Abstract. Multiple studies have demonstrated chemoresistance in multiple types of tumor, which limits the effectiveness of cancer treatments. Chemoresistance often contributes to cancer relapse. Non-coding RNAs, are a group of regulatory RNAs, that are involved in tumor drug resistance. Exosomes, membranous vesicles secreted by cells, are reported to mediate cell-to-cell communication, including in cancer. Furthermore, exosomal non-coding RNAs have been reported to mediate chemoresistance via exchange of biological information. In the present review, the main roles of exosomal non-coding RNAs, including micro(mi) RNAs, long non-coding (lnc) RNAs, and circular (circ) RNAs in cancer are described and their potential roles in chemoresistance in various types of cancer are also discussed.

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1. Introduction

Cancer is a leading cause of death, with increasing incidence and mortality rates, worldwide. Globally, there were an estimated 18.1 million new cancer cases and 9.6 million cancer-associated deaths in 2018. More than 50% of the cancer-associated deaths occurred in Asia (1,2). Effective chemotherapy is beneficial against cancer; however, the development of chemoresistance, whether intrinsic or acquired, is the primary concern to ensure good outcomes, and contributes to distant metastasis, tumor recurrence, and disease deterioration, resulting in cancer progression (3). Chemoresistance may result from various factors, including increased drug efflux pumps, resistance to apoptosis, DNA repair defects, and mutations affecting drug targets (4-7). Thus, it is crucial to identify mechanisms underlying chemotherapy to improve cancer outcomes.

Advances in whole genome and transcriptome sequencing technologies have revealed that non-coding (nc) RNAs modulate disease pathogenesis at the cellular and molecular levels (8). ncRNAs include microRNAs (miRNA/miR), long non-coding (Inc) RNAs, circular (circ) RNAs, small nuclear RNAs, small nucleolar RNAs, small interfering RNAs, and piwi-interacting RNA. Of these, miRNAs, lncRNAs, and circRNAs are known to regulate cancer cell proliferation, invasion and metastases, at the transcriptional and post-transcriptional levels (9). Recent studies have shown that ncRNAs was associated with cancer cell chemoresistance. For example, GBCDRlnc1, a lncRNA, was reported to induce chemoresistance in gallbladder cancer cells by interacting with phosphoglycerate kinase 1 and upregulating autophagy-related gene levels (10). CRIM1, a circRNA, has been shown to promote nasopharyngeal cancer metastasis and docetaxel chemoresistance by competitively binding Forkhead box Q1 (11). While these findings show that ncRNAs may modulate cancer chemotherapy, the underlying mechanisms are unclear.

Exosomes, which are 30-100 nm in diameter, are nanoscale membrane vesicles derived from endosomal multivesicular bodies released by various cell types, including immune cells, neurons, mesenchymal stem cells, Schwann cells and epithelial cells (12) and have been associated with cancer growth, metastasis and chemoresistance (13-15). Exosomes carry various cargo, including DNAs, RNAs and proteins, that are involved in the exchange of genetic information between donor and recipient cells in tumor microenvironments, which may transmit drug resistance (13,16). In the present review, research on exosomal ncRNAs in different types of cancer,
will be discussed, with the aim to highlight their role in cancer treatment.

2. Non-coding RNAs: Definition, features, biogenesis, and functions

Non-coding RNAs comprise ~98% of the human genome, which was once considered to be transcriptional noise (17). Extensive research has revealed that ncRNAs regulate various molecular processes and human diseases (18).

miRNAs are small ncRNAs, comprised of 20-22 nucleotides in length, excised from 60-110 nucleotide foldback RNA precursor structures (19) and are widely expressed in various types of cancer, including breast, gastric, and colorectal cancer, and have been associated with prognosis (20-22).

