REVIEW

Tumor-derived exosomal non-coding RNAs as diagnostic biomarkers in cancer

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Abstract

Almost all clinical oncologists agree that the discovery of reliable, accessible, and non-invasive biomarkers is necessary to decrease cancer mortality. It is possible to employ reliable biomarkers to diagnose cancer in the early stages, predict the patient prognosis, follow up the response to treatment, and estimate the risk of disease recurrence with high sensitivity and specificity. Extracellular vesicles (EVs), especially exosomes, have been the focus of translational research to develop such biomarkers over the past decade. The abundance and distribution of exosomes in bodily fluids, including serum, saliva, and urine, as well as their ability to transport various biomolecules (nucleic acids, proteins, and lipids) derived from their parent cells, make exosomes reliable, accessible, and potent biomarkers for diagnosis and follow-up of solid and hematopoietic tumors. In addition, exosomes play a vital role in various cellular processes, including tumor progression, by participating in intercellular communication. Although these advantages underline the high potential of tumor-derived exosomes as diagnostic biomarkers, the lack of standardized effective methods for their isolation, identification, and precise characterization makes their application challenging in clinical settings. We discuss the importance of non-coding RNAs (ncRNAs) in cellular processes, and the role of tumor-derived exosomes containing ncRNAs as potential biomarkers in several types of cancer. In addition, the advantages and challenges of these studies for translation into clinical applications are covered.

Keywords Tumor-derived exosomes · Diagnostic biomarkers · Non-coding RNAs · Early diagnosis · Cancer prognosis

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Introduction

Despite a huge research effort over the past decades, cancer remains a leading cause of death from non-infectious disease and is the second leading cause of death in the USA [1, 2]. Although there have been advances in different therapies over the past two decades, and patient survival has increased markedly, the overall prognosis of patients remains poor. Modern cancer treatment includes surgery radiotherapy, chemotherapy (systemic or regional), targeted therapy, immunotherapy, and anti-cancer vaccines, but the overall success has been limited [3]. Mainly due to delays in diagnosis, many tumors have reached an advanced or metastatic stage and are resistant to treatment. Therefore, prompt non-invasive diagnostic methods are required in the fight against cancer [2, 4]. DNA damage has been known for decades to be a leading cause of carcinogenesis. Although protein products arising from DNA mutations are generated in cancerous cells, only 2% of the entire genome is translated into these functional carcinogenic proteins. Advances in whole genome sequencing have led to rapid and easily accessible methods, such as microarrays and next generation sequencing (NGS), to understand the function and nature of the non-protein-coding portion of the genome. It is now accepted that the 98% non-coding part of the genome is as important as the protein-coding regions [5].

The role of biological molecules, such as circulating RNAs and exosomal proteins, is gaining increased interest from cancer biologists, because of the current emphasis on liquid biopsies for improving cancer diagnosis. If cancer-specific biomarkers can be detected in biological fluids, this removes the requirement for traditional invasive tissue biopsy procedures. Moreover, the heterogeneity of cancer cells, often leads to problems in diagnosis and treatment [6]. The use of bodily fluid-derived exosomes as biomarkers could address the problems of tumor heterogeneity and invasive procedures. In both cancer patients and healthy individuals, cell-free circulating RNAs, such as messenger RNAs and non-coding RNAs (microRNA, short nuclear RNA, long non-coding RNA, circular RNA, and piwi-interacting RNA), have been identified in reasonably high amounts in plasma, serum, urine, and other bodily fluids [7].

Membrane vesicles with varying contents (nucleic acids, lipids, and proteins) can be released from specific cell populations into the microenvironment. According to the definition, by the International Association of Extracellular Vesicles (ISEV), vesicles isolated from biological fluids and cellular environments are known as extracellular vesicles (EVs). Cell-derived EVs are divided into three distinct categories in terms of size and origin, including apoptotic bodies, microvesicles, and exosomes [8]. Exosomes can function as carriers of circulating nucleic acids and are involved in almost all pathological and physiological processes of any organism. Exosomes are one of the most important sources of microRNAs (miRNA) in human serum or plasma [6]. Many miRNAs are significantly dysregulated in different types of cancers (over-expressed or under-expressed) and have therefore been investigated as diagnostic biomarkers and therapeutic targets in many studies over the last three decades [7]. However, there is still a lack of accurate biomarkers for the diagnosis and prognosis of several cancers. For this reason, many scientists have turned their attention to another type of ncRNAs, called long non-coding RNAs (lncRNA), which in turn regulate the expression of specific miRNAs. Circulating lncRNAs could be new biomarkers for the diagnosis and prognosis of different types of cancers. Disruption of lncRNA expression levels is associated with the progression and metastasis of cancers, according to recent studies. LncRNAs are involved in regulating the expression of oncogenes, tumor suppressor genes, and cellular signaling pathways [9–12]. Given the presence of ncRNAs, especially lncRNAs, contained within exosomes as circulating ncRNAs, the simultaneous detection of both species could provide biomarkers for the diagnosis and prognosis of various cancers, as well as possible therapeutic targets.

Biogenesis of exosomes in cancer

Exosomes are small membrane vesicles secreted by all types of cells and can be found in all bodily fluids [13]. Exosomes are smaller (30–150 nm) compared to microvesicles (100–1000 nm) and apoptotic bodies (800–5000 nm) and have a similar size to viruses. In addition to the size, exosomes differ from other EVs in terms of their biogenesis mechanism. Endosomal components are involved in the biogenesis of exosomes, which play a potential role in maintaining cellular homeostasis [14]. This process begins with an extrusion of the cell plasma membrane and endosome formation. The early endosomes then mature and form late endosomes. Next, the late endosome membrane is invaginated in an inwards direction, which leads to the generation of multiple intraluminal vesicles. The endosome is then transformed into a multivesicular body (MVB), which contains several vesicles, each encapsulating a tiny portion of the cytoplasm, including nucleic acids and proteins [15]. MVBs are next fused to the plasma membrane, and then the exosomes are released out of the cell. However, not all the MVBs combine with the plasma membrane to release exosomes, because some are destroyed during fusion with lysosomes. Because of the high percentage of the membrane

lipid ceramide, the exosomes are protected from lysosomal degradation. Through this cellular process, millions of exosomes are released by each tumor cell, containing several cellular components, including nucleic acids, lipids, enzymes, proteins, and cytokines [13]. The exosomal contents do not exactly match that of the parent cells, but there are many similarities in the molecular and genetic profiles. This partial resemblance has led to the concept of exosomes as potential cancer biomarkers [16]. According to recent reports, the rate of production of exosomes is higher in cancer cells, so that the number of exosomes released from cancer cells is many times that of normal cells. Indeed, exosome levels in bodily fluids of cancer patients were found to be significantly higher. Cellular stress, including the hypoxic tumor microenvironment, is the leading cause of increased exosome secretion by tumor cells. Many tumors show an increased expression of p53 and heparanase enzyme, as well as increased activity of Rab GTPase proteins, which could explain the higher secretion of exosomes from tumor cells [17]. The biogenesis of exosomes is illustrated in Fig. 1.

The importance of tumor-derived exosomes as biomarkers

The absence of severe symptoms before metastasis occurs, as well as the high heterogeneity of tumors, has significant challenges in cancer diagnosis. Although cancer treatment methods have made tremendous progress over the past few decades, none of them have been able to reduce cancer-related mortality entirely. More precisely, cancer mortality reduction is directly related to its detection in the early stages, and definitely before metastasis. Current diagnostic methods mainly include general tests and biopsies, lacking sufficient sensitivity and specificity to identify cancer in the early stages of its formation. In addition, some of these diagnostic methods, including biopsy, are invasive and pose a threat to patient health [18]. For example, the risk of bleeding, infection, and trauma in surgical biopsies is high. On the other hand, sampling and biopsy of some tumors is impossible or difficult due to the inaccessibility of many organs. Urogenital malignancies, for example, are challenging to treat due to their position deep within the pelvic area [19].

Tumor-derived exosomes (TDEs) can be found in the blood and in other bodily fluids, including urine, semen, and breast milk. The molecular and genetic cargos, at least in part, mirror the contents of the parental tumor cells. Therefore, these exosomes may be used as a "liquid biopsy,"

Fig. 1 Exosome biogenesis. The first step involves endocytosis producing early endosomes. Endosomes and specific cargos such as nucleic acids, proteins, and lipids are then encased in multivesicular bodies (MVBs). Finally, these multivesicular bodies merge with the plasma membrane and the exosomes are released into the extracellular space. Exosomal contents (proteins, lipids, DNAs, RNAs and non-coding RNAs) are delivered to recipient cells by direct cell membrane fusion, receptor contact, and endocytosis
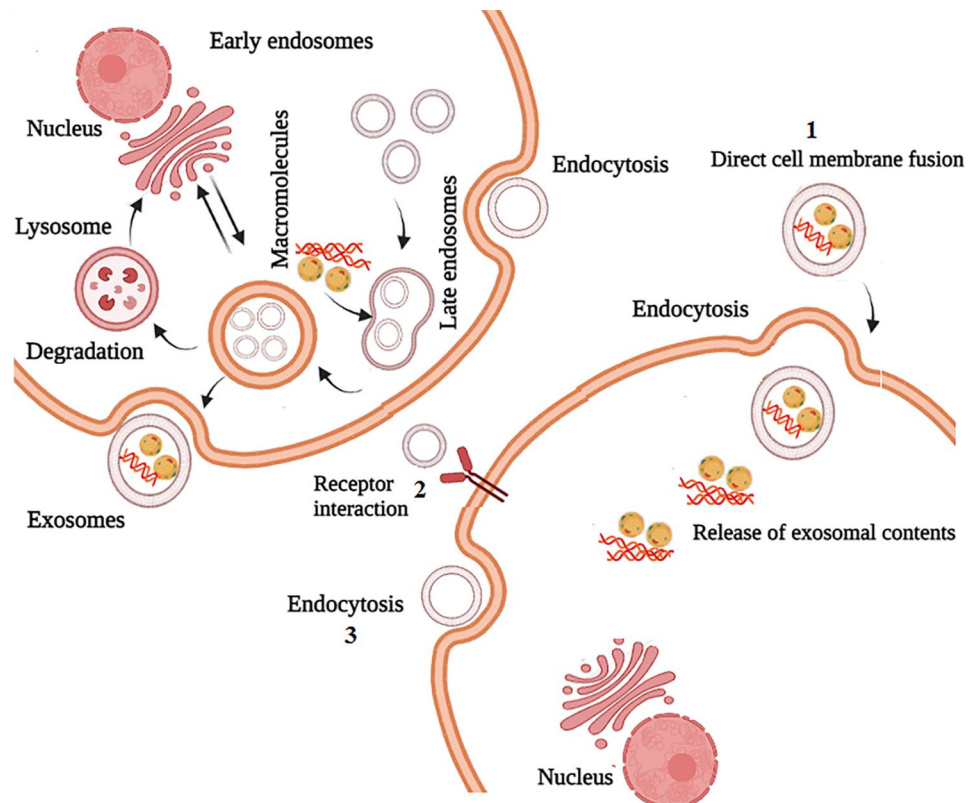
allowing for noninvasive tumor detection in real time. Examining the contents of these exosomes could allow scientists to discover more accurate diagnostic biomarkers, especially ncRNAs [20]. TDEs have properties that make them particularly suitable surrogates for tumor-derived proteins and RNAs. Given the importance of ncRNAs (especially miRNAs and lncRNAs) as cancer biomarkers, tumor-derived exosomes containing RNA have attracted much attention as discussed in this review. Exosomal miRNAs could be highly valuable biomarkers for early stage diagnosis of cancer. Exosomes are capable of transferring miRNAs to other cells in order to regulate specific gene expression by suppressing or degrading the relevant mRNAs. Horizontal transfer of miRNAs from tumor cells to normal recipient cells causes transcriptional reprogramming, which can affect tumor progression and metastasis [21]. Although both free circulating ncRNAs and tumor-derived exosomal ncRNAs have the same origin, the higher stability of exosomal ncRNAs has made them more powerful biomarkers. Exosomal ncRNAs are encapsulated within the vesicular (phospholipid) membrane and are therefore protected from the degrading enzymes such as RNAses [22]. On the other hand, exosomes can also contain proteins attached to DNA, RNA or lipoprotein complexes. Therefore, the exosomes are more stable under adverse physical conditions, such as extreme pH, repeated freeze-thawing, and prolonged storage time [23].

