The emerging roles of exosomal long non-coding RNAs in bladder cancer

Qiang Liu

INTRODUCTION

Bladder cancer (BC) is one of the most common malignant tumours of the genitourinary system, accounting for the 9th most common malignant tumour in the world.1,2 According to pathological classification, 90% of patients with BC have urothelial cancer. About one-third of these patients are first diagnosed with muscle invasive bladder cancer (MIBC).3,4 In some patients, even if the first diagnosis is non-muscle invasive bladder cancer (NMIBC), 10%–30% of patients progress to MIBC.4,5 BC has become a disease that seriously affects human health.6,7 At present, its early diagnosis and treatment have made great progress,8,9 but its specific mechanism of occurrence and development is still unclear.

In recent years, non-coding RNAs (ncRNAs) have become a research hotspot. NcRNAs can be divided into housekeeping ncRNAs and regulatory ncRNAs. Among them, regulatory ncRNAs can be mainly divided into microRNA (miRNA), long noncoding RNA (lncRNA) and circular RNA (circRNA).10-13 LncRNA is a general term for single-stranded nucleotide sequences exceeding 200 bp.14 Although it does not have the function of encoding proteins, it can participate in gene regulation at the epigenetic level, transcription level and post-transcriptional level.15-17 affect tumour occurrence, development, metastasis and malignant progression of drug resistance.18-23 Based on the current research on the mechanism of lncRNA, the competitive endogenous 'ceRNA' mechanism is the most common type and a widely recognized regulatory mechanism, that is, some...
ncRNAs have binding sites with microRNAs. The cell acts as a miRNA sponge, thereby releasing the inhibition of miRNA on the target gene, thereby increasing the expression level of the target gene. For instance, elevated LINC00909 can promote tumour progression of ovarian cancer via regulating the miR-23b-3p/MRC2 axis. Long noncoding RNA IL6-AS1 is upregulated in chronic obstructive pulmonary disease and is interrelated to interleukin 6 via sponging miR-149-5p and regulating early B-cell factor 1 expression. Guo et al. found that we can detect the occurrence of gastric cancer (GC) and improve the early diagnosis rate of GC. Lin et al. reveal that the AUC values of lncUEGC1 in distinguishing EGC patients from healthy individuals and patients with precursor chronic atrophic gastritis were 0.8760 and 0.8406, respectively, which were higher than the diagnostic accuracy of carcinoembryonic antigen and were a good marker for early diagnosis of GC.

In this review, we focused on the latest evidence of major exosomal lncRNAs related to BC, and discussed the latent biological role of exosomal lncRNAs in the development, treatment and clinical applications of BC.

2. Biogenesis and Characteristics of Exosome

2.1. Biochemical characteristics of exosomes

There are two main secretion mechanisms of exosomes: continuous secretion dependent on Golgi and induced secretion. Different subtypes of exosomes may have different release mechanisms and carry different cargo components. A large number of proteins are enriched on and in the exosomal membrane, such as membrane transport and membrane fusion proteins (such as GTPases, Annexins and Flotillins), proteins required for the synthesis of multivesicles (such as tumour susceptibility gene 101), four Transmembrane proteins (such as CD9, CD63, CD81), apoptosis-linked gene 2 interacting protein X (ALIX), heat shock proteins (such as HSP70, HSP90). Exosomes carry many nucleic acid molecules, such as miRNA, ncRNA and mRNA. In addition, it also carries cytokines and growth factor proteins similar to the source cells. The biological process of exosome biogenesis and release was showed in Figure 1.

The separation methods of exosomes have not yet been unified, including sucrose gradient centrifugation, differential ultracentrifugation, filtration centrifugation, immunoaffinity capture technology, chromatography technology, microfluidic chip technology and PEG polymer precipitation. The appropriate combination of these technologies may be effective. Even better, there are more commercial kits based on the above principles. The gold standard method is differential ultracentrifugation. The exosomes obtained by the sucrose gradient centrifugation method have high purity, but the preliminary preparation is time-consuming, the extraction process is very time-consuming and the yield is low. Exosomes can be stored at 4°C for a short term (within 1–2 days) and stored at 80°C for a long term.

The identification of exosomes relies on morphological observation and protein composition analysis. Observe the morphology of exosomes under an electron microscope. It can be seen that they are cup-shaped or flat balloons. Nanoparticle tracking analysis (NTA) can also be used to measure their diameters; protein composition analysis usually uses Western blot to detect exosomes. The protein expression level of body enrichment, as usual, chooses to identify.
2.2 | Exosomes and tumours

Exosomes were first discovered to participate in antigen presentation and immune activation and suppression. Mast cells transport their mRNA and miRNA to recipient cells through the released exosomes, and translate proteins in the recipient cells, thus proving that exosomes have the function of transporting substances. The lipid bilayer membrane of exosomes reduces the degradation of exosomes by proteases and ribonuclease, and is shed from the cell membrane through autocrine, paracrine and endocrine secretion pathways. The membrane carries proteins and nucleic acid signal molecules. Body–ligand interaction, direct membrane fusion and endocytosis (or phagocytosis) are 3 ways to transfer signals from exosomes to recipient cells, and participate in intercellular communication, angiogenesis, immune response and tumour growth physiology and pathology process.