IncRNAs, which are >200 nucleotides in length, do not encode protein (23), but regulate transcription in cis or trans by modulating mRNA processing, post-transcriptional control, protein activity, and organization of nuclear domains (24). Advances in next-generation sequencing have revealed that IncRNA dysregulation has been associated with tumorigenesis, cancer growth, invasion, autophagy, and chemoresistance (25-28).

circRNAs are single-stranded covalently closed RNA molecules, that were first identified in RNA viruses in 1976 using electron microscopy (29). circRNAs fall into four different types: Exon circRNAs, circular intronic RNAs, exon-intron circRNAs, and intergenic circRNAs or fusion circRNAs (30-32). circRNAs are protected from RNase digestion, as they lack free 5' and 3' structures, therefore they are more stable than linear RNAs (33). Functionally, circRNAs modulate gene expression transcriptionally and post-transcriptionally, in physiological and pathological contexts, primarily by acting as miRNA sponges. For example, circ-TCF4.85 has been reported to promote hepatocellular carcinoma (HCC) development by competitively binding to miR-486-5p (34). Hsa_circ_0091570 knockdown significantly enhanced cell proliferation and migration, and inhibited apoptosis in HCC by sponging miR-1307 (35).

3. Exosomes: Origins, biogenesis, and functions

Exosomes were first described in 1983, as vesicles with a 30-100 nm diameter (36-38). Exosomes mainly originate from multivesicular bodies, through membrane invagination. This process produces intraluminal vesicles under the control of the Endosomal Sorting Complex Required for Transport proteins (39). The main surface exosomal markers are CD9, CD81, CD82, and TSG101 (40). Exosomes are released by various cell types, including T-cells, B-cells, dendritic cells, and mesenchymal stem cells (MSCs), and have been found to be enriched in various body fluids, including serum, plasma, saliva, milk, urine, and cerebrospinal fluid (41-43). Exosomes are involved in intercellular communication under physiological and pathological conditions (44). They can transfer active components like DNA, RNA (coding and non-coding) and proteins from donor to recipient cells, thereby exerting regulatory effects on them (45) (Fig. 1). Tumor-derived exosomes may contribute to tumorigenesis, metastasis, tumor microenvironments, and chemoresistance (46,47). However, the exact mechanisms by which exosomes act in tumors requires further investigation.

4. Significance of exo-miRNAs in cancer chemoresistance

There is an increasing number of studies which have shown that exosomes contain specific miRNAs in response to cancer therapy, resulting in chemoresistance or chemosensitivity in body fluids (48,49) (Table I). Exosomes have been found to transfer miR-196a to recipient cells, promoting cisplatin resistance by sponging CDKN1B and ING5 in plasma and tissues from patients with head and neck cancer (50). Exosomal miR-1238 derived from resistant cancer cells could confer drug resistance to sensitive cells by activating the EGFR-Pt3-Akt-mTOR signaling pathway (51). In tumors from the digestive system, miR-374a-5p was found to be upregulated in the serum from patients with gastric cancer and was associated with poor prognosis (52). miR-374a-5p suppressed apoptosis and increased the expression of multi-drug resistant and topoisomerase II by negatively regulating its target gene, Neurod1. In addition, inhibition of exosome-mediated miR-374a-5p activity may re-sensitize gastric cancer cells to oxaliplatin (52). Reduced miR-744 expression levels were reported in the exosomes from serum and tissues in patients with HCC (53,54). PAX2 was found to be upregulated in HCC tissue and was a miR-744 target. Knockdown and overexpression functional assays found that HepG2-resistant cells treated with miR-744-overexpressing exosomes were more sensitive to sorafenib. Treating HCC cells with exosomes from mature adipocytes transferred miR-23a/b to them, conferring 5-fluorouracil resistance and an aggressive phenotype. These findings indicated that exosomal miR-744 or miR-23a/b are potential HCC biomarkers (53,54). miR-196b-5p promoted chemoresistance to 5-fluorouracil by targeting negative regulators of SOCS (suppressor of cytokine signaling)-1 and -3 in colorectal cancer, activating the STAT3 signaling pathway. In addition, miR-196b-5p expression in serum exosomes from patients with colorectal cancer was markedly higher compared with that in healthy controls (55).