On the other hand, due to the absence of contaminating matrix proteins and other biomacromolecules, exosomes show reduced assay noise and therefore have higher sensitivity and specificity compared to other biomarkers. Several studies have shown the superiority of exosome-based biomarkers compared to conventional serum and urine biomarkers [24, 25]. For example, exosomes containing miRNAs isolated from sera showed 90% sensitivity in colorectal cancer, while the sensitivity of carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9) both typical biomarkers in CRC diagnosis was 30.7% and 16%, respectively [26]. Furthermore, in transcriptome analysis of RNA, it is difficult to differentiate the noise signals from normal cells from the signals of malignant cells. Furthermore, because of the strong RNA background from megakaryocytes created by platelet-derived RNA, RNA obtained directly from plasma is much more difficult to evaluate. Because exosomes carry tumor-specific surface proteins, they are capable of eliminating normal cell noise [27].

Another advantage of using exosomes as biomarkers is the possibility of monitoring the patient's condition and response to treatment. The abundance and easy access to exosomes in bodily fluids make it possible to monitor and track the patient's response to anticancer treatment in real-time. If the cancer marker directly corresponds to the clinical status, the amount of the biomarker should alter if the patient responds to treatment [28]. Despite the advantages

of exosomal RNAs as cancer diagnostic biomarkers, their effective use in clinical applications requires rapid and effective isolation methods and extraction from patient samples, which remains challenging. We discuss exosome isolation methods and the advantages and disadvantages of each below. The selection of exosome-based biomarkers and their clinical applications are illustrated in Fig. 2, adopted and modified from [29].

## Isolation of exosomes, methods, and challenges

Various methods are used to separate exosomes based on their morphology, size, protein markers, and flotation density. Conventional methods for isolating exosomes from cell culture medium or bodily fluids include ultracentrifugation, ultrafiltration, immunoaffinity, size exclusion chromatography (SEC), commercial kits, and microfluidic-based techniques. The progress in this field, especially in the last decade, has been significant; however, the isolation of exosomes with high speed and purity is challenging for the following reasons: first and most importantly, the high complexity of biological samples; secondly the heterogeneity of exosomes; and thirdly the similarity of the biochemical and physiochemical properties of exosomes, which makes it challenging to work with them compared to other EVs [30].

Currently, ultracentrifugation is the gold standard method for exosome separation, which separates similar exosomes from other components based on the difference in density and size. However, the disadvantages of this method are time-consuming, poor reproducibility, low stability, and lack of accurate separation of exosomes (based on size and not contents). In addition, ultracentrifugation has a high possibility of impurities, with protein and lipoprotein contamination in the final product [31].

In the ultrafiltration method (the simplest separation method), exosomes are passed through a membrane and separated based on size and molecular weight. However, despite its simplicity, ultrafiltration is very time-consuming and reduces the life and stability of the exosome membrane. On the other hand, in this method, the possibility of binding exosomes to the membrane is high, which leads to insufficient amounts of exosomes for subsequent analyses. In other words, the final product can be insufficient to produce good results [32].

In the SEC technique, gravity flow is used, and as a result, the structure and integrity of exosomes remain intact, and their biological activity is maintained. In addition, SEC is highly reproducible, but its major limitation is the requirement for complex equipment. Moreover, the SEC process is time-consuming and this restricts its application on a large scale for clinical purposes [33]. In the

Fig. 2 Validation steps for exosomal biomarkers for clinical applications. A possible flowchart for the validation and clinical use of extracellular vesicle-based biomarkers. The flowchart depicts a step-by-step procedure for analyzing and discovering exosomal cargo molecules, which might eventually be turned into a therapeutically useful biomarker signature. To advance to the next level, stated goals and criteria must be accomplished at each phase. The figure is adopted and modified from [29]
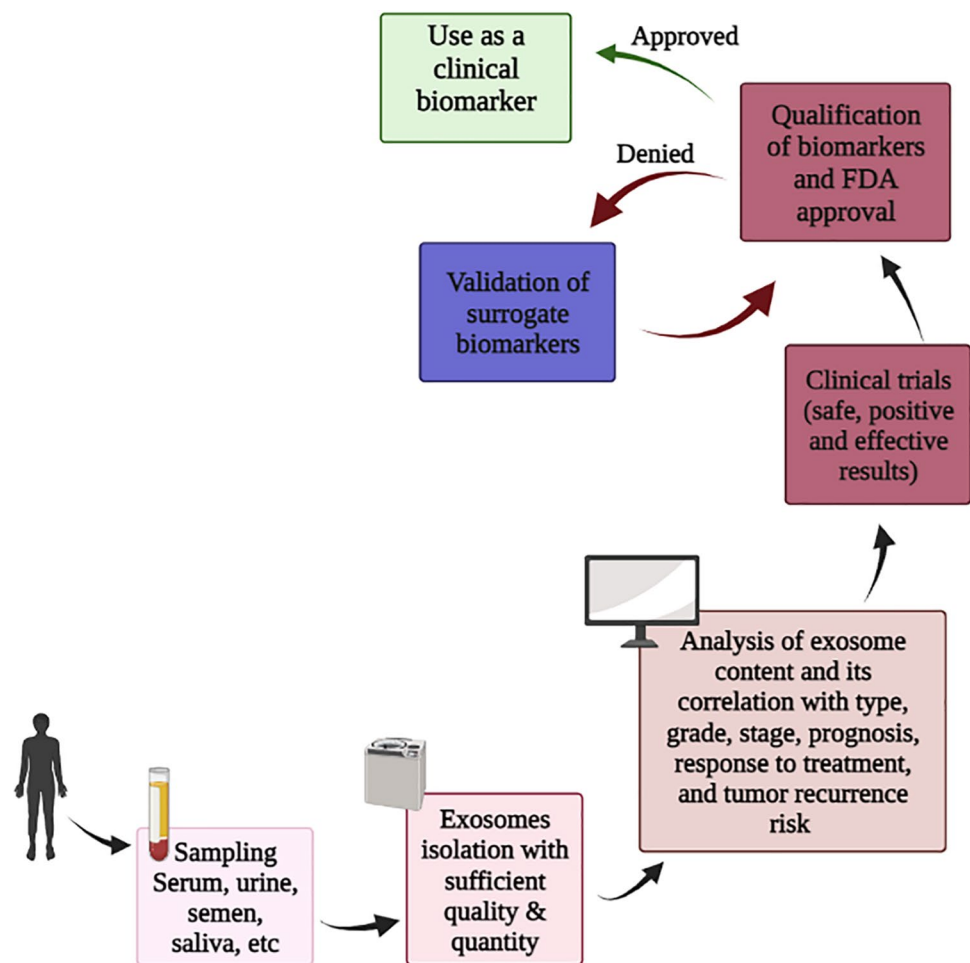
immunoaffinity method, a recognition between antibody and antigen is used. In general, the surface of exosomes is rich in various receptors and proteins, and these molecules have the ability to bind to their specific antibodies. Unlike the previous methods, this method has high specificity. However, the final product, although pure, is confined to the isolation of a particular subset of exosomes [34]. Furthermore, tumor heterogeneity in antigen expression and antigen modification as the tumor progresses may result in underestimation and false negative results. The antigenic epitope may also be inhibited or disguised. Although the initial steps are simple in exosome-antibody precipitation methods, the sample preparation and purification steps are tedious and time-consuming [34]. Finally, if the purity is poor, it can cause errors in the data analysis steps. For example, exosome precipitation in serum and plasma samples leads to simultaneous precipitation of other cellular particles such as protein aggregates and other EVs. Furthermore, the varying viscosity of the sample matrix leads to distinct exosome precipitation stringency requirements, compromising the standardization of precipitation techniques.

Microfluidics is a revolutionary technique for exosome isolation that has advantages of rapidity, high purity, high recovery rates, and has a wide range of applications [35]. Despite significant advances in microfluidics techniques, these devices are not yet suitable for clinical applications. Significant obstacles such as lack of validation, scalability, and standardization have limited their use. In addition, some devices require pretreatment of the samples, which takes more time. Some types of microfluidics devices suitable for intact samples have low separation efficiency. All microfluidics devices are designed to isolate a specific class of exosomes; therefore, the volume of their products is small and specific. In addition, their processing capacity is low, and the lack of sufficient DNA, RNA or protein inside the extracted exosomes limits the subsequent analysis steps [36].

Exosomes have been widely studied in the laboratory using mass spectrometry, fluorescent cell activation sorting (FACS), Western blotting, flow cytometry, electron microscopy, and liquid chromatography. Although nanoparticle tracking analysis and dynamic light scattering approaches are rapid, dependable, and semi-quantitative, they are not be able to distinguish between different exosome types.

Microarray analysis, surface plasmon resonance, and using specific antibodies against proteins in the extracellular domain of exosomes have been applied for detection and characterization of tumor-derived exosomes quantitatively without any purification and/or enrichment, resulting in a simple and a more effective novel technique for exosome detection and their characterization [37]. The next-generation sequencing (NGS) method and high-throughput RNA sequencing (RNA-seq) have made it possible to quickly and accurately scan the nucleic acid contents of exosomes. Using RNA-seq, the isolated exosome contents can be accurately determined, and the cancer diagnostic markers monitored and analyzed on a large scale [38].

Breast cancer exosomal miRNAs (Exo-miRNAs)

There have been many reports of cell-derived exosomes occurring in breast cancer. Based on these results, exosomes containing cancer-derived miRNAs could be involved in tumor initiation, angiogenesis, epithelial-mesenchymal transition (EMT), tumor-stromal communication, and treatment resistance [39]. In addition, these exosomes are highly heterogeneous, and in a single cancer sample, there may be several types of exosomes with different miRNA profiles. MiRNAs are clustered in a non-random manner within exosomes [40]. The cargo carried by each exosome is governed by the type of cell from which it was produced. Exosomal information is transferred in various ways to distinct types of cells in the tumor microenvironment [41]. NGS techniques and microarrays can make it easier to study exosomes, and determine the role of their contents in breast cancer. These findings will be useful for early diagnosis, prognosis, and prediction of treatment response in breast cancer patients.

Tumor-derived miR-9 was detected inside exosomes secreted from breast cancer by Baroni et al. [42]. miR-9 is able to transform normal fibroblasts into cancer-associated fibroblasts (CAFs), which promote breast tumor growth and metastasis. In addition, the role of other miRNA-containing exosomes in the cellular processes involved in tumorigenesis and progression has been elucidated. For example, miR-143, miR-378, and miR-21 contained in CAF-derived exosomes can induce the EMT in breast cancer cells [43]. CAFs can also secrete exosomes containing miR-181d-5p, which promotes EMT, cell division, cell migration, invasion, and suppresses apoptosis by inhibiting HoxA5 and CDX2 in breast cancer [44, 45].