Exosomes participate in the composition of the tumor microenvironment and promote soluble proteins, nucleic acids, functional transmembrane proteins, chemokine receptors, epidermal growth factor receptors to mediate tumorigenesis, growth, tumor vascular growth, tumor metastasis, tumor immune escape, formation of tumor microenvironment. Tumour cells release exosomes, and the signal molecular characteristics they carry can reflect the phenotype of tumour cells, such as tumour-specific antigen proteins and RNA. They have great potential as tumour diagnostic markers. At the same time, tumour cells can excrete anti-tumour drugs by secreting exosomes, resulting in multiple tumours. Exosomes are closely related to tumours, participating in tumour formation, metastasis, drug resistance, evading immune surveillance and can also assist in diagnosis and treatment.

3 | EXOSOMAL-LNCRNA IN BLADDER CANCER

3.1 | The potential biological role of exosomal IncRNAs in BC

Previous studies have shown that not only exosomal miRNAs serve as a vital role in the occurrence and progression of tumours, but also IncRNAs in exosomes have important biological effects. We
summarized the biological role of exosomal-lncRNAs in BC (Figure 2; Table 1).

3.1.1 Exosomal lncRNAs and epithelial-mesenchymal transition (EMT) in BC

Epithelial-mesenchymal transition is intimately interrelated to the development of tissues or organs during embryogenesis. Additionally, this phenomenon is significantly associated with tumour development and is a trigger for invasion, migration and acquisition of stem cell-like phenotype in cells of diverse cancers, including BC.

EMT is established by EMT-inducible transcription factors, such as ZEB1, ZEB2, Snail, Slug and Twist. These transcription factors can inhibit the expression of epithelial marker E-cadherin and increase the mesenchymal marker N-cadherin expression to promote EMT. Besides, EMT can also be regulated by several diverse upstream regulators, including signalling molecules and exosomal lncRNAs by various mechanisms.

Studies have shown that exosomal lncRNAs can regulate the EMT of BC (Figure 2A). Berondo et al. showed that HOX transcribed antisense RNA (HOTAIR) and several tumour-related lncRNAs were rich in biological fluids, such as urine from EU patients with urothelial bladder cancer (UBC) with highly aggressive muscle diseases (HGM pT2-pT4) (EU). Inhibition of HOTAIR in UBC cell lines could reduce cell migration and invasion. Besides, the loss of HOTAIR expression in UBC cell lines altered the expression of EMT-related genes. They also utilized RNA sequencing to identify four 4 EU-rich lncRNAs from UBC patients. Xue et al. proved that hypoxic BC cells could reshape the tumour microenvironment to promote tumour growth and progression, and secrete carcinogenic exosomes rich in lncRNA-UC1A. Besides, exosomal Inc-UC1A might be used as a latent diagnostic biomarker for BC. Huang and colleagues reported that LINC00960 and LINC02470 from high-grade BC cell exosomes could promote the malignant behaviour of receptor low-grade BC cells and induce EMT by up-regulating receptor β-catenin, Notch and Smad2/3 signalling.

3.1.2 Exosomal lncRNAs and cell proliferation in BC

Cell proliferation is a precision control process, which is vital for embryonic and postnatal development. Under pathological conditions, abnormal cell proliferation is a central mechanism attributing to disease progressions. Abnormal cell proliferation includes both...
abnormal cell division and abnormal cell differentiation. Besides, cell proliferation is also a main characteristic of cancer cells and the base of metastasis. Studies have shown that exosomal lncRNAs can regulate the cell proliferation of BC (Figure 2B). Zheng and colleagues showed that exosomal PTENP1 was a novel biomarker that could be applied for clinical detection of BC. Exosomes secreted by normal cells could transfer PTENP1 to BC cells and suppress cell growth and metastasis. The results indicated that exosomal PTENP1 might participate in the communication between normal cells and BC cells in the process of BC carcinogenesis. In addition, exosome-mediated could transfer LINC01133 inhibits the progression of BC by regulating the Wnt signalling pathway.

### 3.1.3 | Exosomal lncRNAs and lymphangiogenesis in BC

Lymphatic vessels play an essential role in promoting tumour growth and metastasis. Studies have shown that exosomal lncRNAs can regulate the lymphangiogenesis of BC (Figure 2C). Chen et al. identified that lncRNA lymph node metastasis-associated transcript 2 (LNMAT2) could stimulate the tube formation and migration of human lymphatic endothelial cell (HLEC) and enhance lymphatic metastasis of tumour generation and LN metastasis. Mechanically, exosomal LNMAT2 could be secreted by BC cells and interact with the heterogeneous ribonucleoprotein A2B1 (hnRNPA2B1). Subsequently, the expression of prospero homeobox 1 (PROX1) was upregulated by the recruitment of hnRNPA2B1, leading to lymphangiogenesis and lymphatic metastasis. Zheng et al. discovered through which exosomal BCYRN1 synergistically enhances lymphatic metastasis induced by VEGF-C/VEGFR3 signalling from BCa, indicating that BCYRN1 may serve as an encouraging therapeutic target for BCa patients.

### 3.1.4 | Exosomal lncRNAs and chemoresistance in BC

Chemoresistance can be divided into primary drug resistance and multiple drug resistance (MDR). The former refers to cancer cells that develop resistance to induced drugs, whereas the latter refers to cancer cells that are resistant to induced drugs, whereas the former refers to cancer cells. The establishment of chemoresistance in cancer cells involves various mechanisms, including downregulation of apoptosis, increased DNA repair, altered drug targets and overexpression of MDR proteins.

