the other hand, exosomes from immune cells and stromal cells can reverse the phenotype and...
biological behaviors of cancer cells. For example, exosomes from tumor-associated macrophages (TAMs) can transmit HIF-1α-stabilizing long noncoding RNA (HISLa) to breast cancer cells, thus enhancing aerobic glycolysis and apoptosis resistance of breast cancer cells. Exosomes from cancer-associated fibroblasts have been discovered to promote colorectal cancer (CRC) metastasis, and chemotherapy by delivering miR-92a-3p to CRC cells. Additionally, immune cells can interact with other immune cells and endothelial cells. In epithelial ovarian cancer (EOC), TAM-derived exosomes can transmit miR-29a-3p and miR-21-5p to CD4+ T cells and suppress STAT3 expression, which induces an imbalance of Treg/Th17 cells. TAM-derived exosomes can also regulate endothelial cells in EOC. Exosomal mir-146b-5p from TAMs suppresses the migration of human vessel endothelial cells through the TRAF6/NF-κB/BMP2 pathway. Interestingly, the suppressive effect can be reversed by exosomal lncRNAs from EOC. In summary, exosome-mediated interactions are widely prevalent in different cell types within the cancer microenvironment. Regulatory molecules such as lncRNAs, miRNAs, and proteins carried by exosomes play an important role in altering the phenotypes and biological behaviors of recipient cells, which is significantly associated with cancer progression.

The role of exosomal IncRNAs in cancer biology
In recent years, the roles of exosomal IncRNAs in cancer development have gained increasing attention. Exosomal IncRNAs are involved in multiple important steps in cancer development, including cancer cell proliferation, angiogenesis, invasion and metastasis, drug resistance, and immune modulation (Fig. 1). In this section, we will further elaborate on the role of exosomal IncRNAs in different processes of cancer development.

Exosomal IncRNAs and cancer cell proliferation
Cancer cell proliferation is the basic step in cancer progression. Exosomal IncRNAs in the cancer microenvironment are found to promote this process. For example, in esophageal squamous cell carcinoma (ESCC), IncRNA ZFAS1 is elevated in cancer tissues and can be transmitted among cancer cells via exosomes. Exosomal ZFAS1 can competitively inhibit miR-124 expression and thereby upregulate the expression of STAT3 protein. Through the regulation of the miR-124/STAT3 axis, exosomal ZFAS1 can promote ESCC cell proliferation and inhibit apoptosis. Moreover, in vivo experiments show that exosomal ZFAS1 can promote ESCC tissue proliferation in tumor-bearing mice. In GC tissues and cells, ZFAS1 knockdown can suppress cancer cell cycle progression, induce apoptosis, and inhibit EMT, while high levels of exosomal ZFAS1 can promote GC cell proliferation and migration. Hypoxia is often present in the cancer microenvironment and can promote cancer progression. In bladder cancer under hypoxic conditions, the bladder cancer cell line 5637 can release more exosomes containing IncRNA UCA1. Exosomal UCA1 can be internalized by other bladder cancer cell lines and promote cell proliferation through EMT in vitro and in vivo. Together, exosomal IncRNAs from cancer cells or other cells in the cancer microenvironment can be delivered to recipient cancer cells. With the activation of related signaling pathways and changes in cell phenotypes, the proliferation potential of cancer cells is enhanced.