In another study, exosomal-miR-222 was associated with increased metastasis in breast cancer cells. This was explained by the fact that miR-222 directly targets the PDLIM2-tumor suppressor gene, and consequently activates the NF-κB signaling pathway [46]. One study by

Camacho et al. also showed that exosomes derived from MDA-MB-231 breast cancer cells contained high levels of miR-210, which promoted angiogenesis and brain metastasis in breast cancer. Survival rates are usually poor in patients with breast cancer brain metastases with high levels of miR-210 [47]. Surprisingly, Le et al. showed that the metastatic potential could be transferred from metastatic cancer cells to non-metastatic cancer cells through exosomal miRNAs [48]. In their study, exosomes containing miR-200 secreted by breast cancer cells transferred metastatic properties to non-metastatic cells as demonstrated in human xenograft mouse models [48, 49]. The transfer of miR-770 and miR-105 via exosomes can regulate the migration and metastasis of breast cancer cells [50, 51]. These findings illustrate the role of tumor-derived exosomes in cancer progression and metastasis and highlight the importance of studying exosomal miRNAs as diagnostic and predictive biomarkers. Higher levels of these exosomes could act as a warning sign that the cancer is progressing towards metastasis.

Elevated serum exosomal miR-373 levels have been found in receptor-negative breast tumors, and could be used as a diagnostic biomarker [52]. An increase in exosomes containing miR-21 and miR-1246 was found in the plasma of breast cancer patients compared with healthy individuals in a study by Hannafon et al. [53]. A recent study by Shen et al. also showed that exo-miR-7641 could promote the progression and metastasis of breast cancer [54]. MiR-7641 plasma levels in patients with distant metastases were much higher than in healthy individuals. Increased exo-miR-7641 could explain the connection between tumor growth and metastasis. In addition, Shen et al. suggested that exo-miR-7641 could be a non-invasive diagnostic biomarker, and could also be a target for breast cancer treatment [54].

Some exosomal miRNAs have been associated with survival and response to treatment and could therefore be used as predictive markers for patient response to treatment. For example, increased levels of exo-miR-455-5p and exo-miR-255 were associated with low patient survival rates, and could be considered to be therapeutic targets [55]. In a study by Jaiswal and colleagues it was indicated that exosomes derived from doxorubicin-resistant breast cancer cells contained high levels of miR-362, which was involved in the drug resistant phenotype [56–58]. According to other studies, some exosomal RNAs, such as miR-100, miR-30a, miR-222, and miR-17 derived from breast cancer cells, have been implicated in resistance to paclitaxel and doxorubicin [59]. A study by Shah and coworkers showed that exosomes derived from breast cancer associated fibroblasts (CAFs) suppressed estrogen receptor expression in ER-positive breast cancer cells, which may explain the effects of CAFs on tumorigenesis and treatment resistance to treatment in breast cancer [60]. Exosome-mediated cell reprogramming could alter the

metabolic profiles of cancer cells and the tumor microenvironment, leading to the acquisition of properties in cancer cells that make them more resistant to therapy. Cancer cells can transmit these properties to each other with the help of exosomal cargos. According to Fong et al. breast, cancer-derived exosomes containing miR-122 could alter glucose metabolism in favor of cancer progression, and inhibition of miR-122 could reduce lung and brain metastasis in breast cancer [61]. MiR-155 is also involved in altering energy metabolism in cancer cells, and acts as an oncogenic signal transmitted through secreted exosomes in breast cancer. Exo-miR-155 led to cell reprogramming and cancer-associated cachexia by targeting PPARγ [62]. In addition to reprogramming of cellular metabolism, cancer-derived exosomal miRNAs can also induce the cancer stem cell (CSC) phenotype, thus enhancing tumor progression. According to a study by Shen et al., exo-miRNAs (miR-203a-3, miR-195-5p, and miR-9-5p) were released in response to neoadjuvant chemotherapy. These exo-miRNAs reduced the expression of the One Cut Homeobox 2

(ONECUT2) transcription factor to induce the CSC phenotype in adjacent breast cancer cells [63] (Fig. 3)

Exosomal lncRNAs in breast cancer

Dysregulation of lncRNA expression in breast cancer patients has been the subject of extensive research [64]. For example, increased exosomal lncRNA-UCA1 in breast cancer cells has been associated with increased resistance to tamoxifen. This resistant phenotype can be transferred to other cells via exosomal-UCA1 [65]. Similar results were obtained for SNHG14 in a study by Dong et al. [66]. In trastuzumab-resistant cells, the expression of SNHG14 was higher, suggesting that exosomal SNHG14 could be a suitable biomarker for monitoring treatment response [66]. As mentioned above, cancer cells and adjacent tumor cells can exchange their phenotype through the effects of exosomes. Transfer of the endogenous signal recognition particle RNA, RN7SL1 contained in exosomes between breast cancer cells,
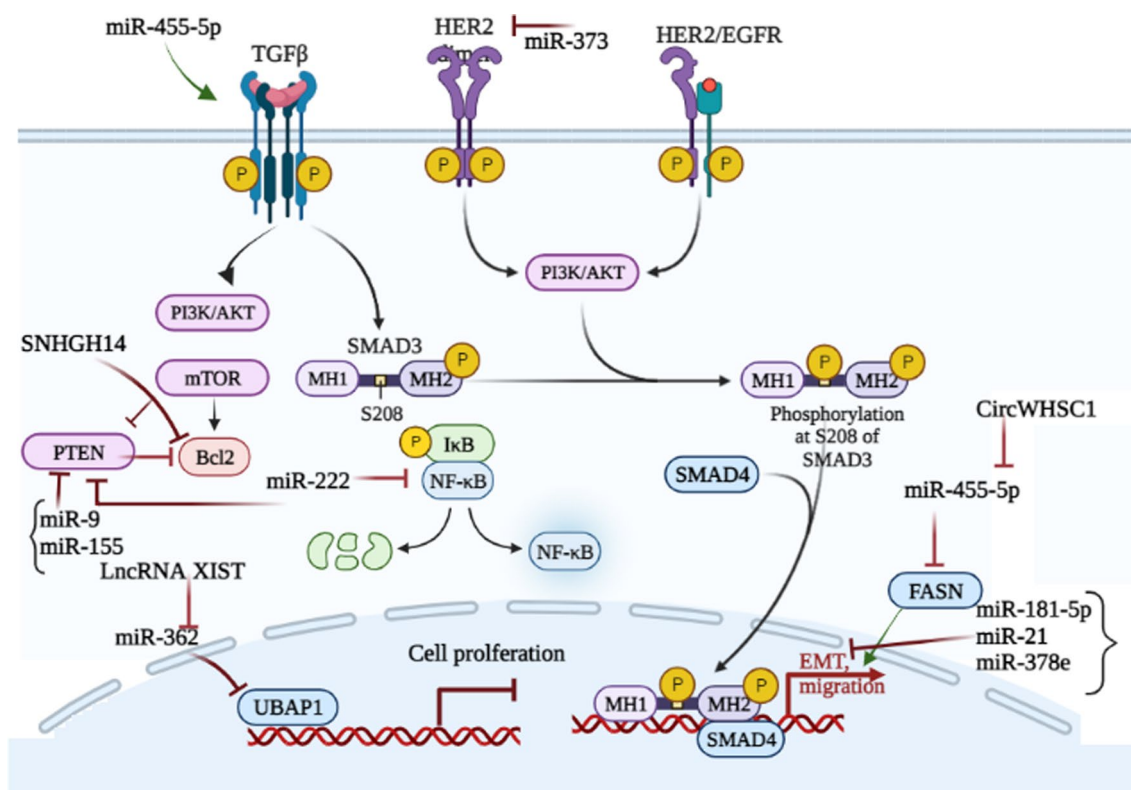
Fig. 3 Role of exosomal ncRNAs and their related pathways in breast cancer progression. miR-455 activates the TGF-beta receptor, ultimately leading to activation of its canonical pathway and increases the division, migration, and EMT of breast cancer cells. miR-222, miR-9, and miR-155, by inhibiting PTEN lead to the activation of Bcl2 (apoptosis inhibitor), which ultimately promotes cell division and survival. On the other hand, LncRNA SNHGH14 enhances apoptosis by inhibiting Bcl2, and was found to be reduced as a tumor suppressor in breast cancer. lncRNA XIST leads to increased cell division and tumor progression by regulating the miR-362/UBAP1 axis. CircWHSC1 increases EMT and invasiveness of cancer cells by inhibiting FASN/miR-455-5P axis. miR-373 acts as an estrogen receptor inhibitor and is overexpressed in breast cancer. *EMT* epithelial–mesenchymal transition, *UBAP1* ubiquitin associated protein 1, *PETN* Phosphatase and tensin homolog, *FASN* fatty acid synthase

immune cells, and stromal fibroblasts resulted in increased tumor growth, metastasis, inflammation, and drug resistance [67]. Previous studies have shown high levels of lncRNA MALAT1 expression in breast cancer and confirmed its association with drug resistance. Recently, increased levels of exosomes containing MALAT1 have been shown in breast cancer, and have been proposed to be responsible for disease progression [68]. HOTAIR is a lncRNA found in circulating exosomes, and was found to be positively linked with ErbB2 (HER2/neu) expression, implying that it could be used as a liquid biomarker [69]. Exo-AFAP-AS1 is another known exosomal-lncRNAs in drug resistant breast cancer, which binds to the AU-rich element RNA-binding protein 1 (AUF-1) and promotes trastuzumab resistance by activating ERBB2 translation [69]. Some fibroblast-derived exosomes contain SNHG3, which are involved in cell reprogramming thereby altering cell metabolism and increasing the proliferation of breast cancer cells [70]. Doxorubicin resistance can also be transmitted to breast cancer cells via lncRNA-H19 in exosomes derived from cancer cells [71]. The exosomal-ncRNAs involved in breast cancer progression and their mechanism of action are summarized in Fig. 1.

Exosomal ncRNAs involved in lung cancer

About 20% of cancer deaths are due to lung cancer, which is the most common malignancy worldwide [72]. Lung cancer includes two main histological categories: non-small cell lung cancer (NSCLC) and small cell lung cancer. Eighty-five percent of all lung cancers are NSCLC, underlining the need for further study and improved treatment for this type of cancer [73]. In recent years, the expression profiles of several ncRNAs in lung cancer cells have been investigated. Increased expression of many of these circulating ncRNAs in lung cancer cells is found in EVs, including exosomes. Exosomal lncRNAs are responsible for the increased serum levels of MALAT1 in NSCLC [68]. Similar to breast cancer, increased MALAT1 expression promotes tumor metastasis and invasion. MALAT1 inhibits apoptosis and promotes cell division. Therefore, exosomes containing MALAT1 could serve as biomarkers for the diagnosis and prognosis of NSCLC [68]. Exosomal lncRNAs in lung cancer cells can also be altered following interaction with mesenchymal stem cells (MSCs), according to one report [74, 75]. MSCs are thought to act as tumor-promoting cells by encouraging metastasis and invasion, and also by inhibiting the immune response. One study identified the top ten altered exosomal lncRNAs in the NSCLC cell line A549, following treatment with MSCs. This study suggests that cancer-derived exosomes can be affected by MSCs via aberrant lncRNA expression [74] (Table 1).