Table 1: Potential role and mechanism of exosomal lncRNA in BC

| LncRNAs       | Parent cell/source | Target cell | Mechanism | Biological function                                      | Reference |
|---------------|--------------------|-------------|-----------|--------------------------------------------------------|-----------|
| HOTAIR       | Urine              | T24 and TCC-SUP | Regulate EMT signalling pathway | Promote cell migration and invasion | [91]      |
| UCA1         | 5637               | UMUC2       | Regulate EMT signalling pathway | Promote tumor growth and progression | [92]      |
| PTENP1       | 293A               | J82 and EJ | PTENP1/miR-17/PTEN | Increase cell apoptosis and reduce the ability to invade and migrate | [97]      |
| LNMAT2       | UMUC3/5637         | HLEC       | LNMAT2/HNRNPA2B1/PROX1 | Stimulated HLEC tube formation and migration enhanced tumour lymphangiogenesis | [102]     |
| LINC00960    | T24 and J82        | TSGH-8301  | Regulate EMT | Enhance the cell viability, migration, invasion and clonogenicity | [93]      |
| LINC00355    | CAFs               | T24 and 5637 | LINC00355/miR-34b-5p/ABC1 | Promotes BC cell resistance to cisplatin | [107]     |
| LINC01133    | SV-HUC-1           | T24 and J82 | Regulate Wnt signalling pathway | Restrains cell viability, proliferation, migration. | [98]      |
| BCRYRN1      | UMUC3/5637         | HLEC       | BCRYRN1/hnRNPA1/WNT5A/VEGFR3 | Promote tube formation and migration of HLECs, lymphangiogenesis and LN metastasis of BCa-HOTAIR | [103]     |
| LINC00355    | CAFs               | T24 and 5637 | LINC00355/miR-15a-5p/HMG2A | Promote BC cell proliferation and invasion | [107]     |

Abbreviations: ABCB1, ATP-binding cassette subfamily B member 1; BC, bladder cancer; BCRYRN1, brain cytoplasmic RNA 1; CAFs, cancer-associated fibroblasts; EMT, epithelial–mesenchyme transition; HLECs, human lymphatic endothelial cells; hnRNPA2B1, heterogeneous nuclear ribonucleoprotein A2B1; HOTAIR, HOX transcript antisense RNA; lncRNA, long non-coding RNA; LNMAT2, lymph node metastasis-associated transcript 2; miRNA, micro RNA; PROX1, prospero homeobox 1; PTEN, phosphatase and tensin homologue deleted on chromosome ten; UCA1, urothelial cancer-associated 1; VEGF3, Vascular endothelial growth factor receptor 3; Wnt5a, integration site family member 5A.
Studies have shown that exosomal lncRNAs can regulate the chemoresistance of BC (Figure 2D). Luo et al. proved that the CAF-derived exosome LINC00355 could promote the resistance of BC cells to cisplatin by regulating the miR-34b-5p/ABCB1 axis.\(^{107}\)

### 3.2 Exosomal IncRNAs could act as diagnostic and prognostic Biomarkers in BC

Previous studies have shown that exosomal lncRNAs play a crucial role in the early diagnosis and prognostic evaluation of tumors.\(^{108-111}\) We summarized the diagnostic and prognostic value of exosomal lncRNAs in BC (Table 2).

Table 2: Potential of exosomal IncRNA as diagnostic and prognostic tool in BC

| LncRNA | Source of exosome | Exosome isolation techniques | Biomarker potential | References |
|--------|------------------|-----------------------------|---------------------|------------|
| HYMA1, LINC00477, LOC100506688 and OTX2-AS1 | Urine | Ultracentrifugation | Biomarkers for BC prognosis | [91] |
| UCA1 | Serum | ExoQuick solution | A biomarker for BC diagnosis | [92] |
| MALAT1, PCAT1 and SPRY4-IT1 | Urine | Ultracentrifugation | Biomarkers for BC diagnosis and prognosis | [112] |
| PTENP1 | Plasma | ExoQuick solution | A biomarker for BC diagnosis | [97] |
| PCAT-1, UBC1 and SNHG16 | Serum | ExoQuick solution | Biomarkers for BC diagnosis and prognosis | [113] |
| H19 | Serum | ExoQuick solution | A biomarker for BC diagnosis and prognosis | [114] |
| UCA1-201, HOTAIR, HYMA1 and MALAT1 | Urine | Ultracentrifugation | Biomarkers for BC diagnosis | [115] |

Abbreviations: BC, bladder cancer; H19, H19 imprinted maternally expressed transcript; HOTAIR, HOX transcript antisense RNA; lncRNA, Long noncoding RNA; MALAT1, metastasis associated lung adenocarcinoma transcript 1; OTX2-AS1, orthodenticle homeobox 2 antisense 1; PCAT1, prostate cancer associated transcript 1; PTENP1, phosphatase and tensin homolog pseudogene 1; SNHG16, small nuclear RNA host gene 16; SPRY4-IT1, SPRY4 intronic transcript 1; UCA1, urothelial cancer associated transcript 1; PTENP1, phosphatase and tensin homolog pseudogene 1; SNHG16, small nucleolar RNA host gene 16; SPRY4-IT1, SPRY4 intronic transcript 1; UCA1, urothelial cancer associated transcript 1.