Gene function and bioinformatics analyses revealed that miR-23a-3p, miR-27a-3p, miR-30a-5p, and miR-320a were markedly upregulated in exosomes derived from adriamycin-resistant cells compared with that in parental breast cancer cells (56). These miRNAs may contribute to chemoresistance via multiple signaling pathways, including the MAPK, and Wnt signaling pathways (56). Furthermore, 14 miRNAs were found to be significantly elevated in oxaliplatin/5-fluorouracil resistant colorectal cancer cells compared with that in the control parental cells (49). Of these, miR-21-5p, miR-1246, miR-1229-5p, miR-135b, miR-425, and miR-96-5p were highly abundant in exosomes from the resistant cells. In addition, exosomal miR-21-5p, miR-1246, miR-1229-5p and miR-96-5p levels in the serum of patients with colorectal cancer (CRC) who were chemoresistant were markedly higher compared with that in patients who were chemosensitive. Notably, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analysis revealed that these miRNAs were enriched in the PI3K-AKT, FOXO, and autophagy pathways. These 4 exosomal miRNAs could be potential biomarkers for chemoresistance restoration in colorectal cancer (49). Signaling pathways have...
been found to be involved in miRNA-mediated chemoresistance via tumor exosomes. For example, exosome-mediated transfer of miR-21 promoted cisplatin resistance via the PTEN/PI3K/AKT signaling pathway (57). Exosomal transfer of miR-142-3p from bone marrow-derived MSCs suppressed Numb expression, activating the Notch signaling pathway (58).

Intercellular communication was found to be initiated by surface interactions between circulating exosomes and transmembrane molecules expressed on target cells. The release and uptake of exosomes, containing miRNAs, are a crucial form of cell-cell communication in tumors, as cells acquire malignant phenotypes by engulfing tumor-derived oncogenic factors in the exosomes (59). In addition to cancer cells, cancer-associated fibroblasts (CAF) are intrinsically resistant and contribute to cancer cell chemoresistance (60). CAF-derived miR-21 was reported to be significantly upregulated in ovarian cancer cells. Exosomes carrying miR-21 from CAFs to recipient cells conferred chemoresistance and aggressive phenotypes (61). Furthermore, as CAFs are intrinsically resistant to cisplatin, their exosomes accelerated resistance (50). CAF-derived exosomes transferred miR-196a to head and neck cancer (HNC) cells, promoting proliferation and cisplatin resistance, which was mediated by nuclear ribonucleoprotein A1. Functionally, miR-196a conferred cisplatin resistance by suppressing the expression level of CDKN1B and ING5, both in the plasma and tissues from patients with HNC, indicating that miR-196a might be an independent predictor for chemoresistance in patients with head and neck cancer (50).

Figure 1. Schematic illustration of exosome non-coding RNAs biogenesis and release on the development of chemoresistance. Circ, circular; lnc, long non-coding; mi, micro.
co-culture assays revealed that the exosome-transferred miR-155 significantly induced DOX and paclitaxel resistance in breast cancer cells. The study by Santos et al. (64) highlighted the importance of inhibiting transfer of drug-resistance from resistant breast cancer cells to sensitive ones. One cut homeobox 2 promoted breast cancer cell growth and its overexpression may suppress stemness-associated gene expression via chemoresistant extracellular vesicles (EVs), aiding the reverse of chemoresistance (65). This mechanism was negatively mediated by miR-9-5p, miR-195-5p, and miR-203a-3p in circulating EVs (65). Thus, cell-cell communication via exosomal miRNAs may be an important mechanism for cancer chemotherapy.