Table 1 Exosomal LncRNAs as diagnostic biomarkers in lung cancer

LncRNA	Regulation	References
MALAT-1	Up-regulated	[68, 74]
NR_046464	Up-regulated	[74]
ENST00000420309	Up-regulated	
NR_024596	Up-regulated	
ENST00000440436	Up-regulated	
ENST00000440714	Down-regulated	
NR_048550	Down-regulated	
uc002rwa.2	Down-regulated	
Cb112975	Down-regulated	
ENST00000444164	Up-regulated	
ENST0000043768	Up-regulated	
HMlincRNA1636+	Up-regulated	
NR_052024	Up-regulated	
NR_046466	Up-regulated	
NR_045370	Up-regulated	
uc010hbj.3	Up-regulated	
ENST00000428453	Down-regulated	
ENST00000426501	Down-regulated	
TCONS_00006633	Down-regulated	
uc010ciy.1	Down-regulated	
uc011aef.2	Down-regulated	
ENST00000488190	Down-regulated	

Deng and colleagues found the role of exosomes containing lncRNA MSTRG.292666.16 in osimertinib-resistant NSCLC [76]. In recent years, many studies have focused on targeting epidermal growth factor receptors (EGFR), and EGFR tyrosine kinase inhibitors (TKIs) have shown promise in the treatment of lung cancer. However, in many cases, mutations occurring in EGFR alleles can cause resistance to TKIs, such as osimertinib [77]. Osimertinib is a third-generation anti-EGFR inhibitor that can inhibit a variety of mutated alleles. Understanding TKI resistance mechanisms could pave the way to find better treatments to increase patient survival [78]. In a study by Deng et al., exosomes derived from patients with NSCLC were isolated before and after treatment with osimertinib, and their lncRNA profiles were determined. Differentially expressed lncRNAs were found in osimertinib-resistant and osimertinib-sensitive exosomes, and the activity of one key lncRNA in promoting osimertinib resistance was investigated in vivo [76]. This study showed that exosomes containing MSTRG.292666.16 in plasma of osimertinib-resistant patients were significantly increased compared to drug-sensitive patients. Based on these results, exosomal-MSTRG.292666.16 was implicated in the development of a drug-resistant phenotype. Therefore, it could be used as a biomarker to predict treatment response, and to identify TKI-resistant patients, as well as a possible therapeutic target [12]. In another study, Zhou

et al. [79] examined the molecular mechanism of EGFR TKI resistance in the NSCLC cell line H1975. The study investigated the relationship between macrophages and cancer cells in the tumor microenvironment mediated by exosomes. Macrophages have two different phenotypes, M1 and M2 macrophages. M1 macrophages are responsible for producing proinflammatory cytokines, interleukin-6 (IL-6), IL-12, and TNF-α. On the other hand, M2 macrophages produce anti-inflammatory cytokines, including IL-10 and TGF-β [80]. In the tumor microenvironment, macrophages show a M2 phenotype and are known as tumor-associated macrophages (TAMs), which can suppress the immune response and promote angiogenesis. According to studies, a high ratio of M2/M1 is associated with a high rate of cell division, invasion, migration, as well as drug resistance in lung cancer cells [80, 81]. It has recently been shown that the lncRNA SOX2 overlapping transcript (SOX2-OT) is present at a high concentration in serum-derived exosomes from cancer patients [82]. A study by Zhou et al. showed that NSCLC cells can increase the M2 polarization of macrophages by the transfer of SOX2-OT exosomes, thereby increasing resistance to EGFR-TKIs. The mechanism of action of SOX2-OT is to regulate the expression of genes involved in M2 polarization. This study showed that SOX2-OT could target miR-627-3p, thereby increasing the expression of genes, such as Smad 2, Smad 3, and Smad 4. These studies underline the importance of investigating tumor-derived exosomes in treatment-resistant tumors [79]. On the other hand, the treatment response could be predicted by determining the concentration of specific ncRNAs in exosomes as biomarkers. As a result, more effective decisions could be made to select the best treatment. Due to the limited time available to treat cancer and prevent its metastasis, the identification of such biomarkers could play a vital role in time management during cancer treatment.

Distal-less homeobox 6 antisense RNA 1 (lncRNA DLX6-AS1) expression was found to be increased in various solid tumors. Zheng et al. demonstrated its role in the diagnosis of NSCLC by measuring its expression in tumor-derived exosomes [83]. The level of DLX6-AS1 expression in lung cancer tissue samples was significantly higher compared to healthy controls. In addition, it was shown that the knockdown of DLX6-AS1 in the NSCLC cell line could reduce proliferation and migration. Interestingly, the results showed that the sensitivity and specificity of DLX6-AS1 were higher compared to CYFRA21-1 when used as a diagnostic biomarker. CYFRA21-1 is considered to one of the most reliable biomarkers for the diagnosis of NSCLC. Therefore, the higher DLX6-AS1 levels in circulating tumor-derived exosomes from patients with NSCLC could be an acceptable diagnostic biomarker for early detection [83]. Current studies have shown that the expression of lncRNA-GAS5 (a tumor suppressor lncRNA) is lower in most cancers. In a study by Li et al., exo-GAS5 was studied in NSCLC patients and showed a significant reduction compared to exosomes derived from healthy individuals. Based on these findings, the expression of exo-GAS5 was related to the cancer stage, so that in more advanced cancer the expression level of exo-GAS5 was sharply lower. Exo-GAS5 might therefore be used to differentiate stage I NSCLC patients from other stages. Finally, exo-GAS5 might be a non-invasive serum-based biomarker for detecting patients with early NSCLC [84].

One non-invasive approach to diagnose cancer, especially in the early stages of the disease, is to measure the concentration of biomarkers in bodily fluids, such as plasma, serum, sputum, and urine. Examination of exosomes is doubly useful, because ribonucleases usually degrade circulating RNAs in the bloodstream, while exosomes can protect them. Although much effort has focused on diagnostic biomarkers in lung cancer, only a handful of these studies have reported specific miRNAs profiles for early-stage NSCLC [85]. Detection of exosomal miRNAs in bodily fluids has potential for clinical diagnosis and prognosis of NSCLC. In a study by Jin et al., tumor-derived exosomes were isolated from patient plasma [86]. Using the miRNA-seq technique, the profile of these exosomes in patients was compared with healthy individuals. In this study, in addition to determining the miRNA expression profile, six specific exosomal-miRNAs for lung adenocarcinoma were identified, which had much higher expression than healthy controls. Jin et al. showed that these tumor-derived exosomes (TMEs) were only elevated in patients with lung cancer and were not detected in healthy individuals. Comparison of miRNAs in TMEs with the whole plasma miRNA profile can eliminate the interference of exosomal miRNAs secreted by normal cells. The levels of circulating plasma miRNAs were not correlated with tumor-derived exosomal miRNAs, indicating that the miRNA content of cell-free plasma samples could be different from that of plasma exosomes. In both circulating RNA and exosomal RNA, the miRNA expression levels employed for cancer diagnosis or prognosis might be different producing unreliable results. The findings of this study might explain some of the differences in expression patterns observed between serum, plasma, and cell-free exosomes, which have been identified in prior investigations. Their results finally identified exosomal miR-21-5p and miR-24-3p as prognostic and diagnostic biomarkers for lung cancer [41]. Analysis of TMEs in NSCLC patients showed a significant increase in the expression of miR-4257 and miR-21 in patients with recurrent disease [87]. In contrast, the expression of miR-51 and miR-373 was lower in TMEs from lung cancer patients and was associated with a poor prognosis [88]. Other exosomal miRNAs have been identified as biomarkers of therapeutic response in lung cancer, including miR1246 and miR-208a, which bind to DR5mRNA and

P21, respectively. These miRNAs can lead to faster tumor growth and increased resistance to radiotherapy [89, 90]. Moreover, in another study, exo-miR-23b, exo-miR-21-5p, exo-miR-146a-5p, and exo-miR-10b-5p were investigated as prognostic biomarkers in NSCLC patients [91]. Zhang et al. studied tumor-derived exosomes containing miR-5684 and miR-125b-5p as biomarkers for NSCLC using a microarray method. They found a lower expression of exo-miR-125b-5p, which was also associated with a poor response to chemotherapy, suggesting that this exosomal miRNA could be a prognostic marker in NSCLC [92].

Tang et al. investigated whether miR-620 could be a diagnostic biomarker in NSCLC [93]. Recent studies have shown that miR-620 is involved in various biological processes, including cell division, and its expression was lower in various cancers [94]. Exo-miR-620 in lung cancer patients showed a pronounced difference compared to healthy individuals, and was significantly lower in patients with metastatic NSCLC. In addition, Tang et al. found that exo-miR-620 expression was associated with a good response to chemotherapy. Based on this finding, this research group suggested that exo-miR-620 could be a suitable diagnostic biomarker for lung cancer [93]. Kim et al. showed the role of miR-619-5p in angiogenesis and metastasis in NSCLC. They found that NSCLC-derived-miR-619-5p targeted the RCAN 1.4 gene [95]. The endogenous protein human regulator of calcineurin 1 (RCAN1) binds to calcineurin, and subsequently suppresses its activity by interfering with the calcineurin–nuclear factor of activated T-cells (NFAT) pathway [96]. RCAN1.4 has a variety of biological functions, such as VEGF-mediated angiogenesis, cardiac hypertrophy, and defending against calcium-mediated oxidative stress [97, 98]. In NSCLC, RCAN1.4 is targeted by miR-619-5p resulting in its lower expression. Based on the results of a study by Kim et al. using exosomes extracted from the plasma of NSCLC patients, miR-619-5p expression was higher than expected. Finally, hypoxic conditions caused more miR-619-5p to be incorporated into exosomes from NSCLC cells. Exosomal miR-619-5p promotes the development and metastasis of NSCLC through regulating RCAN1.4, suggesting that it might be a diagnostic marker for lung cancer [95]. miR-3157-3P is another tumor-derived exosomal miRNA associated with lung cancer. According to recent studies, exo-miR-3157-3P promotes angiogenesis, vascular permeability, and metastasis. In patients with metastatic lung cancer, the expression level of miR-3157-3P in circulating exosomes was much higher than in patients with non-metastatic lung cancer [99]. Ma and colleagues found that miR-3157-3P could be transported in exosomes from lung cancer cells to vascular epithelial cells, and contributed to formation of a pre-metastatic niche. MiR-3157-3P targeted the TIMP/KLF2 pathway, and thus led to increased expression of matrix metalloproteinases (MMP) 2, MMP9, and VEGF in endothelial cells. Ma et al. suggested that tumor-derived exo-miR-3157-3P could be used as a blood-based biomarker to diagnose metastatic lung cancer [100].

Colorectal cancer (CRC)

Colorectal cancer (CRC) is the third most common cancer worldwide and ranks second in mortality. Early diagnosis of CRC is vital for more effective treatment and improved patient survival [101]. Several studies have shown that dysregulation of exosomal-ncRNA expression is involved in various tumorigenic processes in CRC [3, 102]. Therefore, exosomal-ncRNAs have the potential to be used as diagnostic and prognostic biomarkers. The studies on exosomal-ncRNAs associated with CRC have been relatively extensive, compared to other cancers.