Exosomal IncRNAs and angiogenesis in cancer
Angiogenesis plays a key role in cancer development. Noncoding RNAs are associated with cancer angiogenesis by acting on vascular endothelial cells. Recently, IncRNAs from cancer exosomes were found to promote angiogenesis by acting on human umbilical vein endothelial cells (HUVECs) in cancers. In EOC, IncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) from cancer cells can be transferred to HUVECs via exosomes. Exosomal MALAT1 was demonstrated to promote angiogenesis in both in vitro and in vivo assays. A study on the mechanism of exosomal MALAT1 activity revealed that it can possibly stimulate the expression of angiogenesis-related genes, including VEGF-A, VEGF-D, and angiogenin, thereby facilitating cancer angiogenesis. Similarly, IncRNA taurine upregulated 1 (TUG1) is elevated in cervical cancer cells and can be delivered to HUVECs via exosomes. Exosomal TUG1 can suppress caspase-3 activity and impact apoptosis-related proteins to promote HUVECs proliferation, thus promoting angiogenesis. Exosomal IncRNAs can act on miRNAs to activate downstream pathways that participate in angiogenesis. In pancreatic cancer, cancer cells under hypoxic conditions can release high levels of exosomes carrying IncRNA UCA1. When internalized by HUVECs, exosomal UCA1 from hypoxic pancreatic cancer cells can inhibit miR-96-5p, upregulate the expression of its target gene AMOTL2, and subsequently activate the ERK signaling pathway, which promotes the migration and tube formation of HUVECs. Collectively, exosomal IncRNAs derived from cancer cells can act on vascular endothelial cells to promote angiogenesis by stimulating the expression of angiogenesis-related proteins or inhibiting the function of antiangiogenic miRNAs. However, the exact mechanism underlying this process needs to be elucidated with further research.

Exosomal IncRNAs and cancer metastasis
Exosomal IncRNAs can promote cancer invasion or metastasis by targeting cancer cells or cancer-promoting cells. For example, crosstalk between cancer cells and lymphatic endothelial cells mediated by exosomal IncRNAs can promote lymph node metastasis. In bladder cancer with VEGF-C-independent lymph node metastasis, IncRNA lymph node metastasis-associated transcript 2 (LNMAT2) is enriched in bladder cancer cell-derived exosomes. When taken up by human lymphatic endothelial cells (HLECs), exosomal LNMAT2 can increase prospero homeobox 1 (PROX1) expression by recruiting hnrNPA2B1 and enhancing H3K4 trimethylation in the PROX1 promoter and ultimately promote lymphangiogenesis and lymphatic metastasis. Exosomal IncRNAs from metastatic cancer cells can also act on primary cancer cells and contribute to metastasis. In patients with CRC, IncRNA MALAT1 is upregulated in both metastatic CRC cells and their exosomes. Exosomal MALAT1 can increase FUT4 expression in primary CRC cells by sponging miR-26a/26b. Furthermore, upregulated FUT4 was demonstrated to enhance fucosylation levels and activate the PI3K/AKT/mTOR pathway in vitro and in vivo, which finally resulted in the invasion and metastasis of CRC. Likewise, in pancreatic ductal adenocarcinoma (PDAC), exosomal IncRNA Sox2ot derived from highly invasive PDAC cells can be delivered and taken up by less invasive PDAC cells. Exosome-mediated transfer of IncRNA Sox2ot can competitively bind to the miR-200 family to regulate the expression of Sox2, which promotes the EMT process and induces stem cell-like properties in recipient cells. Ultimately, these phenotypic alterations make recipient cells more invasive and contribute to cancer metastasis.

Exosomal IncRNAs and drug resistance in cancer
Drug resistance in cancer is a crucial reason for the poor outcome of cancer patients. The mechanisms underlying cancer drug resistance are largely unclear. Recently, exosomes have been found to deliver specific IncRNAs to cancer cells and contribute to drug resistance. In breast cancer, cancer cells resistant to trastuzumab can release high levels of exosomes containing IncRNA SNHG14 and transmit the IncRNA to drug-resistant cancer cells. Exosomal SNHG14 uptake by recipient cells is likely to activate the Bcl-2/Bax signaling pathway and inhibit apoptosis. Subsequently, these drug-sensitive cancer cells gained trastuzumab resistance from resistant cancer cells. A similar phenomenon has also been found in the resistance of
non-small-cell lung cancer (NSCLC) cells to erlotinib. LncRNA RP11-838N2.4 levels were higher in NSCLC cells resistant to erlotinib than in NSCLC cells without erlotinib resistance. Functional experiments showed that the knockdown of RP11-838N2.4 could promote erlotinib-induced cytotoxicity. Moreover, exosomes loaded with RP11-838N2.4 can be taken up by NSCLC cells sensitive to erlotinib and induce erlotinib resistance. However, the mechanism underlying the transmission of erlotinib resistance by exosomal RP11-838N2.4 needs further research. Exosomal lncRNAs can act as ceRNAs to miRNAs and promote drug resistance in cancer. In glioblastoma tissues and cells with temozolomide resistance, lncRNA SBF2-AS1 is overexpressed and can be secreted by exosomes. LncRNA SBF2-AS1 can sponge miR-151a-3p, which relieves the suppression to its target, X-ray repair cross-complementing 4, thus enhancing DNA double-strand break repair in glioblastoma cells, which reportedly promotes temozolomide resistance. In vitro and in vivo assays showed that exosomal SBF2-AS1 from temozolomide-resistant glioblastoma cells can accelerate DNA damage repair in recipient cells and enhance chemoresistance to temozolomide.