EMT contributes to cancer chemoresistance. miR-128-3p has been reported to suppress EMT and enhance intracellular oxaliplatin accumulation in colorectal cancer. Delivery of

| Cancer type | miRNA | Exosome origin | Drug | Regulation of chemoresistance | Related genes (Refs.) |
|-------------|-------|----------------|------|-----------------------------|---------------------|
| HNC         | miR-196a | Cell/plasma/tissue | DDP | Promotion | hnRNPA1, CDKN1B, ING5 (50) |
| GBM         | miR-151a | Cell/serum/CSF | TMZ | Inhibition | XRCC4 (48) |
| GBM         | miR-1238 | Cell/serum/CSF | TMZ | Promotion | CAV1 (51) |
| OSCC        | miR-21 | Cell | DDP | Promotion | PTEN, PDCD4 (6) |
| NSCLC       | miR-425-3p | Cell/serum | DDP | Promotion | AKT1, c-Myc (68) |
| GC          | miR-501 | Cell | DOX | Promotion | BLID (7) |
| GC          | miR-374a-5p | Cell/serum | OXA | Promotion | Neurod1 (52) |
| GC          | miR-214 | Cell/serum | DDP | Promotion | PARP9 (90) |
| GC          | miR-21 | Cell | DDP | Promotion | PTEN/PI3K/AKT (57) |
| GC          | miR-155-5p | Cell | PTX | Promotion | TP53INP1, GATA3 (67) |
| GC          | miR-106a-5p | Cell | 5-FU | Promotion | E2F1, STAT3 (91) |
| HCC         | miR-744 | Cell/serum/tissue | Sorafenib | Inhibition | PAX2 (53) |
| HCC         | microRNA-23a/b | Cell/serum/tissue | 5-FU | Promotion | VHL/HIF-1α (54) |
| PC          | miR-155 | Cell/serum/tissue | GEM | Promotion | TP53INP1 (5) |
| PC          | miR-146a | Cell | GEM | Promotion | Snail (62) |
| PC          | miR-155 | Cell | GEM | Promotion | DCK (92) |
| CRC         | miR-21-5p | Serum | OXA/5-FU | Promotion | NA (49) |
| CRC         | miR-1246 | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-1229-5p | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-96-5p | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-196b-5p | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-128-3p | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-46146 | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-142-3p | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-155 | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-9-5p | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-195-5p | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| CRC         | miR-203a-3p | Serum | OXA/5-FU | Promotion | STAT3 (55) |
| OC          | miR-126a | Cell | DOX | Promotion | S100A8/9a (69) |
| OC          | miR-223 | Cell/serum/tissue | Platinum | Promotion | PTEN (70) |
| OC          | miR-1246 | Cell | PTX | Promotion | Cav1 (95) |
| OC          | miR-433 | Cell | PTX | Promotion | CDK6, MAPK14, E2F3, CDKN2A (96) |

HNC, head and neck cancer; GBM, glioblastoma; OSCC, oral squamous cell carcinoma; NSCLC, non-small cell lung cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; PC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; BC, breast cancer; OC, ovarian cancer; CSF, cerebrospinal fluid; DDP, cisplatin; TMZ, temozolomide; DOX, doxorubicin; OXA, oxaliplatin; PTX, paclitaxel; 5-FU, 5-fluorouracil; GEM, gemcitabine; miRNA/miR, microRNA.
miR-128-3p to resistant cells via secreted exosomes improved oxaliplatin response (66). Delivery of miR-155-5p to MGC-803 cells, in tumor-derived exosomes induced EMT and chemoresistance by suppressing the expression level of GATA binding protein 3 expression and tumor protein p53-inducible nuclear protein 1, highlighting a prospective strategy for reversing paclitaxel resistance in gastric cancer (67).

An increasing number of studies have shown that exosomal miRNAs also trigger tumor drug resistance via autophagy, angiogenesis, inflammation and hypoxia induction (68‑70). Cisplatin elevated circulating exosomal miR-425-3p levels and exo-miRNA release in non-small cell lung cancer (68). Furthermore, exosomal miR-425-3p may target AKT1, activating autophagy by negatively regulating the AKT/mTOR signaling pathway and causing resistance to cisplatin-induced apoptosis (68). miR-126a was released from myeloid-derived suppressor cell exosomes, promoting lung metastasis induced by DOX (69). Hypoxia has been reported to induce macrophage M2-polarization and enhance the level of tumor-associated macrophage protein 1, highlighting a prospective strategy for reversing paclitaxel resistance in gastric cancer (67).