Exosomal miRNAs in CRC

According to a study by Li et al., decreased expression of miR-149 and miR-96 was observed in both CRC tissues, and exosomes derived from patients. This was associated with decreased apoptosis, increased cell division, and increased GPC1 expression [103, 104]. The exo-miR-92 expression was also significantly lower in CRC patients compared to healthy individuals. Decreased expression of exo-miR-92 was observed primarily in patients with more advanced CRC stages, and not in non-cancerous lesions [105]. In contrast, tumor-derived exosomes containing miR-320, miR-181, miR-17, miR-125a, miR-18a, and miR-18b were significantly higher in CRC patients [106]. According to recent findings, exo-miR-125a and exo-miR-320 have a higher expression in the early stages of CRC and could therefore be considered as diagnostic biomarkers [107]. Typically, two blood-based biomarkers are screened for colorectal cancer diagnosis, carbohydrate antigen 19–9 (CA19-9) and carcinoembryonic antigen (CEA) [108]. Studies have shown that the efficiency and sensitivity of these diagnostic biomarkers, were significantly higher when combined with some exosomal miRNAs [109]. For example in patients with metastatic CRC, miR-320d has been reported as a biomarker with 64.7% specificity and 62% sensitivity. The combination of exo-miR-320d and CEA increased the specificity up to 91.3% [110]. Due to the differences in the expression profile of these exosomal miRNAs between the early or advanced stages of the disease, they can be used for early detection or diagnosis of metastatic CRC. Some other exo-miRNAs have been studied as prognostic biomarkers in CRC. For example, the expression level of exo-miR-193a was higher in CRC metastatic cell lines, and in plasma from patients with CRC lung metastasis. Increased expression of exo-miR-193a

has been associated with decreased survival of CRC-bearing mice [103]. Another study by Liu et al. showed an association between lower expression of exo-miR-4772-3p and recurrence in CRC patients [111]. Decreased expression of exo-miR-4772-3p was associated with a higher risk of cancer recurrence and death in patients. A connection between decreased expression of exo-miR-6869 and toll-like receptor 4 (TLR4) expression has been observed in serum exosomes from CRC patients. Decreased expression of exo-miR-6869 is related to increased cell division, inflammatory cytokines, activity of the NF-κB pathway, and decreased apoptosis. Therefore, a decrease in serum exo-miR-6869 levels was associated with poor three-year survival rates in CRC patients [112]. In contrast, higher expression of some exo-miRs, such as exo-miR-1229, has been observed in CRC patients compared with healthy individuals, and was associated with lymph node metastasis and poor survival, High levels of exo-miR-19a were associated with CRC progression, and increased liver and lymph node metastasis [113]. In addition, other exo-miRNAs can predict the response to treatment. The applications of CRC-derived exosomes as biomarkers are listed in Table 2.

Exosomal lncRNAs in CRC

Recent studies have shown the role of various lncRNAs in cellular processes, including tumorigenesis and tumor growth, by regulating miRNA expression. For example, urothelial carcinoma-associated 1 (UCA1) was higher in CRC tissue samples, but lower in the serum exosomes of CRC patients compared to healthy individuals [141]. The sensitivity of using the UCA1 level to distinguish CRC patients from healthy individuals was 100%, while the specificity was more than 40%. In addition, UCA1 was found to reduce the expression level of miR-135a, miR-143, miR-214, and miR-1271 [141]. In a study by Liu et al., the level of the lncRNA called colorectal neoplasia differentially expressed–h (CRNDE-h) was higher in CRC cell lines and exosomes derived from patients, compared to healthy individuals. Moreover the high level of CRNDE-h was associated with regional lymph node metastasis, distant metastasis, and poor patient survival. Exosomal CRNDE-h levels were found to be an independent predictive factor for five-year overall survival rates [117]. They also looked at the effect of combining serum exosomal CRNDE-h and CEA levels to improve the prognostic prediction. It was discovered that patients with low levels of both exosomal CRNDE-h and CEA, followed by low CRNDE-h and high CEA, then high exosomal CRNDE-h alone, and finally patients with high levels of both biomarkers had progressively worse overall survival rates [117]. Like lung cancer, exo-GAS5 levels in CRC

were associated with disease progression. GAS5 inhibited the expression of miR-221, which is involved in cell division, migration, and invasion of CRC cells [116]. A study by Oehme et al. demonstrated a decrease in lncRNA HOTTIP expression in CRC patients. Therefore, HOTTIP could be a prognostic biomarker for a poor prognosis in CRC patients [119].

Circular RNAs (circRNA) are a class of ncRNAs with a closed loop-like structure and are highly resistant to exonucleases. Some recent studies have examined the level of exosomal circRNAs in CRC [142]. For example, exosomal-circFMN2 and exosomal-circIFT-80 were both higher in CRC, and were correlated with tumor size, tumor stage, and distant metastasis [140, 143]. However, a human colonic epithelial cell line did not respond to circFMN2 knock-down. Cell proliferation was not reduced by circFMN2 knock-down or enhanced by circFMN2 over-expression. Because normal cells were not affected, it was suggested that circFMN2 could be a possible therapeutic target. Furthermore, knock-down of circIFT80 increased CRC cell apoptosis, but knock-down of circFMN2 had no effect on CRC cell apoptosis. Furthermore, circIFT80 was shown to promote the EMT. CRC cell migration and invasion were increased by exogenous over-expression of circIFT80. CircFMN2 was found to affect the miR-1182/hTERT axis, while circIFT80 affected the miR-1236-3p/HOXB7 axis [140, 143]. The expression of hTERT and HOXB7 was both higher in CRC tissues than in normal tissue. Furthermore, in both cell lines and serum exosomes from CRC patients, there was an inverse association between the expression levels of these circRNAs and their corresponding miR targets. Furthermore, knock-down of circFMN2 and circIFT80 reduced the expression of hTERT and HOXB7, respectively. This effect was counteracted by using a miRNA inhibitor to target their specific miRNA targets. These findings suggest that the exosomal circRNAs circFMN2 and circIFT80 could be used as prognostic biomarkers [64, 143].

Hon et al. studied the role of hsa-circ-000338 in predicting the response to the treatment in CRC patients [138]. The level of exosomes containing hsa-circ-000338 was two times higher in CRC patients showing resistance to 5-FU and FOLFOX (oxaliplatin). According to this study, exosomes containing hsa-circ-0000338 could transmit it to non-resistant cells, thus imparting 5-FU resistance to the CRC cell line. Therefore, exo-hsa-circ-0000338 could be a predictive biomarker for response to treatment in CRC patients [138]. According to a study by Pan et al., exo-hsa-circ-0004771 levels were > 14-fold higher in CRC patients compared with healthy individuals. Exo-hsa-circ-0004771 was associated with disease severity and metastasis and had more than 80% specificity and sensitivity to differentiate CRC patients from healthy controls. Therefore, exo-hsa-circ-0004771 could be a diagnostic biomarker for CRC [139].

Table 2 Role of exosomal ncRNAs in colorectal cancer as biomarkers

ncRNA	Regulation	Function	Mechanism	References
lncRNAs				
CCAL	Up-regulated	Predictive biomarker	Inhibits cancer cell apoptosis and promotes oxaliplatin (Oxa) resistance through activation of β-catenin pathway and direct interaction with human antigen R	[114]
SNHG10	Up-regulated	Prognostic biomarker	Suppresses viability and cytotoxicity of natural killer cells	[115]
GAS5	Down-regulated	Diagnostic and prognostic biomarker	Regulates miR-221 expression which promotes cell proliferation, metastasis and invasion	[116]
CRNDE-h	Up-regulated	Diagnostic and prognostic biomarker	Overexpression of Exo-CRNDE-h was associated with low survival rate in CRC patients	[117]
LNCV6_84003, LNCV6_116109, LNCV_108266, LNCV6_38772, LNCV6_98602, LNCV6_98390	Up-regulated	Diagnostic biomarker	All six lncRNAs were overexpressed significantly in CRC patients compared to healthy controls	[118]
HOTTIP	Down-regulated	Diagnostic and prognostic biomarker	HOTTIP inhibits miR-214 expression and upregulates KPNA3 expression which leads to mitomycin resistance	[119, 120]
UCA1	Down-regulated	Diagnostic biomarker	Leads to cetuximab-resistant, Regulates cell migration through MAPKs pathway	[121]
RPPH1	Up-regulated	Diagnostic and prognostic biomarker	Interacts with β-III tubulin (TUBB3) and induces EMT. Compared to CA199 and CEA has better diagnostic value	[113]
miRNAs				
miR-23b-3p, miR-23a-3p, miR-30b, miR-27a-3p, miR-16, miR-222 miR-27b-3p, miR-30c	Up-regulated	Diagnostic biomarker	Overexpression of these eight miRNAs in exosomes from CRC patients	[122]
miR-96, miR-149	Down-regulated	Diagnostic biomarker	Downregulation of miR-96 and miR-149 was detected in GPC1 + exosomes from CEC patients compared to peritumoral tissues and control plasma	[123]
miR-23a, miR-301a	Up-regulated	Diagnostic biomarker	Both exsosomal miR-23a and miR-301a were upregulated in CRC patients	[124]
miR-92b	Down-regulated	Diagnostic biomarker	Significantly downregulated in stage II CRC patients compared to controls	[105]
miR-125a and miR-320c	Up-regulated	Diagnostic biomarker	Both were overexpressed at early stages of CRC and can be combined with conventional biomarkers to improve CRC diagnosis in early stages	[107]
miR-320d	Up-regulated	Diagnostic biomarker	miR-320d upregulation was associated with the Rab1 signaling pathway and was significantly correlated with metastatic CRC	[110]

Table 2 (continued)

ncRNA	Regulation	Function	Mechanism	References
miR-1229, miR-150, miR-1246, miR-23a, miR-223, let-7a, miR-21	Up-regulated	Diagnostic biomarker	Their overexpression showed high sensitivity in CRC diagnosis in early stages, compared to CA19-9 and CEA	[25]
miR-4772-3p	Down-regulated	Prognostic biomarker	Downregulation in CRC patients treated with FOLFOX adjuvant was correlated with high risk of tumor recurrence	[111]
miR-19a	Up-regulated	Prognostic biomarker	Its overexpression was correlated with high recurrence rate and poor prognosis in CRC patients	[125]
miR-1229	Up-regulated	Prognostic and diagnostic biomarker	Promoting angiogenesis by inhibiting HIPK2 expression	[126]
miR-25-3p	Up-regulated	Prognostic biomarker	Targeting KLF2 and KLF4 and regulating expression of ZO-1, Claudin5, and VEGF promotes angiogenesis in CRC	[127]
miR-21	Up-regulated	Prognostic biomarker	Its overexpression was correlated with liver metastasis and TNM stage in CRC	[128]
miR-146a	Up-regulated	Prognostic biomarker	Targeting Numb and promoting stem-like properties as the major miRNA in CRC stem cells	[129]
miR-6869	Down-regulated	Prognostic biomarker	Targeting toll-like receptor 4 (TLR4) and its downregulation was correlated with poor prognosis in CRC patients	[112]
miR-17, miR-18a, miR-18b	Up-regulated	Prognostic and diagnostic biomarker	Significantly upregulated in CRC plasma exosomes	[106]
miR-20b, miR-19b miR-106a, miR-20a,	Up-regulated		Overexpression was correlated with high risk of tumor relapse and poor response to treatment	[130]
miR-17-5p, miR-92a-3p	Up-regulated	Prognostic biomarker	Overexpression was correlated with pathologic stage of CRC	[131]
miR-1246, miR-96, miR-21, miR-1229	Up-regulated	Predictive biomarker	Expression was associated with chemoresistance in CRC patients and were upregulated through PI3K, FoxO and autophagy pathways	[132]
miR-548c-5p	Down-regulated	Prognostic and diagnostic biomarker	Reduced expression was associated with liver metastasis and was significant in stages III and IV	[133]
miR-6803	Up-regulated	Prognostic and diagnostic biomarker	Overexpression was detected in advanced TNM stages, correlated with liver and lymph node metastasis and reduced disease-free and overall survival	[134]
miR-150	Down-regulated	Prognostic and diagnostic biomarker	Overexpression was correlated with longer survival in CRC patients	[135]
miR-125b	Up-regulated	Prognostic and diagnostic biomarker	Overexpression was correlated with mFOLFOX6 resistance in CRC	[136]
miR-196b	Up-regulated	Prognostic and predictive biomarker	Targeting negative regulator of STAT3, SOCS1/SOCS3 signaling pathway and was correlated with 5-FU resistance in CRC	[137]

circRNA

Table 2 (continued)

ncRNA	Regulation	Function	Mechanism	References
hsa-circ-0067835 (circIFT80)	Up-regulated	Prognostic biomarker	Its silencing can reduce FOLFOX-resistance in CRC cells	[138]
hsa-circ-0004771	Up-regulated	Diagnostic and prognostic bio-marker	Overexpression was detected in CRC patients compared to healthy controls	[139]
hsa-circ-0005100 (circFMN2)	Up-regulated	Prognostic biomarker	It regulates miR-1182/hTERT signaling pathways and leads to tumor progression	[140]
hsa-circ-0000338	Up-regulated	Predictive biomarker	Its silencing can reduce FOLFOX-resistance in CRC cells	[138]