Additionally, Kaplan–Meier analysis revealed that NMIBC patients with high UBC1 expression had a significantly lower recurrence-free survival rate. Cox multivariate analysis showed that UBC1 was independently correlated to tumour recurrence in NMIBC. Wang et al. showed that the detection of exosomal H19 serum clarifies the use of exosomal lncRNA as a non-invasive diagnostic and prognostic biomarker for BC patients.\(^{114}\) Yu et al. selected four lncRNAs, namely UCA1-201, HOTAIR, HYMA1 and MALAT1, to form a set of urine biomarkers of BC.\(^{115}\) With the help of this panel, BC patients could be distinguished from patients with allantoicitis, with sensitivity and specificity reaching 95.7% and 94.3%, respectively. Finally, they confirmed the applicability of the four lncRNA combinations in an independent validation study involving 60 patients with BC and 60 patients with allantoicitis.

### 4 FUTURE EXPECTATIONS OF EXOSOME IN BC

No matter how hard the current multidisciplinary treatment is, the high recurrence rate of BC is still the biggest obstacle for treatment.\(^{116-118}\) The important role of exosomes-mediated signal transduction in cancer progression makes exosomes a potential new therapeutic target, which focuses on inhibiting the key components of the tumour cell communication network. Exosomes are expected to play an important role in the treatment of BC patients, help early diagnosis and monitoring and provide accurate predictive markers.

4.1 Exosomes are used to develop carriers for the transportation of anti-cancer drugs

The lipid bilayer membrane of exosomes can protect nucleic acids and proteins in the membrane from being degraded. At the same time, there are recognition molecules on the membrane, and exosomes...
can become a good carrier for targeted drug delivery. It can accurately transport interfering RNA, suicide mRNA, protein, miRNA and drugs. Despite the huge therapeutic potential of exosomes, the field still needs new in vivo models and powerful imaging systems to track the pathways of the synthesis, release, transportation and function of single-cell exosomes.

4.2 Inhibition of tumour progression and metastasis by targeting tumour-derived exosomes

Exosomes participate in the formation of the tumour microenvironment, and the signal transduction between tumour cells can inhibit the occurrence and development of tumours. There are currently several potential strategies. By interfering with the pathway components involved in the formation of exosomes (such as ESCRT, neural Amide) or release (such as Rab27, ARF6, RhoA) to inhibit the biogenesis or release of exosomes. Remove exosomes from the circulation through extracorporeal hemofiltration. Block those exosomes involved in exosome binding or internalization. Exosomal ligands (such as four transmembrane proteins) or cell surface receptors (such as HSPG) inhibit the uptake of exosomes by recipient cells.

4.3 Future prospects of exosomal IncRNAs in BC

At present, studies have found that exosomal IncRNA has an important biological role in BC, but more research is still needed to explore the clinical translational value of exosomal IncRNAs in BC. Many studies have confirmed that exosomal IncRNAs can promote the malignant progression of tumours by promoting angiogenesis. In addition, exosomal IncRNA can also mediate immunosuppressive microenvironments, regulate cell radiosensitivity and mediate metabolic reprogramming, but there is no relevant research report in BC. In the future, more research should be done to explore the role of exosomal IncRNAs in the above aspects and the prospects of clinical application. The role of Exosomal IncRNAs in tumour liquid biopsy has been confirmed by research. The current research on exosomal IncRNAs in the diagnosis of BC is mostly focused on the experience of a single centre, and the diagnostic potential of exosomal IncRNAs can only be tested by further verification in a multicentre joint study.

5 CONCLUSION

Due to its very aggressive nature, BC has the lower survival rate of urology cancers. This extremely high mortality rate is primarily the result of its early asymptomatic development, so it is diagnosed as late. Therefore, there is an urgent need for new diagnostic tools and new treatment strategies. In recent years, the potential role of IncRNAs as biomarkers, therapeutic targets and therapeutics in cancer research have attracted increasing interest. However, the pathophysiological function of IncRNAs still remains unknown, and whether they are the cause or consequence of cancer remains to be determined. Additionally, the same IncRNA can play completely distinct roles in various cancer environments, which makes the characterization of IncRNA particularly difficult. Although most studies are still in the preclinical stage, the diagnostic and prognostic applications of IncRNA related to exosomes are very promising for BC treatment. New advances in IncRNAs-related studies in specific fields, such as bioinformatics, pharmacokinetics, and improved nanotechnology to deliver IncRNAs-containing exosomes to the tumour microenvironment, will lay the foundation for future clinical applications. Understanding the function and role of IncRNAs is essential for their effective use as biomarkers, precision medicine or therapeutic targets.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Qiang Liu: Original draft preparation, allocation, revision, supplement and edition.

DATA AVAILABILITY STATEMENT

The data in the current study are available from the corresponding authors on reasonable request.