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5. Significance of exo-lncRNAs in cancer chemoresistance

lncRNAs, which were previously regarded as transcriptional junk, due to their lack of protein coding capacity, are involved in numerous biological processes at the transcriptional, post-transcriptional, and chromatin levels. An increasing number of studies have indicated that exosomal lncRNAs modulate chemoresistance (Table II).

Trastuzumab, a humanized monoclonal antibody against the extracellular region of human epidermal growth factor receptor 2 (HER-2) is used to treat HER2-positive breast cancer; however, its effects are limited by resistance (71). The lncRNA, actin filament associated protein 1 antisenseRNA 1 (AFAP1-AS1) has been reported to be elevated in trastuzumab-resistant cells compared with that in sensitive cells, and was associated with poor prognosis and survival time in patients with breast cancer (72). In addition, knockdown of AFAP1-AS1 has been shown to reverse chemoresistance. Furthermore, AFAP1-AS1 was transferred from resistant cells to recipient cells by the incorporation of exosomes, inducing trastuzumab resistance. Mechanically, AFAP1-AS1 has been reported to promote ERBB2 translation by combining with AU-binding factor 1 (AUF1) protein. Thus, exosomal AFAP1-AS1 promoted trastuzumab resistance by binding to AUF1 (72). Similarly, the lncRNA, AGAP2 antisense RNA 1 (AGAP2-AS1) has been reported to promote trastuzumab resistance in breast cancer cells via packaging into exosomes (73). Exosomal small nucleolar RNA host gene 14 (SNHG14) lncRNA induced trastuzumab resistance by upregulating the Bcl-2/Bax signaling pathway. Serum exosomal SNHG14 has biomarker potential in breast cancer (74).
Breast cancer cell-derived exosomes might enhance DOX resistance by transferring lncRNA H19. Serum exosomal H19 is highly expressed in patients who are non-responsive to DOX compared with that in patients who are responsive (75). Crosstalk between CAFs and cancer cells has been reported to promote tumor progression and induce chemoresistance in the tumor microenvironment. CAFs promoted stemness and chemoresistance by transmitting exosomal H19 in CRC. Mechanically, H19 mediated oxaliplatin resistance by activating the WNT/β-catenin signaling pathway by sponging miR-141 (76). CAFs transferred CRC-associated lncRNA to tumor cells in exosomes, conferring oxaliplatin and 5-fluorouracil resistance and activating the WNT/β-catenin signaling pathway (59). The WNT/β-catenin signaling pathway modulates various tumor processes, including cancer growth, invasion and angiogenesis (77,78) and its abnormal activation may result in cancer drug resistance (79,80).

Exosomal lncRNA dysregulation has been observed in different types of cancer, where they act as competitive endogenous RNAs against active factors, such as miRNAs (76,81). In gastric cancer (GC), exosomes have been reported to down-regulate HOXA at the distal tip, a lncRNA, hence conferring cisplatin resistance by sponging miR-218, highlighting a potential exosome lncRNA-directed therapy against GC (82). The lncRNA, prostate androgen-regulated transcript 1 (PART1) was differentially expressed in gefitinib-resistant cells compared with that in parental esophageal squamous cell carcinoma cells (83). By binding to PART1's promoter region, signal transducer and activator of transcription participated in chemoresistance. In addition, exosome-mediated transfer of PART1 induced resistance by targeting miR-129. Furthermore, serum exosomal PART1 was stably upregulated in patients with esophageal squamous cell carcinoma who were also gefitinib-resistant (83). A binding site is often located in the promoter region of lncRNAs, and a gene can bind to this site to regulate expression, thus affecting tumor biology. For example, lncRNA SBF2 antisense RNA 1 (SBF2-AS1) overexpression contributed to temozolomide (TMZ) resistance in glioblastoma (GBM) cells, while its downregulation could reverse this effect (84). The transcription factor, ZEB1 combined with the promoter region of SBF2-AS1 to alter chemoresistance. SBF2-AS1-containing exosomes secreted by cancer cells transmitted TMZ to the recipient cells. SBF2-AS1-containing serum exosomes were associated with poor response to TMZ treatment in patients with GBM (84). Notably, acetylated histone 3 lysine 27 was enriched at the promoter region of AFAP1-AS1, which might trigger drug resistance (72). In non-small cell lung cancer (NSCLC), exosome-mediated transfer of lncRNA RP11-838N2.4 induced erlotinib resistance. Forkhead box protein O1 could bind to the promoter region of RP11-838N2.4, and silenced it by recruiting histone deacetylase. Therefore, lncRNA RP11-838N2.4 may be a valuable target for reversing NSCLC chemoresistance (85). Taken together, exosomal lncRNAs play important roles in transmitting chemoresistance. However, the regulatory mechanism of chemoresistance is unclear and warrants further investigation.