Exosomal lncRNAs in bladder cancer

Bladder cancer is the sixth most common cancer in men worldwide. The diagnosis of bladder cancer relies on the histopathological evaluation of cystoscopic biopsy specimens. The high percentage of false positives or false negatives, high cost, and patient discomfort are the main disadvantages of this approach [101]. Non-invasive biomarkers that can be detected in urine samples, such as bladder tumor antigen (BTA) and nucleus matrix protein 22 (NMP 22) have been used to detect early-stage bladder cancer [144]. However, scientists are still seeking to identify more efficient and less expensive biomarkers for the diagnosis of early-stage bladder cancer. Similar to studies in other cancers, exosomal-ncRNAs are being investigated in bladder cancer as promising diagnostic biomarkers in urine. Higher expression of several lncRNAs, such as PCAT-1, PVT-1, and ANRIL, has been reported in bladder cancer specimens [145]. Abbastabar et al. examined the expression level of these exosomal lncRNAs in patients with bladder cancer. The level of urinary exosomes containing PCAT-1 and ANRIL was significantly higher in patients with bladder cancer compared to healthy individuals. PVT-1 can play an oncogenic role in cancer by interacting with MYC, regulating miRNAs, and participating in DNA rearrangement. However, exosomal PVT-1 in bladder cancer patients was not significantly different from exosomes in healthy controls. However, increased ANIRL and PCAT-1 in exosomes from bladder cancer patients could be valid diagnostic biomarkers [145]. Zheng et al. evaluated exosomal PTENP1 in bladder cancer patients as a diagnostic biomarker [146]. According to this study, exo-PTENP1 could be transmitted to bladder cancer cells, thereby increasing apoptosis, and preventing invasion and migration. Exo-PTENP1 controlled tumor growth in vivo, by regulating the expression of the tumor suppressor PTEN (phosphatase and tensin homolog) by competitively binding to miR-17. Therefore, Zheng et al. suggested that lower exosomal PTENP1 levels could be a biomarker for detecting bladder cancer progression [146]. Berrondo et al. [147] measured the expression of lncRNA HOTAIR in urinary exosomes of patients with bladder cancer. HOTAIR can regulate several genes involved in the EMT, including SNAIL, LAMB3, and LAMC2. HOTAIR has also been associated with cell migration and invasion, and the recurrence of high-grade non-muscle invasive UBC (NMIBC) could be predicted by its high expression. This study showed that urinary exosomes containing HOTAIR could be a diagnostic biomarker in bladder cancer patients. They also identified four additional lncRNAs in their exosomes, including OTX2-AS1, HYMAI, LINC00477, and Loc100506688 [147].

BCYRNI is a lncRNA involved in lymphangiogenesis in bladder cancer [148]. BCYRNI promotes the increased activity of VEGF/VEGFR3 via the hnRNPA1/WNT5A/VEGFR3 axis. Zheng et al. [148] showed that exosomes containing BCYRNI were associated with lymph node metastasis and poor prognosis in bladder cancer patients. They suggested that exo-BCYRNI, in addition to its role as a diagnostic biomarker, could also be an effective therapeutic target. They demonstrated that silencing of exo-BCYRNI suppressed VEGF/VEGFR3 signaling, and prevented lymphangiogenesis and lymph node metastasis in bladder cancer, both in vivo and in vitro [148]. A panel of bladder cancer-derived exosomes was recently studied to identify biomarkers for diagnosis and prediction of relapse. Altogether 11 candidate lncRNAs were screened inside the isolated urinary exosomes in this study, the only highly accurate biomarkers were SNHG16, UBC1, and PCAT-1. The findings of this study also suggested exo-lncRNAs could be accurate biomarkers with greater availability and faster processing for detecting bladder cancer and predicting its recurrence [149].

Exosomal miRNAs in bladder cancer

Recent studies have compared miRNAs in tumor tissue, urinary exosomes, plasma, and white blood cells taken from bladder cancer patients. The results identified 7 hallmark

miRNAs (21-5p, 205-5p, 29b-3p, 200c-3p, 4454, and 200b-3p) with higher expression levels in bladder cancer-derived exosomes [150]. These exosomal miRNAs reflected the molecular profile from the source tumor cells, and could be biomarkers for tumor detection. Studies in recent years have examined the expression level of exosomal miRNAs isolated from bladder cancer patients. For example, one study found that 22 separate exo-miRNAs were increased, while 23 exo-miRNAs were decreased in bladder cancer patient urine samples [151]. In a microarray technique-based study, miR-375 and miR-146a were tested to identify high and low stages of bladder cancer compared to healthy individuals [152]. Significant increases in the expression of five miRNAs (miR-31-5p, miR-155-5p, miR-21-5p, miR-132-3p, and miR-15a-5p) in exosomes from bladder cancer patients were reported compared to healthy controls. Of these, exo-miR-21-5p has shown potential as a diagnostic biomarker in bladder cancer [153]. Some exosomal miRNAs have also been studied as prognostic and predictive biomarkers in bladder cancer. For example, low expression of exo-miR-103a-3p and exo-miR-486-3p were associated with worse patient survival [154]. According to current studies, some exosomal miRNAs can induce resistance to cytotoxic drugs. For example, exo-miR-155 promoted resistance to paclitaxel and doxorubicin in a variety of cancers, including bladder cancer [155]. One study by Fanous et al. [156] demonstrated the role of exosomal miRNAs in causing chemotherapy drug resistance in bladder cancer, including gemcitabine and cisplatin. In this study, a total of 759 exosomal miRNAs were screened, of which 16 showed significant changes in expression, which were directly related to drug resistance [156]. While there have been few studies of exosomal miRNAs as treatment response prediction markers, they can provide information about their originating cells, such as the molecular target, degree of malignancy, and potential therapy resistance. As a result, exosomal miRNA biomarkers may be used to monitor and even to reduce tumor resistance, to achieve a personalized therapy. Some studies on the role of bladder cancer-derived exosomal miRNAs as biomarkers are discussed in ref [157].

Gastric cancer

Gastric cancer is the fourth most common malignancy globally and the second leading cause of cancer death in the world, and is still considered a severe challenge to oncologists. Early detection of gastric cancer significantly increases the chance of effective treatment and consequently prolongs the survival rate of patients [158]. Conventional invasive biopsy procedures for diagnosis are often painful and have low sensitivity. The likelihood of precursor or premalignant lesions occurring in gastric cancer makes it challenging to diagnose gastric cancer using non-invasive biomarkers. These predisposing lesions include *Helicobacter pylori* infection, chronic atrophic gastritis, and intestinal metaplasia [159]. Therefore, investigating gastric tumor-derived exosomes could provide a non-invasive diagnostic method with a low error rate. Exosomal RNAs, in particular, are promising candidates for this purpose [160, 161]. In recent studies, exosomal lncRNAs, such as HOTTIP [162], ZFAS1 [163], and LINC00152 [164], were found to be markedly increased in patients with gastric cancer compared to healthy individuals. A comprehensive study by Lin et al. [165] used RNA-Seq techniques to screen novel potential biomarkers. Due to the importance of early stage diagnosis, the analysis was performed on early gastric cancer (EGC) specimens. Exosomal RNA profiles were determined in EGC samples, and 79 separate exo-RNAs showed a pattern of increased expression in patient samples compared to controls. In addition, this study performed RNA-seq analysis on four gastric cancer cell lines and found an increased expression of 289 separate exo-RNAs. Due to the commonality of lncRNA-UEGC1 between patient samples and cell lines, the follow on study focused on UEGC1. The results showed that almost all of the plasma UEGC1 was carried inside exosomes, and thus avoided degradation by RNase. Because UEGC1 was more accurate than CEA (a non-invasion diagnostic biomarker for gastric cancer), Lin et al. suggested that exo-UEGC1 could be a non-invasive, stable, and highly sensitive diagnostic biomarker for ECG [165].

Some recent studies have focused on the role of exosomal lncRNAs in the progression, angiogenesis, metastasis, and drug resistance of gastric cancer. For example, exosomes containing lncRNA HEIH secreted from gastric cancer cells could transform normal gastric cells into a malignant phenotype [166]. Exosomal miR-221 [167] and exo-miR-15b-3p [168] could both promote the migration and invasion of gastric cancer cells by targeting caspase-3 and -9, and inhibiting apoptosis. Exosomes could transport miR-130a from gastric cancer, to target c-MYB and increase angiogenesis in gastric tumors [169]. In general, tumor-derived exosomes can transfer ncRNAs and appear to play a key role in tumorigenesis and metastasis in gastric cancer, suggesting they could be biomarkers and practical therapeutic targets.

Recently, exosomal lncRNAs have been considered as clinical diagnostic and prognostic biomarkers, and therapeutic targets to reverse drug resistance. In a multi-phase study in over 800 gastric cancer patients, lncRNA GC1 was identified as a valid predictive biomarker [170]. In addition, the serum exosomes of gastric cancer patients showed significantly higher expression of miR-106a-5p and miR-19b-3p. These exo-miRNAs showed better sensitivity and specificity compared to CEA and AFP (accepted diagnostic biomarkers for gastric cancer), and could be non-invasive biomarkers for EGC [171]. Exo-LncRNA GNAQ-6 [172] has also recently

been suggested as a new diagnostic biomarker. In addition to diagnostic biomarkers, exo-miRNAs could be used to predict metastasis and recurrence of gastric cancer. For example, Kumata et al. [173] found that the expression level of exo-miR-23b was directly related to tumor size, liver metastasis, depth of invasion, and TNM stage. They suggested that exo-miR-23b levels in gastric cancer could predict patient overall survival [173].