Exosomal lncRNAs and immunomodulation of cancer

Exosomal lncRNAs play an important role in the interaction between cancer cells and immune cells. Thus, exosomal lncRNAs are involved in cancer immunomodulation. In HCC, cancer cell-derived exosomes can transmit lncRNA TU339 to macrophages. The increased expression of lncRNA TU339 polarizes macrophages toward an anti-inflammatory phenotype with reduced proinflammatory cytokine production, decreased costimulatory molecule expression, and compromised phagocytosis. This polarization is probably associated with HCC progression. Similarly, CRC cell-derived exosomal lncRNA RPPH1 can be delivered to macrophages and mediate M2 polarization of macrophages. M2 macrophages are tumorigenic and can promote CRC cell proliferation and metastasis. In addition, exosomal lncRNAs are involved in the establishment of an immunosuppressive cancer microenvironment. In breast cancer, lncRNA SNHG16 can be transmitted to Vδ1 T cells via exosomes. Exosomal SNHG16 can sponge miR-16-5p as a ceRNA and result in the derepression of its target gene SMAD5. Subsequently, the TGF-β/SMAD5 pathway is activated, which induces upregulated expression of CD73 in Vδ1 T cells. CD73+Vδ1 T cells are a group of regulatory T cells that exert immunosuppressive functions in the breast-cancer microenvironment.

The value of exosomal lncRNAs in the clinical management of cancer

Exosome-mediated delivery of lncRNAs to recipient cells in the cancer microenvironment is widely involved in multiple processes of cancer development. Therefore, alterations in exosomal lncRNA levels are indicative of cancer diagnosis, prognosis and medical treatment. Since exosomes can enter the peripheral blood through small vessels, exosomal lncRNAs in circulation could serve as potential biomarkers for the clinical management of cancer. We have summarized the clinical value of exosomal lncRNAs in cancer in Table 1.

Fig. 1  The role of exosomal lncRNAs in cancer biology. Exosomes play an important role in mediating the interaction between cancer cells and both immune cells and stromal cells within the cancer microenvironment. Exosomal lncRNAs from cancer cells can promote immune modulation, angiogenesis, cancer proliferation, metastasis, and drug resistance.
Exosomal lncRNAs and cancer prognosis

Exosome-based biomarkers have gained increasing attention for determining cancer prognosis. For example, proteins and miRNAs in exosomes are often recommended as prognostic biomarkers. Recently, studies have gradually focused on the role of exosomal lncRNAs in cancer prognosis. In EOC, the level of serum exosomal lncRNA aHIF is upregulated and positively correlated with the level of aHIF in cancer tissues. A Cox multivariate regression model revealed that serum exosomal aHIF levels were an independent prognostic factor of EOC. Kaplan-Meier analysis suggested that EOC patients with higher levels of exosomal aHIF had poorer overall survival. In patients with CRC, exosomal lncRNA 91H can enhance CRC metastasis by modifying HNRNPK. Thus, exosomal 91H might serve as a plasma-based biomarker for CRC prognosis. CRC patients with high exosomal 91H also have a higher risk of CRC metastasis and recurrence than patients with low exosomal 91H. In addition, researchers evaluated the prognostic value of exosomal lncRNA ATB in patients with HCC. The level of exosomal ATB was associated with tumor stage and the presence of portal vein thrombosis. The overall survival and progression-free survival of HCC patients with higher levels of exosomal ATB were significantly shortened. However, studies on the use of exosomal lncRNAs as prognostic markers are insufficient. More research is needed to explore the prognostic value of exosomal lncRNAs so that they can be implemented for clinical management of cancer.