6. Significance of exo-circRNAs in cancer chemoresistance

Numerous studies have suggested that circRNAs are novel therapeutic and prognostic biomarkers for various types of cancer, due to their characteristics of closed loop structure and insensitivity to RNase. It is now known that exosomes might be carriers of circRNAs, which are subsequently secreted into body fluids, enabling them to modulate tumor cell proliferation, migration, invasion, and apoptosis, and to affect drug resistance. For example, the circRNA, Cdr1as, has been reported to be downregulated in serum exosomes from patients with cisplatin-resistant ovarian cancer (86). In CRC, hsa_circ_0000338 has been reported to have tumor suppressive function in CRC cells, so that they are sensitive to fluorouracil plus oxaliplatin. Clinical data has validated that hsa_circ_0000338 was markedly downregulated in serum exosomes in patients with CRC who are chemo-resistant (87). Exosomes, from resistant CRC cells, transmitted ciRS-122 to recipient cells by sponging mir-122, thereby resulting in oxaliplatin resistance (88). Serum exosomal circNFI1X has been reported to be upregulated in patients with glioma and who are TMZ-resistant (89). Extracellular circNFI1X secretion in exosomes also conferred TMZ resistance in sensitive cells, while circNFI1X silencing promoted TMZ sensitivity in resistant cells by negatively interacting with miR-132. This finding highlighted the role of prognostic biomarkers and promising therapeutic targets in improving the clinical benefits of TMZ in patients with glioma (89). However, further studies are required to improve the understanding of the roles of exo-circRNAs in overcoming chemoresistance.

7. Conclusions

Since their discovery, extensive research has shown that ncRNAs regulate multiple molecular processes. In addition, due to sequence conservation, they are more stably expressed in various types of tissues, cells, and body fluids. Recent studies have indicated that ncRNAs affect tumor chemoresistance; therefore, they are promising biomarkers for cancer therapy and reversal of chemoresistance (97-99). Despite the increasing number of studies on ncRNAs chemoresistance, they have not yet been targeted clinically.

Exosomes deliver various cargo, such as DNA, RNA and proteins, from donor cells to recipient cells, thus exerting biological effects. In recent years, it has emerged that exosome-mediated transfer of ncRNAs may enhance chemoresistance. The present review described the importance of exosome-contained ncRNA in cancer chemotherapy. However, their effects in cancer are still controversial, and most of the evidence only comes from cell-based and animal studies. Thus, comprehensive studies into the roles and mechanisms of exosome ncRNAs in different types of cancer may uncover novel effective treatment strategies. Thus, comprehensive clinical studies in this area are warranted.

Acknowledgements

Not applicable.

Funding

This study was supported by grants from the Natural Science Foundation of Anhui Province (grant no. 2008085QH404)
and the Science Research Project of Bengbu Medical College (grant no. BYKY2019048ZD).

Availability of data and materials
Not applicable.

Authors' contributions
YYW and QL designed the study. YYW drafted the manuscript. YYW and QL designed the tables and figures. FCW critically discussed and revised the manuscript. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate
Not applicable.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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