Peritoneal metastasis is the most common site of metastasis in gastric cancer, and is usually associated with short survival rates. In patients with peritoneal metastasis, the expression levels of exo-miR 1225-e5p, exo-miR-21, and exo-miR-29 were all significantly altered compared with healthy individuals, or those with localized EGC [174]. According to a study by Yang et al. [175], high levels of exosomal miR-423-5p was associated with a poor prognosis in patients with gastric cancer. Exosome-derived PIWI (P-element induced wimpy testis)-interacting RNAs (piRNAs) were found to be more frequent than cell miRNAs by Ge and colleagues [176], and could be employed as non-invasive diagnostic biomarkers with significant specificity and sensitivity. These exosomal ncRNAs can be combined with other biomarkers for detecting gastric cancer more

Table 3 Exosomal ncRNAs in gastric cancer

ncRNA	Regulation	Function	References
miRNA			
let-7	Up-regulated	Metastasis	[177]
miR-221	Up-regulated	Proliferation and migration	[167]
miR-18a-3p and miR-4286	Up-regulated	Biomarker for *H. pylori*-associated GC diagnosis; promotes cell proliferation and motility by targeting BZRAP1	[178]
miR-15b-3p	Up-regulated	Migration and invasion	[168]
miR-196a-1	UP-regulated	Migration and invasion	[179]
miR-130a	Up-regulated	Angiogenesis	[169]
miR-106	Up-regulated	Peritoneal metastasis induction	[180]
miR-423-5p	Up-regulated	Lymph node metastasis	[175]
miR-301a-3p	Up-regulated	Diagnosis biomarker, promote metastasis through HIF-1α signaling in hypoxia conditions	[181]
miR-27a	Up-regulated	Transformation of local fibroblasts into CAFs	[182]
miR-522	Up-regulated	Promotes acquired chemoresistance	[183]
miRNA-34 and miR-139	Down-regulated	Suppress tumor progression	[184]
MiR-106a-5p MiR-19b-3p	Up-regulated Up-regulated	Diagnostic biomarker, Related to lymphatic metastasis and overexpressed in stages III and IV	[171]
miRNA-107	Up-regulated	Induction of myeloid-derived suppressor cells	[185]
miR-1246	Up-regulated	Biomarker for early diagnosis	[186]
miR-21	Up-regulated	Induces cisplatin resistance	[187]
miR-155-5p	Up-regulated	Induces paclitaxel resistance	[188]
LncRNA, circRNA			
lncHEIH	Up-regulated	Malignant transformation	[23]
lnc-ZFAS1	Up-regulated	Proliferation and migration	[163]
lnc01559	Down-regulated	Suppresses proliferation, migration, and stemness	[189]
circ-SHKBP1	Up-regulated	Targets miR-582-3p to enhance VEGF signaling	[190]
PCGEM1	Up-regulated	Metastasis by increasing levels of SNAI1	[191]
circPRRX1	Up-regulated	Induces doxorubicin-resistance	[192]
HOTTIP	Up-regulated	Diagnostic and prognostic biomarker, promoting cisplatin resistance, inhibiting miR-218 that targets HMGA1	[193]
LncRNA-GC1	Up-regulated	Diagnostic biomarker for detecting GC in early stages	[30]
LncUEGC1	Up-regulated	Diagnostic biomarker for EGC, higher accuracy than carcinoembryonic antigen	[165]
Lnc-GNAQ-6	Down-regulated	Diagnostic biomarker, and was not dependent to traditional biomarker such as CEA, CA72-4, and CA19-9)	[172]
Linc-00152	Down-regulated	Diagnostic biomarker for EGC, a novel blood-based biomarker, encapsulated in exosomes	[194]

specifically. Recent studies on the role of exosomal ncR-NAs in gastric cancer are exhibited in Table 3.

Liver cancer

Hepatocellular carcinoma (HCC) is one of the most deadly malignancies, and its high mortality rate and resistance to treatment represents a severe challenge [195]. Recent studies have shown that cancer cells acquire a more malignant phenotype as infiltration progresses, and exosomes appear to contribute to the progression and metastasis of HCC by transferring their contents from premalignant cells to cancer cells [196]. According to a study by Liu et al. [197], exosomes derived from liver cancer increase the invasion and metastasis of cancer cells by transferring miR-25-5p. High expression of miR-25-5p reduces the expression of leucine-rich repeat-containing 7 (LRRC7). LRRC7 is involved in intercellular attachment and therefore reduced expression leads to increased cell motility. Moreover, increased exosomal miR-25-5p levels in HCC were associated with cancer progression and could be a prognostic biomarker [197].

Highly-metastatic HCC cells have a stronger ability to convert normal fibroblasts into cancer-associated fibroblasts (CAFs) in the lung metastatic niche, according to Fang et al. [198]. They found that highly-metastatic HCC cells could release exosomal miR-1247-3p, which specifically targeted B4GALT3 in fibroblasts, and activated β1 integrin–NF-κB signaling. Activated CAFs secrete pro-inflammatory cytokines, including IL-6 and IL-8, which promote cancer growth. Exosomal miR-1247-3p levels in serum were linked to lung metastasis in HCC patients, according to clinical studies. Therefore, tumor-derived exosomes can mediate intercellular interactions between tumor cells and fibroblasts to regulate HCC lung metastasis, and could be prospective targets for prevention of metastasis and improved therapy [198]. Tumor-derived exosomes affect cell behavior by carrying a variety of ncRNAs as epigenetic factors. NcRNAs can alter the tumor phenotype, and exosomes act as their transporters. Conversely, ncRNAs also appear to affect the secretion and regulation of exosomes. For example, Cao et al. [199] found that the lncRNA HULC was not only contained in exosomes to modulate metastasis and TNM in HCC, but it also increased exosome secretion in HCC cells.

Ovarian cancer

Ovarian cancer often has a poor prognosis and a high mortality rate [200]. Therefore, the identification of diagnostic biomarkers for ovarian cancer is important to save patients' lives and increase survival rates. The recent adoption of exosomes as biomarkers has led researchers to study ovarian cancer-derived exosomal ncRNAs, particularly exo-miRNAs. For example, increased expression levels of exo-miR-200c and exo-miR-214 in ovarian cancer were found compared to control samples, suggesting they could be used as diagnostic biomarkers [200]. A study by Vaksman et al. [201] also examined the expression of exosomal miRNAs in ovarian cancer patients. They found that the expression levels of exo-miR-23b, exo-miR-21b, and exo-miR-29a were associated with lower survival rates. Interestingly, ovarian cancer exosomes could transfer miR-21 from stromal cells to cancer cells, leading to the induction of therapeutic resistance. Therefore, exo-miR-21 has been suggested as a predictive biomarker for treatment response. Furthermore, when the miRNA profiles of exosomes acquired from patients were compared to tumor tissue profiles from the same patient, similar miRNAs were found, indicating that the exosomal miRNA profile might be used as a biomarker. In addition, Ma and colleagues [202] showed that tumor-derived exo-circRNA051239 promoted the division and migration of epithelial ovarian cancer cells. They found that exo-circRNA051239 expression levels were significantly higher in patients with metastatic ovarian cancer. Therefore, increasing levels during the course of the disease could be a warning signal for metastasis [202]. In previous studies, the expression profile of exosomal miRNAs in ovarian cancer has been investigated. Some exosomal miRNAs were found to elevated in ovarian cancer versus healthy controls, were associated with invasion or metastasis, and had the potential to be used as diagnostic biomarkers. These exosomal miRNAs are summarized in Table 4.

Other cancers

The role of exosomal ncRNAs in kidney and prostate cancer has also been investigated [224]. Some exosomal miRNAs, including exo-miR-151, exo-miR-650, and exo-miR-29a, were found to be involved in metastasis and invasion [225], while others have been reported as diagnostic biomarkers (Fig. 4) [36]. Studies on the role of exo-lncRNAs as biomarkers in kidney and prostate cancer are limited. According to Qu et al. [226] exo-lncARSR increased the expression of AXL and c-MET in RCC cells by competitively binding to miR-34/miR-449, resulting in sunitinib resistance. Exosomal lncRNAs have a crucial role in tumor biology, and further research is needed to fully understand their function in renal cancer. Moreover, Xiao et al. [227]. discovered that circ400068 was elevated in exosomes secreted from RCC cells using circRNA expression array data. CircRNAs in exosomes produced from RCC cells have only been reported in a few studies so far, so further research is needed.

Guo et al. [228] examined exosomes derived from pancreatic tumors. These exosomes had high levels of

Table 4 Ovarian cancer derived exosomal miRNAs as diagnostic biomarkers

miRNA	Regulation	Function	Mechanism of action	References
miR-214	Up-regulated	Diagnostic biomarker	Inhibit LHX6 and malignancy progression	[203]
miR-608	Up-regulated	Diagnostic biomarker	Promote migration through JAK/STAT pathway	[204]
miR-205	Up-regulated	Diagnostic biomarker	Promotes metastasis via PTEN-AKT pathway and angiogenesis	[205]
miR-147	Up-regulated	Diagnostic biomarker	–	[204]
miR-140	Up-regulated	Diagnostic biomarker	Induces angiogenesis through Wnt/β-catenin signaling pathway	[206, 207]
miR-222-3p	Up-regulated	Diagnostic biomarker	Induces polarization of M2 phenotype	[208]
miR-634	Down-regulated	Diagnostic biomarker	Cisplatin resistance regulates cell cycle through Ras-MAPK pathways	[209]
miR-485-5p	Up-regulated	Diagnostic biomarker	Contributes to cisplatin resistance	[210]
miR-206	Up-regulated	Diagnostic biomarker	Regulates KRT80 through MEK/ERK pathway	[211]
miR-149	Up-regulated	Diagnostic biomarker	Induces cisplatin resistance through TIMP2 and CDKN1A pathways	[212]
miR-612	Up-regulated	Diagnostic biomarker	–	[204]
miR-202	Down-regulated	Diagnostic biomarker	Suppressed cell proliferation and migration via regulation HOXB2	[213]
miR-373	Up-regulated	Diagnostic biomarker	Overexpression in lymph node metastasis	[214]
miR-324-3p	Down-regulated	Diagnostic biomarker	Targets WNK2/RAS pathway and suppresses tumor invasion	[215]
miR-103	Up-regulated	Diagnostic biomarker	–	[204]
miR-200a	Up-regulated	Promotes invasion	Overexpression in lymph node metastasis	[214, 216]
miR-21	Up-regulated	Diagnostic biomarker	Inhibits cyclin-dependent kinase 6 (CDK6) and was correlated with increase in tumor size and volume	[204, 217]
miR141	Up-regulated	Diagnostic biomarker	Targets p38α and promotes cell proliferation	[218]
let-7e	Up-regulated	Promotes invasion	–	[216]
miR-642	Down-regulated	Diagnostic biomarker	Downregulation was correlated with chemotherapy resistance in ovarian cancer	[204, 219]
miR-18a	Down-regulated	Diagnostic biomarker	Downregulation was associated with cisplatin resistance, cell proliferation and metastasis	[220]
miR-649	Up-regulated	Diagnostic biomarker	–	[204]
miR-527	Down-regulated	Diagnostic biomarker	Downregulation was correlated with cisplatin resistance through YWHAZ signaling and it was sponged by circ_C20orf11	[221]
miR-4732-5p	Up-regulated	Diagnostic biomarker	Overexpression was associated with tumor progression in ovarian cancer	[222]
miR-593	Up-regulated	Diagnostic biomarker	Correlated with cisplatin resistance, metastasis and invasion	[223]

lncRNA-UCA1, which was associated with poor patient survival. In addition, UCA1 promoted tumor growth and angiogenesis in pancreatic cancer cell lines and in a rat model. UCA1 acts as a sponge for miR-96-5p and inhibits its expression. miR-96-5p targets AMOTL2, a protein involved in the formation of new blood vessels, and suppresses its expression. Overall, exosomal UCA1 promoted angiogenesis and tumor growth by regulating miR-96-5p expression, and could be a predictive biomarker for metastatic pancreatic cancer.