Exosomal lncRNAs and cancer therapy

Since exosomal lncRNAs can promote cancer development or convey drug resistance among cancer cells, exosomal lncRNAs are potential therapeutic targets for cancer treatment. Developing drugs to inhibit the transfer of exosomal lncRNAs between drug-resistant cells and drug-sensitive cells may improve therapeutic efficacy and prevent cancer progression. LNMAT2 is an upregulated lincRNA in bladder cancer patients with lymph node metastasis. Exosomal LNMAT2 from bladder cancer cells can be internalized by HLECs and promote lymphatic metastasis. An in vitro study showed that exosomes from LNMAT2-silenced cells could inhibit HLEC tube formation and migration. The results indicated that decreased LNMAT2 expression could prevent lymph node metastasis and that LNMAT2 might be a therapeutic target for bladder cancer with lymph node metastasis. In renal cancer, IncARSR functions as an oncogene, and exosomal IncARSR can transfer sunitinib resistance from sunitinib-resistant cells to sunitinib-sensitive cells. Researchers established a nude mouse model of renal cancer with sunitinib resistance xenografting renal cancer cells or patient-derived xenografts. When treated with locked nucleic acids (LNAs) targeting IncARSR, the xenografts showed reduced expression of IncARSR and restored responsiveness to sunitinib. Thus, IncARSR can serve as a therapeutic target for renal cancer with sunitinib resistance. Exosomal IncARSRs are also promising biomarkers for guiding drug therapy, as the level of exosomal IncARSRs is associated with drug treatment responses in cancer patients. For example, in CRC patients receiving cetuximab, patients who did not respond to the treatment had higher levels of exosomal UCA1 than did patients who showed a partial or complete response. Thus, the detection of exosomal UCA1 can be used to predict the treatment response of CRC patients receiving cetuximab.

DISCUSSION AND PERSPECTIVES

The membrane structure of exosomes can protect lncRNAs, miRNAs, and proteins from degradation; thus, exosomes are important biological molecule carriers and play an essential role in intercellular communication. In the body fluids of cancer patients, exosomes are mainly derived from cancer cells. The exploration of exosomes provides us with new insight into cancer biology, and it helps us develop new cancer diagnosis and treatment strategies. Exosomal lncRNAs are involved in multiple processes of cancer development, including cancer cell proliferation, angiogenesis, metastasis, drug resistance, and immunomodulation. Capturing important biological information from exosomal lncRNAs can help us better understand and manage cancers. The levels of cancer-related exosomal lncRNAs are associated with the severity of disease in cancer patients; thus, exosomal lncRNAs are potential cancer biomarkers. As an emerging class of cancer biomarker, exosomal lncRNAs have advantages over traditional markers. In addition to their role in cancer diagnosis and prognosis, exosomal lncRNAs can be used as treatment targets. Since exosomal lncRNAs play a crucial role in cancer progression and the spread of drug resistance, drugs that inhibit the function of exosomal lncRNAs may be effective in cancer therapy. At present, some studies have partially elucidated the value of exosomal lncRNAs in cancer. Nevertheless, the contribution of exosomal lncRNAs in cancer needs further exploration, and exosomal lncRNAs are expected to play a more important role in the clinical management of cancer.

Table 1. The value of exosomal lncRNAs in the clinical management of cancer.

| Cancer type        | Value           | lncRNA | Reference |
|--------------------|-----------------|--------|-----------|
| Gastric cancer     | Cancer diagnosis| UEGC1  | Ref. 29   |
| Colorectal cancer  | Cancer diagnosis| CRNDE-h| Ref. 30   |
| Non-small-cell lung cancer | Cancer diagnosis | GASS   | Ref. 31   |
| Epithelial ovarian cancer | Prognosis evaluation | aHIF  | Ref. 32   |
| Colorectal cancer  | Prognosis evaluation | 91H   | Ref. 33   |
| Hepatocellular carcinoma | Prognosis evaluation | ATB   | Ref. 34   |
| Bladder cancer     | Therapeutic target | LNMAT2| Ref. 20   |
| Renal cancer       | Therapeutic target | IncARSR| Ref. 35   |
| Colorectal cancer  | Treatment efficacy | UCA1  | Ref. 36   |
REFERENCES