ORCID

Qiang Liu https://orcid.org/0000-0001-6751-7096

REFERENCES

1. Li R, Zhang J, Gilbert SM, Conejo-Garcia J, Mule JJ. Using oncolytic viruses to ignite the tumour immune microenvironment in bladder cancer. Nat Rev Urol. 2021;18(9):543-555. 10.1038/s41585-021-00483-z
2. Witjes JA, Bruins HM, Cathomas R, et al. European association of urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol. 2021;79(1):82-104. 10.1016/j.euro.2020.03.055
3. Jain P, Kathuria H, Momin M. Clinical therapies and nano drug delivery systems for urinary bladder cancer. Pharmacol Ther. 2021;226:107871. 10.1016/j.pharmthera.2021.107871
4. Jiang DM, Gupta S, Kitchlu A, et al. Defining cisplatin eligibility in patients with muscle-invasive bladder cancer. Nat Rev Urol. 2021;18(2):104-114. 10.1038/s41585-020-00404-6
5. van Puffelen JH, Keating ST, Oosterwijk E, et al. Trained immunity as a molecular mechanism for BCG immunotherapy in bladder cancer. Nat Rev Urol. 2020;17(9):513-525. 10.1038/s41585-020-0346-4
6. Meeks JJ, Al-Ahadie H, Faltas BM, et al. Genomic heterogeneity in bladder cancer: challenges and possible solutions to improve outcomes. Nat Rev Urol. 2020;17(5):259-270. 10.1038/s41585-020-0304-1
15. Zhang H, Liu B, Shi X, Sun X. Long noncoding RNAs: Potential therapeutic targets in cardiocerebrovascular diseases. J Hematol Oncol. 2021;14(1):947-960. 10.1016/j.jhem.2021.01.003

16. Yang S, Lim KH, Kim SH, Joo JY. Molecular landscape of long noncoding RNAs in brain disorders. Mol Psychiatry. 2021;26(4):1060-1074. 10.1038/s41380-020-00947-5

17. Yang Y, Qiu J, Diao J, Xue Z, et al. The role of long noncoding RNAs in cancer: an overview of current status and future perspectives. J Hematol Oncol. 2020;13(1):154. 10.1186/s12943-020-01162-0

18. Hu Q, Egranov SD, Lin C, Yang L. Long noncoding RNA loss in immune suppression in cancer. Pharmacol Ther. 2021;242:107391. 10.1016/j.pharmthera.2021.107391

19. Schulte C, Kock A, Zeller T, May M. Noncoding RNAs versus protein biomarkers in cardiovascular Disease. Trends Mol Med. 2020;26(6):583-596. 10.1016/j.molmed.2020.02.001

20. Huang Z, Zhou JK, Peng Y, He W, Huang C. The role of long noncoding RNAs in hepatocellular carcinoma. Mol Cancer. 2020;19(1):77. 10.1186/s12943-020-01188-4

21. Cheng J, Meng J, Zhu L, Peng Y. Exosomal noncoding RNAs in Glioma: Biological functions and potential clinical applications. Mol Cancer. 2020;19(1):66. 10.1186/s12943-020-01189-3

22. Liu K, Gao L, Ma X, et al. Long noncoding RNAs regulate drug resistance in cancer. Mol Cancer. 2020;19(1):54. 10.1186/s12943-020-01162-0

23. Zhang L, Xu H, Su X. Noncoding RNAs in cancer immunity: functions, regulatory mechanisms, and clinical application. Mol Cancer. 2020;19(1):48. 10.1186/s12943-020-01154-0

24. Lee H, Zhang Z, Krause HM. Long Noncoding RNAs and repetitive elements: junk or intimate evolutionary partners? Trends Genet. 2019;35(12):892-902. 10.1016/j.tig.2019.09.006

25. Wei L, Wang X, Lv L, et al. The emerging role of microRNAs and long noncoding RNAs in drug resistance of hematopoietic carcinoma. Mol Cancer. 2019;18(1):147. 10.1186/s12943-019-1086-z

26. Rammorena VR, Kobleev M, Gibb EA, et al. The evolution of long noncoding RNA acceptance in prostate cancer initiation, progression, and its clinical utility in disease management. Eur Urol. 2019;76(5):546-559. 10.1016/j.euro.2019.07.040

27. Zhang Y, Du W, Yang B. Long non-coding RNAs as new regulators of cardiac electrophysiology and arrhythmias: Molecular mechanisms, therapeutic implications and challenges. Pharmacol Ther. 2019;203:107389. 10.1016/j.pharmthera.2019.06.011

28. Zhang L, Meng X, Zhu XW, et al. Long non-coding RNAs in Oral squamous cell carcinoma: biologic function, mechanisms and clinical implications. Mol Cancer. 2019;18(1):102. 10.1186/s12943-019-1021-3

29. Liu Y, Cheng Z, Pang Y, et al. Role of microRNAs, circRNAs and long noncoding RNAs in acute myeloid leukemia. J Hematol Oncol. 2019;12(1):51. 10.1186/s13045-019-0734-5

30. Yang X, Wu G, Yang F, et al. Elevated LINCO0909 promotes tumor progression of ovarian cancer via regulating the miR-23b-3p/MRC2 axis. Oxid Med Cell Longev. 2021;2021:5574130. 10.1155/2021/5574130

31. Yi E, Zhang J, Zheng M, et al. Long noncoding RNA IL6-A51 is highly expressed in inflammatory obstructive pulmonary disease and is associated with interleukin 6 by targeting mir-149-5p and early B-cell factor 1. Clin Transl Med. 2021;11(7):e479. 10.1002/ctm2.479

32. Dong P, Xiong Y, Konno Y, et al. Long non-coding RNA DLEU2 drives EMT and glycolysis in endometrial cancer through HK2 by competitively binding with miR-455 and by modulating the EZH2/miR-181a pathway. J Exp Clin Cancer Res. 2021;40(1):216. 10.1186/s13046-021-02018-1