Challenges and advantages of tumor derived exosomes

Many studies based on tumor-derived ncRNAs, including solid and hematological tumors, have shown their role as factors involved in tumor progression. The role of exosomes in tumors can be described as a double-edged sword. Sometimes exosomes can prevent the division and invasion of tumor cells by transferring tumor suppressor genes to tumor cells, which shows the potential of using them for cancer treatment and therapeutic vectors. Moreover, tumor-derived exosomes can accelerate the process of tumorigenesis and invasion and drug resistance by transferring oncogenes to non-cancerous or pre-cancerous cells. From this aspect, tumor-derived exosomes can be considered promising therapeutic targets. However, most recent studies have focused on their potential as diagnostic biomarkers. So far, many studies have been conducted on the contents of exosomes derived from tumors and have shown that countless exosomal ncRNAs are dysregulated in all types of cancers. For several reasons, tumor-derived ncRNA exosomes could be ideal diagnostic and prognostic biomarkers for cancer studies. Firstly, the specificity of the exosomal contents reflects the contents of the source cells. The second reason is the high sensitivity of these EVs. Finally, according to the results of studies, cancer patients have higher levels of circulating exosomes than healthy people. Furthermore, functional ncRNAs are always found in exosomes. When compared to free
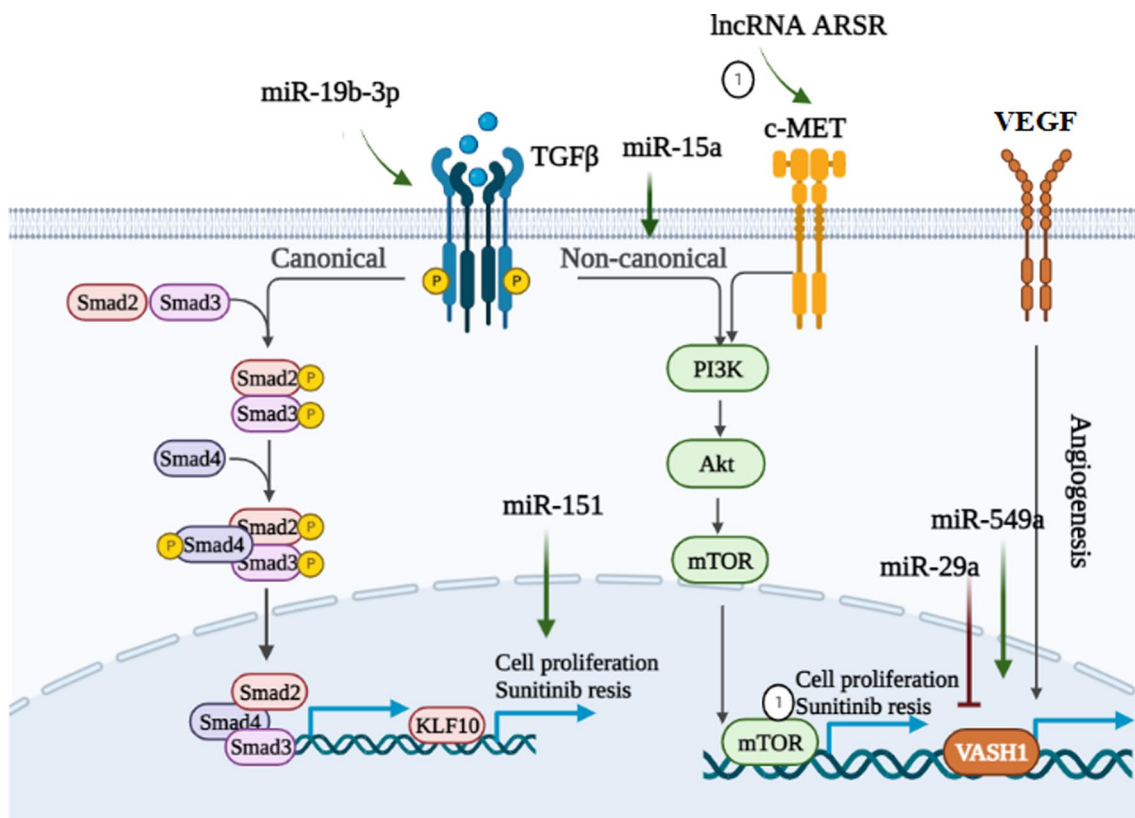
Fig. 4 Exosomal ncRNAs in kidney cancer. miR-19-3b, by activating the TGF/SMAD3,2/KLF10 pathway, leads to the inhibition of cell division and drug resistance (sunitinib resistance). In addition, miR-15a enhances cell division in cancer cells by activating the non-canonical TGF-beta/PI3K/AKT pathway. LncRNA ARSR activates the PI3K/AKT pathway by activating the c-MET receptor, leading to drug resistance. While miR-29a inhibits angiogenesis, miR-549 leads to increased angiogenesis. *KLF10* Kruppel Like Factor 10, Vasohibin 1, *VEGF* vascular endothelial growth factors

ncRNAs in bodily fluids, exosomes will give greater sensitivity for ncRNA identification in clinical samples [229]. The next factor is the stability of the exosomal contents. As mentioned earlier, the exosome membrane can protect ncRNAs from RNase activity. In addition, the level of ncRNAs in exosomes remains constant despite exposure to extreme stress conditions. Another advantage mentioned earlier is the easy availability of exosomes in fluids throughout the body. Therefore, it seems that continued efforts in identifying biomarkers based on exosomes derived from tumors will be valuable and promising. However, many challenges still limit the use of exosomal ncRNAs in clinical applications. So far there is no Food and Drug Administration (FDA)-approved exosomal ncRNA biomarker for cancers. Nevertheless, some possible exosomal ncRNAs which have been investigated in human studies or clinical trials are listed in Table 5.

From an investigative standpoint, the activities of ncRNAs reported in current investigations are often based on experiments involving exogenous ncRNA overexpression in vitro (such as transfecting miRNA mimics) or ncRNA knockdown in overexpressing cell lines. Therefore, it is still unclear if the body generates a comparable number of ncRNAs which promote the same activities. In addition, many studies that have reported ncRNAs function and mechanism of action have only been conducted in vitro and on cultured cells. In these methods, pure and prepared exosomes are incubated with recipient cells. It is unclear whether the applied exosomal ncRNAs correspond to the amounts found in physiological conditions. Exogenous exosomes may exaggerate the function of native exosomal ncRNAs, although the role of exosomal ncRNAs in tumor progression and invasion has been proven. To use exosomal ncRNAs as key biomarkers in clinical applications, ncRNAs that are consistently dysregulated in exosomes should be identified [230]. Next-generation sequencing (NGS) and RNA-seq techniques are powerful tools for profiling and analyzing these biomolecules. In any case, the varying origin of circulating exosomes limits the accurate detection of patient-specific exosomes in peripheral blood samples. Other exosomes released from normal cells could reduce the concentration of tumor-derived exosomes, leading to a decrease in the actual contribution of tumor-associated ncRNAs in sequencing libraries [231]. Most importantly, there is still no standardized and fully validated method for the extraction

Table 5 Samples of conducted clinical trials around the world about exosomal non-coding RNAs as diagnostic biomarkers in cancers

Cancers	Sample	Exosomal lncRNA	Findings	Cohort number	References
Lung cancer	Serum	–	Not reported	1000 samples as actual enrollment	clinicaltrials.gov (NCT03830619)
Prostate Cancer (PCA)	Urine	–	Not reported	500 samples as actual enrollment	clinicaltrials.gov (NCT04661176)
		lncRNA-p21	Specificity, sensitivity, and AUC of LincRNA-21 was 63%, 67%, and 0.663, respectively; High levels of exosomal lincRNA-p21 in PCA patients ($P=0.016$)	PCA: 30 Benign prostatic hyperplasia: 49	[234]
		PCA3	Normalized AUC of exosomal PCA3 values to PSA was 0.64; Exosomal PCA3 AUC after DRE was 0.52	Pairs before and after digital rectal examination: 30	[235]
Laryngeal squamous cell carcinoma (LSCC)	Serum	HOTAIR	Specificity, sensitivity, and AUC of HOTAIR was 57.1%, 92.3%, and 0.727, respectively; Along with miR-21: Specificity, sensitivity, and AUC was 73.5%, 94.2%, and 0.876, respectively; High levels of HOTAIR ($P=0.0264$) and elevated TNM stage and metastasis of lymphatic node in patients ($P<0.01$)	LSCC: 49 Vocal cord polyps: 52	[236]
Urothelial bladder cancer (UBC)	Urine	MALAT-1 HOTAIR HYMA1 HOX-AS-2 LOC100506688 OTX2-AS1 LincRoR LINC00477	High mentioned exosomal lncRNAs in UBC patients ($P<0.01$)	Phase 1: UBC: 8, Controls: 5 Phase 2: UBC: 10, Controls: 7	[147]

Table 5 (continued)

Cancers	Sample	Exosomal lncRNA	Findings	Cohort number	References
Colorectal cancer (CRC)	Serum	CRNDE-h	Sensitivity, Specificity, and AUC of CRNDE-h was 70.3%, 94.4%, and 0.892, respectively; High levels of exosomal CRNDE-h in CRC patients ($P < 0.01$); Elevated metastasis grade of lymph node ($P = 0.019$); Shorter overall survival associated with high exosomal CRNDE-h levels	Controls: 80 Hyperplastic polyp: 80 Inflammatory bowel disease: 80 Colorectal adenomas: 80 CRC: 148	[117]
		ZFAS1	Sensitivity, Specificity, and AUC of ZFAS1 was 80%, 75.7%, and 0.837, respectively; High levels of exosomal ZFAS1 in patients ($P < 0.01$); High TNM stage ($P = 0.025$) and lymphatic metastasis ($P = 0.002$)	Controls: 37 CRC: 40	[163]
		BCAR4	In training cohort AUC was high (0.936) and in test cohort the combination of two mRNA, KRTAP5-4 and MAGEA with BCAR4 AUC was 0.877; Down-regulated exosomal BCAR4 in CRC patients	Colorectal adenomas: 20 Controls: 76 CRC: 76	[237]
Non-small cell lung cancer (NSCLC)	Serum	MALAT-1	Sensitivity, Specificity, and AUC was 60.1%, 80.9%, and 0.703, respectively; High levels of exosomal MALAT-1 in patients; Increased TNM stage and metastasis of lymphatic nodes ($P < 0.001$)	Controls: 30 NSCLC: 77	[68]
Cervical cancer (CC)	Cervico-vaginal lavage	MEG-3H MALAT1 OTAIR	High levels of exosomal HOTAIR and MALAT1 Low exosomal MEG3 levels in CC patients compared to controls	HPV⁻ controls: 30 HPV⁺ controls: 30 CC: 30	[237]

and isolation of exosomes, which was discussed in the previous sections. Exosome separation procedures differ between studies, and purity is difficult to maintain within a particular range; these issues may impact the precision and reproducibility of NGS or other exosome study outcomes.

The small amounts of RNA extracted from exosomes compared to tissues and cells are among the limitations of the isolation methods. Therefore, ultra-sensitive commercial kits are needed to achieve accurate and sufficient measurements. Apart from the high price of these kits, each kit with a different brand produces a different quantity and quality of the product, which can ultimately affect the test results. That is why, to date, finding techniques for pure exosome isolation and in sufficient quantities is the most crucial step before tumor-derived exosomes can translate into clinical applications.

Another obstacle is the contamination of exosomes collected from blood and plasma with extracellular vesicles derived from non-tumor cells. How to identify and enrich tumor-derived exosomes from the complex microenvironment is another problem preventing their clinical use. The expression of specific proteins on the cell surface provides a suitable method for their isolation with the help of specific antibodies [232]. It has been shown that the epithelial cell adhesion molecule (EpCAM) may be employed as a marker to identify epithelium-derived extracellular vesicles from CRC patient blood samples via immunoaffinity capture. Rupp et al. [233], on the other hand, found that EpCAM may be cleaved from exosomes by serum metalloproteinases, which could impede tumor exosome enrichment by immune-affinity isolation in breast cancer. More research is needed to identify and develop specific and stable indicators for exosome enrichment. Furthermore, while the stability of the exosome contents allows them to be used in gene therapy, further study is needed to confirm that exosomes harboring therapeutic ncRNAs can safely evade the immune system and precisely home to malignant sites.

Conclusion

In both normal and pathological conditions, exosomes can mediate communication between the same or different cell types, and with their surroundings. Tumor-derived exosomes are gaining traction as a likely mode of communication between malignant cells and the tumor microenvironment, with implications for tumor growth and metastasis. The data gathered thus far employing analysis of tumor-derived exosomes as possible biomarkers for cancer diagnosis and prognosis has provided much information, but further study is still needed. In the near future, the clinical use of tumor-derived exosomes is expected to create a new window for cancer diagnosis, management and therapy.

Data availability Enquiries about data availability should be directed to the authors.

Declaration

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