1. Sadeghipour, S. & Mathias, R. A. HCV viruses hijack host exosomes for viral pathogenesis. Semin. Cell Dev. Biol. 67, 91–100 (2017).
2. Becker, A. et al. Extracellular vesicles in cancer: cell-to-cell mediators of metastasis. Cancer Cell 30, 836–848 (2016).
3. Chen, G. et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. Nature 560, 382–386 (2018).
4. Ferreira, H. J. & Esteller, M. Non-coding RNAs, epigenetics, and cancer: tying it all together. Cancer Metastasis Rev. 37, 55–73 (2018).
5. Fan, Q. et al. The emerging role of exosome-derived non-coding RNAs in cancer biology. Cancer Lett. 414, 107–118 (2018).
6. Yang, B. et al. High-metastatic cancer cells derived exosomal miR92a-3p promotes epithelial–mesenchymal transition and metastasis of low-metastatic cancer cells by regulating PTEN/ARK pathway in hepatocellular carcinoma. Oncogene 39, 6529–6543 (2020).
7. Ni, C. et al. Breast cancer-derived exosomes transmit IncRNA SNHG16 to induce CD73⁺γδT Treg cells. Signal Transduct. Target. Ther. 5, 41 (2020).
8. Ringuette Goulet, C. et al. Exosomes induce fibroblast differentiation into cancer-associated fibroblasts through TGFβ signaling. Mol. Cancer Res. 16, 1196–1204 (2018).
9. Yang, H. et al. Exosome-derived miR-130a activates angiogenesis in gastric cancer by targeting C-MYB in vascular endothelial cells. Mol. Ther. 26, 2466–2475 (2018).
10. Chen, F. et al. Extracellular vesicle-packaged HIF-1α-stabilizing IncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells. Nat. Cell Biol. 21, 498–510 (2019).
11. Hu, J. L. et al. CAFs secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and epithelial-mesenchymal transition in colorectal cancer. Mol. Cancer 18, 91 (2019).
12. Zhou, J. et al. Exosomes released from tumor-associated macrophages transfer miRNAs that induce a Treg/Th17 cell imbalance in epithelial ovarian cancer. Cancer Immunol. Res. 6, 1578–1592 (2018).
13. Wu, Q. et al. Suppression of endothelial cell migration by tumor-associated macrophage-derived exosomes is reversed by epithelial ovarian cancer exosomal IncRNA. Cancer Cell Int. 17, 62 (2017).
14. Li, Z. et al. Exosomal IncRNA ZFAS1 regulates esophageal squamous cell carcinoma cell proliferation, invasion, migration and apoptosis via microRNA-124/STAT3 axis. J. Exp. Clin. Cancer Res. 38, 477 (2019).
15. Pan, L. et al. Exosomes-mediated transfer of long non-coding RNA ZFAS1 promotes gastric cancer progression. J. Cancer Res. Clin. Oncol. 143, 991–1004 (2017).
16. Xue, M. et al. Hypoxic exosomes facilitate bladder tumor growth and development through transferring long non-coding RNA-UCAM1. Mol. Cancer 16, 143 (2017).
17. Qiu, J. J. et al. Exosomal metastasis-associated lung adenocarcinoma transcript 1 promotes angiogenesis and predicts poor prognosis in epithelial ovarian cancer. Int. J. Biol. Sci. 14, 1960–1973 (2018).
18. Lei, L. & Mou, Q. Exosomal taurine up-regulated 1 promotes angiogenesis and endothelial cell proliferation in cervical cancer. Cancer Biol. Ther. 21, 717–725 (2020).
19. Guo, Z. et al. Hypoxic tumor-derived exosomal long non-coding RNA UCA1 promotes angiogenesis via miR-96-5p/AMOTL2 in pancreatic cancer. Mol. Ther. Nucleic Acids 22, 179–195 (2020).
20. Chen, C. et al. Exosomal long non-coding RNA LNMAT2 promotes lymphatic metastasis in bladder cancer. J. Clin. Invest. 130, 404–421 (2020).