33. Shirejini SZ, Inci F. The Yin and Yang of exosome isolation methods: Conventional practice, microfluidics, and commercial kits. Biotechnol Adv. 2022;54:107814. 10.1016/j.biotechadv.2021.107814

34. Li YJ, Wu JY, Liu J, et al. Artificial exosomes for translational nanomedicine. J Nanobiotechnology. 2021;19(1):242. 10.1186/s12951-021-00986-2

35. Yao Y, Fu C, Zhou L, Mi QS, Jiang A. DC-derived exosomes for cancer immunotherapy. Cancers (Basel). 2021;13(15):3667. 10.3390/cancers13153667

36. Fu P, Zhang J, Li H, Mak M, Xu W, Tao Z. Extracellular vesicles as delivery systems at nano-/micro-scale. Adv Drug Deliv Rev. 2019;179:113910. 10.1016/j.addr.2021.113910

37. Cheng S, Li Y, Yan H, et al. Advances in microfluidic extracellular vesicle analysis for cancer diagnostics. Lab Chip. 2021;21(17):3219-3243. 10.1039/D1LC00443C

38. Tian Y, Fu C, Wu Y, Lu Y, Liu X, Zhang Y. Central nervous system cell-derived exosomes in neurodegenerative diseases. Oxid Med Cell Longev. 2021;2021:6301433. 10.1155/2021/6301433

39. Lu J, Zhang Y, Liang J, Diao J, Liu P, Zhao H. Role of exosomal microRNAs and their crosstalk with oxidative stress in the pathogenesis of osteoporosis. Oxid Med Cell Longev. 2021;2021:6301433. 10.1155/2021/6301433

40. Tang XH, Guo T, Gao XY, et al. Exosome-derived noncoding RNAs in gastric cancer: functions and clinical applications. Mol Cancer. 2021;20(1):99. 10.1186/s12943-021-01396-6

41. Zheng W, Ji D, Zhou Y, et al. Exosomal non-coding RNAs in hepatocellular cancer: A rising star. Mol Cancer Ther. 2021;20(10):1777-1788. 10.1186/s13555-7163-MCT-21-0363

42. Burgos-Ravanal R, Campos A, Díaz-Vesga MC, et al. Extracellular vesicles as mediators of cancer disease and as nanosystems in theranostic applications. Cancers (Basel). 2021;9(3):320. 10.3390/cancers1303320. 10.1155/2021/6301433

43. Reed SL, Escayg A. Extracellular vesicles in the treatment of neurological disorders. Neurobiol Dis. 2021;157:105445. 10.1016/j.nbd.2021.105445

44. Zhong Y, Li X, Wang F, et al. Emerging potential of exosomes on adiogenic differentiation of mesenchymal stem cells. Front Cell Dev Biol. 2021;9:649552. 10.3389/fcell.2021.649552

45. Chen J, Zhang Q, Liu D. Exosomes LZ. Advances, development and potential therapeutic strategies in diabetic nephropathy. Metabolism. 2021;122:154834. 10.1016/j.metabol.2021.154834

46. Sharma S, Masud MK, Kaneti YV, et al. Extracellular vesicle nanoarchitecture for novel drug delivery applications. Small. 2021;17(42):e2102220. 10.1002/smll.202102220
47. Uddin MH, Al-Hallak MN, Philip PA, et al. Exosomal microRNA in pancreatic cancer diagnosis, prognosis, and treatment: from bench to bedside. Cancers (Basel). 2021;13(11):2777. 10.3390/cancers13112777

48. Ruan S, Greenberg Z, Pan X, Zhuang P, Erwin N, He M. Extracellular vesicles as an advanced delivery biomaterial for precision cancer immunotherapy. Adv Healthc Mater. 2021:e2100650. 10.1002/adhm.202100650

49. Parada N, Romero-Trujillo A, Georges N, Alcyayaga-Miranda F. Camouflage strategies for therapeutic exosomes evasion from phagocytosis. J Adv Res. 2021;31:61-74. 10.1016/j.jare.2021.01.001

50. He X, Kuang G, Wu Y, Ou C. Emerging roles of exosomal miRNAs in drug delivery vehicles and biomarkers for neurological and auditory disorders with a special focus on mesenchymal stem cells. Cancers (Basel). 2021;9:653296. 10.3389/fcell.2021.007971

51. Grieco GE, Fignani D, Formichi C, et al. Extracellular vesicles in immune system regulation and Type 1 diabetes: Cell-to-cell communication mediators, disease biomarkers, and promising therapeutic tools. Front Immunol. 2021;12:682948. 10.3389/fimmu.2021.682948

52. Khalaf K, Hana D, Chou JT, Singh C, Mackiewicz A, Kaczmarek M. Aspects of the tumor microenvironment involved in resistance and drug resistance. Front Immunol. 2021;12:656364. 10.3389/fimmu.2021.656364

53. Xiong H, Huang Z, Yang Z, et al. Recent progress in detection and profiling of cancer cell-derived exosomes. Small. 2021;17(35):e2007971. 10.1002/sml.202007971

54. Ni C, Fang QQ, Chen WZ, et al. Breast cancer-derived exosomes transmit IncRNA SNHG16 to induce CD73- and gammadelta T reg cells. Signal Transduct Target Ther. 2020;5(1):41. 10.1038/s41399-020-0129-7

55. Li W, Zhang L, Guo B, et al. Exosomal FMR1-AS1 facilitates cancer drug resistance and tumor progression: An insight towards immune system regulation and Type 1 diabetes. J Hematol Oncol. 2021;14(1):152. 10.1186/s12050-020-00987-y

56. Whiteside TL. Exosomes and tumor-mediated immune suppression. J Clin Invest. 2016;126(4):1216-1223. 10.1172/JCI81136

57. Tian X, Shen H, Li Z, Wang T, Wang S. Tumor-derived exosomes, associated long noncoding RNA1 as a biomarker for early detection and monitoring progression of gastric cancer: Dissemination, immune evasiveness and metastatic colonization. Cancers (Basel). 2021;13(4):847. 10.3390/cancers13040847

58. Jena BC, Mandal M. The emerging roles of exosomes in anti-cancer drug resistance and tumor progression: An insight towards tumor-microenvironment interaction. Biochim Biophys Acta Rev Cancer. 2021;1875(5):188488. 10.1016/j.bbcan.2020.188488

59. Vafaei S, Roudi R, Madjid Z, Aref AR, Ebrahim M. Potential theranostics of circulating tumor cells and tumor-derived exosomes application in colorectal cancer. Cancer Cell Int. 2020;20:288. 10.1186/s12935-020-01389-3

60. Tian X, Shen H, Li Z, Wang T, Wang S. Tumor-derived exosomes, myeloid-suppressor cells, and tumor microenvironment. J Hematol Oncol. 2019;12(1):84. 10.1186/s13045-019-0772-z

61. Cheng L, Zhang X, Tang J, Lv Q, Liu J. Gene-engineered exosomes-thermosensitive liposomes hybrid nanovesicles by the blockade of CD47 signal for combined photothermal therapy and cancer immunotherapy. Biomaterials. 2021;275:120964. 10.1016/j.biomaterials.2021.120964

62. Lee NK, Kothandan VK, Kothandan S, Byun Y, Hwang SR. Exosomes and cancer stem cells in cancer immunity: current reports and future directions. Vaccines (Basel). 2021;9(5):441. 10.3390/vaccines9050441
82. Ma YS, Yang XL, Xin R, Liu JB, Fu D. Power and promise of exosomes as clinical biomarkers and therapeutic vectors for liquid biopsy and cancer control. *Biochim Biophys Acta Rev Cancer*. 2021;1875(1):188497. 10.1016/j.bbcan.2020.188497

83. Di W, Zhang W, Zhu B, Li X, Tang Q, Zhou Y. Colorectal cancer prompted adipose tissue browning and cancer cachexia through transferring exosomal miR-146b-5p. *J Cell Physiol*. 2021;236(7):5399-5410. 10.1002/jcp.30245

84. Kim DH, Park H, Choi YJ, et al. Exosomal miR-1260b derived from non-small cell lung cancer promotes tumor metastasis through the inhibition of HIPK2. *Cell Death Dis*. 2021;12(8):747. 10.1038/s41419-021-04024-9

85. Li J, Sun L, Qin G, et al. Cancer-associated fibroblasts induce monocytic myeloid-derived suppressor cell generation via IL-6/exosomal miR-21-activated STAT3 signaling to promote cisplatin resistance in esophageal squamous cell carcinoma. *Cancer Lett*. 2021;518:35-48. 10.1016/j.canlet.2021.06.009

86. Graziani V, Rodriguez-Hernandez I, Maigues O, Sanz-Moreno V. The amoeboid state as part of the epithelial-to-mesenchymal transition programme. *Trends Cell Biol*. 2021. 10.1016/j.tcb.2021.10.004

87. Taki M, Flax J, Kucherov V, et al. Expression of the long non-coding RNA HOTAIR correlates with disease progression and poor survival in patients with colorectal cancer. *Int J Mol Sci*. 2021;22(21):11469. 10.3390/ijms2111469

88. Berrondo C, Flax J, Kucherov V, et al. Long non-coding RNA FAM72D-3 and lnc-EPC1-4 as diagnostic biomarkers for hepato-cellular carcinoma. *J Clin Lymphoma*. 2021;27(17):4669-4679. 10.11158/jcl.ly.2021.06.009

89. Katsuno Y, Derynck R. Epithelial plasticity, epithelial-mesenchymal transition and aggressiveness of bladder cancer cells. *Front Oncol*. 2021;11(1):4746-10.3390/cancers11194746

90. Campos A, Sharma A, Obermair A, Salomon C. Extracellular Vesicle-Associated miRNAs and Chemoresistance: A Systematic Review. *Cancers*. 2021;13(18):4608. 10.3390/cancers13184608

91. Luo G, Zhang Y, Wu Z, Zhang L, Liang C, Chen X. Exosomal LINC00355 derived from cancer-associated fibroblasts promotes bladder cancer cell resistance to cisplatin by regulating miR-34b-5p/ABC21 axis. *Acta Biochim Biophys Sin (Shanghai)*. 2021;53(5):558-566. 10.1093/abbs/gmab023

92. Hasemipour M, Boroumand H, Mollazadeh S, et al. Exosomal microRNAs and exosomal long non-coding RNAs in gynecologic cancers. *Gynecol Oncol*. 2021;161(1):314-327. 10.1016/j.ygyno.2021.02.004