21. Xu, J. et al. Exosomal MALAT1 sponges miR-26a/26b to promote the invasion and metastasis of colorectal cancer via FUT4 enhanced fucosylation and PI3K/Akt pathway. J. Exp. Clin. Cancer Res. 39, 54 (2020).
22. Li, Z. et al. Tumor-derived exosomal Inc-Sox2ot promotes EMT and stemness by acting as a ceRNA in pancreatic ductal adenocarcinoma. Oncogene 37, 3822–3838 (2018).
23. Dong, H. et al. Exosome-mediated transfer of IncRNA-SNHG14 promotes trastuzumab chemoresistance in breast cancer. Int. J. Oncol. 53, 1013–1026 (2018).
24. Zhang, W. et al. Exosome-mediated transfer of IncRNA RP11-838N2.4 promotes erlotinib resistance in non-small cell lung cancer. Int. J. Oncol. 53, 527–538 (2018).
25. Roos, W. P., Frohnapfel, L., Quiros, S., Ringel, F. & Kaina, B. HRCC3 contributes to temozolomide resistance of glioblastoma cells by promoting DNA double-strand break repair. Cancer Lett. 424, 119–126 (2018).
26. Zhang, Z. et al. Exosomal transfer of long non-coding RNA SBF2-A51 enhances chemoresistance to temozolomide in glioblastoma. J. Exp. Clin. Cancer Res. 38, 166 (2019).
27. Li, X., Lei, Y., Wu, M. & Li, N. Regulation of macrophage activation and polarization by HCC-derived exosomal IncRNA TUC339. Int. J. Mol. Sci. 19, 2958 (2018).
28. Liang, Z. X. et al. IncRNA RPH1 promotes colorectal cancer metastasis by interacting with TUBB3 and by promoting exosomes-mediated macrophage M2 polarization. Cell Death Dis. 10, 829 (2019).
29. Lin, L. et al. Tumor-originated exosomal IncUEGC1 as a circulating biomarker for early-stage gastric cancer. Mol. Cancer 17, 84 (2018).
30. Liu, T. et al. Exosomal long noncoding RNA CRNDE-h as a novel serum-based biomarker for diagnosis and prognosis of colorectal cancer. Oncotarget 7, 85551–85563 (2016).
31. Li, C. et al. Tumor-derived exosomal IncRNA GAS5 as a biomarker for early-stage non-small-cell lung cancer diagnosis. J. Cell Physiol. 234, 20721–20727 (2019).
32. Tang, X. et al. Circulating serum exosomal aHIF is a novel prognostic predictor for epithelial ovarian cancer. Onco Targets Ther. 12, 7699–7711 (2019).
33. Gao, T. et al. Exosomal IncRNA 91H is associated with poor development in colorectal cancer by modifying HNRNPK expression. Cancer Cell Int. 18, 11 (2018).
34. Lee, Y. R. et al. Circulating exosomal noncoding RNAs as prognostic biomarkers in human hepatocellular carcinoma. Int. J. Cancer 144, 1444–1452 (2019).
35. Qu, L. et al. Exosome-transmitted IncARS promotes sunitinib resistance in renal cancer by acting as a competing endogenous RNA. Cancer Cell 29, 653–668 (2016).
36. Yang, Y. N. et al. Predictive role of UCA1-containing exosomes in cetuximab-resistant colorectal cancer. Cancer Cell Int. 18, 164 (2018).

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AUTHOR CONTRIBUTIONS

T.F., W.Z., and P.Z. conceived and designed the study. W.Z. drafted the manuscript. T.F., W.Z., and P.Z. wrote and revised the manuscript. T.F., W.Z., and P.Z. provided funding. T.F., W.Z., and P.Z. supervised the project. This work was supported by grants from the Jiangsu Natural Science Foundation (20191156), the National Natural Science Foundation of China (82000678), the Project of Jiangsu Provincial Medical Youth Talent (QNRC2016267), and the Changzhou Municipal Health Commission Youth Talents Science and Technology Project (QN201926).

ADDITIONAL INFORMATION

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