93. Yao Z, Jia C, Tai Y, et al. Serum exosomal long noncoding RNAs Inc-FAM72D-3 and Inc-EPC1-4 as diagnostic biomarkers for hepatocellular carcinoma. *Aging (Albany NY)*. 2020;12(12):11843-11863. 10.18632/aging10.3355

94. Zheng P, Zhang H, Gao H, et al. Plasma exosomal long noncoding RNA Inc-lncSLC2A12-1:01 as a novel diagnostic biomarker for gastric cancer. *Onco Targets Ther*. 2020;13:4009-4018. 10.2147/OTT.S253600

95. Cai C, Zhang H, Zhu Y, et al. Serum exosomal long noncoding RNA pcSK-2:2:1 as a potential novel diagnostic biomarker for gastric cancer. *Onco Targets Ther*. 2019;12:10035-10041. 10.2147/OTT.S229033

96. Zhan Y, Du L, Wang L, et al. Expression signatures of exosomal long non-coding RNAs in urine serve as novel non-invasive biomarkers for diagnosis and recurrence prediction of bladder cancer. *Mol Cancer*. 2018;17(1):142. 10.1186/s12943-018-0893-y

97. Zhang S, Du L, Wang L, et al. Evaluation of serum exosomal LncRNA-based biomarker panel for diagnosis and recurrence prediction of bladder cancer. *J Cell Mol Med*. 2019;23(12):1396-1405. 10.1111/jcmm.14042

98. Wang J, Yang K, Yuan W, Gao Z. Determination of serum exosomal LncRNA-based biomarker panel for diagnosis and recurrence prediction of bladder cancer. *Cancers*. 2021;12(1):4906. 10.1038/s41467-021-25103-7
117. Miyata Y, Tsurusaki T, Hayashida Y, et al. Intravesical MMC and MMC+Ara-C for non-muscle invasive bladder cancer: A randomized clinical trial. BJU Int. 2021. 10.1111/bju.15571

118. Kobayashi M, Fujiyama N, Tanegashima T, et al. Effect of HLA genotype on intravesical recurrence after bacillus Calmette-Guerin therapy for non-muscle-invasive bladder cancer. Cancer Immunol Immunother. 2021. 10.1007/s00262-021-03032-0

119. Yi Y, Wu M, Zeng H, et al. Tumor-derived exosomal non-coding RNAs: The emerging mechanisms and potential clinical applications in breast cancer. Front Oncol. 2021;11:738945. 10.3389/fonc.2021.738945

120. Li Y, Lin S, Xie X, Zhu H, Fan T, Wang S. Highly enriched exosomal IncRNA OIP5-AS1 regulates osteosarcoma tumor angiogenesis and autophagy through miR-153 and ATG5. Am J Transl Res. 2021;13(5):4211-4223.

121. Han W, Sulidankazha Q, Nie X, Yilidan R, Len K. Pancreatic cancer cells-derived exosomal long non-coding RNA CCAT1/microRNA-138-5p/HMGA1 axis promotes tumor angiogenesis. Life Sci. 2021;278:119495. 10.1016/j.lfs.2021.119495

122. 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. 10.1038/s41388-018-0261-9

123. Guo X, Qiu W, Wang J, et al. Glioma exosomes mediate the expansion and function of myeloid-derived suppressor cells through microRNA-29a/Hbp1 and microRNA-92a/Prkar1a pathways. Int J Cancer. 2019;144(12):3111-3126. 10.1002/ijc.32052

124. Abels ER, Maas SLN, Nieland L, et al. Glioblastoma-associated microglia reprogramming is mediated by functional transfer of extracellular miR-21. Cell Rep. 2019;28(12):3105-3119 e7. 10.1016/j.celrep.2019.08.036

125. Zhao M, Xu J, Zhong S, et al. Expression profiles and potential functions of circular RNAs in extracellular vesicles isolated from radio-resistant glioma cells. Oncol Rep. 2019;41(3):1893-1900. 10.3892/or.2019.6772

126. Kartolo A, Kassouf W, Vera-Badillo FE. Adjuvant immune checkpoint inhibition in muscle-invasive bladder cancer: Is it ready for prime time? Eur Urol. 2021;80(6):679-681. 10.1016/j.eururo.2021.07.019

127. Wigner P, Bijak M, Saluk-Bijak J. The green anti-cancer weapon. The role of natural compounds in bladder cancer treatment. Int J Mol Sci 2021;22(15):7787. 10.3390/ijms22157787

128. Yang N, Gao J, Hou R, Xu X, Yang N, Huang S. Grape seed proanthocyanidins inhibit migration and invasion of bladder cancer cells by reversing emt through suppression of TGF-beta signaling pathway. Oxid Med Cell Longev. 2021;2021:5564312. 10.1155/2021/5564312

129. Eldh M, Mints M, Hiltbrunner S, et al. Proteomic profiling of tissue exosomes indicates continuous release of malignant exosomes in urinary bladder cancer patients, even with pathologically undetectable tumour. Cancers. 2021;13(13):3242. 10.3390/cancers13133242

130. Wang P, Zhou R, Thomas P, et al. Epithelial-to-mesenchymal transition enhances cancer cell sensitivity to cytotoxic effects of cold atmospheric plasmas in breast and bladder cancer systems. Cancers (Basel). 2021;13(12):2889. 10.3390/cancers13122889

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