Role of Exosomal MicroRNAs in Modulating the Response of Cancer Cells to Paclitaxel Treatment

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Abstract

MicroRNAs (miRNAs) play important roles in gene regulation and have been implicated in various human diseases, including cancer. MiRNAs can be packaged in exosomes and transferred between cells. These exosomal miRNAs regulate intercellular communication and influence almost all aspects of cancer biology, including proliferation, apoptosis, invasion, metastasis, and angiogenesis. Over the last two decades, the association between exosomal miRNAs and paclitaxel resistance has been widely studied. However, the mechanisms underlying the effect of exosomal miRNAs on paclitaxel sensitivity require further research. In this review, we summarize the paclitaxel sensitivity-modulating mechanisms of exosomal miRNAs and discuss exosomal miRNAs as a novel therapeutic tool for paclitaxel resistance.

Keywords: MicroRNA, Paclitaxel, Exosome, Cancer, Drug-resistance

Abbreviations: miRNA: MicroRNA; CAA: Cancer-Associated Adipocyte; CAF: Cancer-Associated Fibroblast; BC: Breast Cancer; OC: Ovarian Cancer; GI: Gastrointestinal; G3BP2: GTPase-activated SH3 domain-Binding Protein 2; EV: Extracellular Vehicle; HCC: Hepatocellular Carcinoma; EMT: Epithelial-Mesenchymal Transition; NPC: Nasopharyngeal Carcinoma

Introduction

MicroRNAs (miRNAs) are a class of single-stranded RNAs that participate in the post-transcriptional regulation of gene expression. They are powerful regulators of various cellular activities, including cell growth, differentiation, development, and apoptosis [1], thereby influencing the occurrence, development, invasion, and migration of different types of cancer [2,3]. Exosomes are extracellular vesicles that contain not only proteins but also nucleic acids such as DNA, mRNA, miRNA, and non-coding RNA, which play roles in angiogenesis, exocytosis, and tumorigenesis by modulating gene expression and protein translation [4-8]. Exosomes perform their roles in cellular communication by releasing bioactive molecules, fusing with recipient cell membranes, or interacting with cell surface receptors. As integral components of the tumor microenvironment, exosomes participate in cell proliferation, angiogenesis, metastasis, immune regulation, drug resistance, and the formation of a pre-metastatic environment [9-12]. Previous studies have shown that exosomes produced in the tumor microenvironment in response to chemotherapy promote a chemotherapy-resistant phenotype in tumors [13]. Evidence suggests that miRNAs can be encapsulated in exosomes and transferred between cells...

via a microencapsulation-dependent mechanism [14,15], indicating their potential to influence chemoresistance by regulating intercellular communication. Paclitaxel, a compound derived from the bark of the western yew (Taxus brevifolia), is commonly used to treat various cancers. However, frequent cancer cell resistance significantly decreases its anti-cancer efficacy [16]. A recent study suggests that miRNAs transferred by paclitaxel-sensitive cell-derived exosomes may affect paclitaxel resistance [17]. Nevertheless, studies on exosomal miRNAs in the context of paclitaxel treatment are limited. Moreover, the mechanisms underlying the effects of exosome-derived miRNAs on paclitaxel sensitivity require further investigation. Therefore, it is of considerable scientific significance to analyze and summarize research on exosomal miRNAs to provide a preliminary basis for subsequent research and to create a new mechanistic therapeutic approach to overcome chemoresistance in paclitaxel treatment. In this paper, we discuss the paclitaxel sensitivity-modulating mechanisms of exosome-derived miRNAs, summarize their regulatory roles in various cancer species, and evaluate the application of exosome-derived miRNAs as a novel therapeutic method for inhibiting paclitaxel resistance.

Mechanisms

In vitro and in vivo studies have indicated that alterations in microtubule-protein interactions [18], the expression and activity of multidrug efflux transporters of the ABC superfamily, including P-glycoprotein (P-gp/ABCB1) [19], and changes in the expression of PKC, bcl-2, p53, and ErbB2 in the apoptotic pathway [20,21], are the primary mechanisms contributing to paclitaxel resistance. Researchers have found that exosome-derived miRNAs can bidirectionally regulate paclitaxel sensitivity by intervening in the aforementioned pathways, contingent upon whether exosome-secreting cells are sensitive or resistant to paclitaxel [17,22]. Exosomes containing miRNAs can be derived from paclitaxel-resistant cancer cells. After internalization by paclitaxel-sensitive cancer cells, these miRNAs activate paclitaxel resistance-related pathways, including stem cell pathways (WNT and NOTCH) [23] and inhibit paclitaxel sensitivity-related pathways, including cellular apoptosis (targeting BCL-2) [24] and cellular senescence (targeting CDK6) [25]. A recent study revealed that paclitaxel-sensitive cancer cells can transfer exosomal miRNAs to paclitaxel-resistant cancer cells, mediating the reversal of paclitaxel resistance by negatively regulating the drug transporter P-gp [17]. This may provide new targets for reversing the resistance to paclitaxel therapy. However, studies on exosomal miRNAs that reverse paclitaxel resistance in paclitaxel-sensitive cancer cells are limited. In addition to cancer cells, the tumor microenvironment comprises other cells, such as cancer-associated adipocytes (CAAs) and fibroblasts (CAFs); however, whether exosomal miRNAs derived from these cells play a role in paclitaxel resistance requires further exploration. Given that CAFs are the most abundant and critically involved cell type in cancer progression, their role in paclitaxel resistance requires further discussion [26]. Growing evidence suggests that CAFs support paclitaxel resistance by secreting various bioactive substances, including exosomes. Exosomal miRNAs derived from CAFs suppress cancer apoptosis [27] and ferroptosis [28]. The recent discovery of CAFs that promote paclitaxel resistance via exosomal miRNAs not only enhances our understanding of the tumor microenvironment’s modulatory role in paclitaxel sensitivity but also underscores the potential of CAF-targeting therapies for addressing paclitaxel resistance. Figure 1 summarizes the mechanisms through which exosomal miRNAs influence paclitaxel sensitivity in tumor cells.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Mechanisms by which exosomal microRNAs influence paclitaxel sensitivity of tumor cells.
Exosome-derived microRNAs and response to paclitaxel in various cancer types

Paclitaxel is one of the most effective chemotherapeutic drugs, demonstrating significant efficacy across a broad range of cancers, including breast, ovarian, gastrointestinal, and prostate cancers [29-32]. In this section, we summarize the regulatory functions of exosomal miRNAs in paclitaxel sensitivity, classified by cancer type. Table 1 provides a summary of the results of studies that have assessed the role of exosome-derived miRNAs in modulating the response of various cancer types to paclitaxel.

Breast cancer

Paclitaxel resistance in breast cancer (BC) primarily manifests in its effects on BC cell metastasis and invasiveness. Notably, paclitaxel-treated BC-derived exosomes have been identified as potential drivers of resistance. Xia et al. revealed that paclitaxel-treated BC-derived exosomes promote BC cell resistance by activating the circBACH1/miR-217/G3BP2 signaling pathway. MiR-217 interacts with circBACH1 and targets GTPase-activated SH3 domain-binding protein 2 (G3BP2) in BC cells [33]. The overexpression of G3BP2 promotes metastasis in BC [34,35], thereby inducing paclitaxel resistance. MiR-378 is another upregulated miRNA in the exosomes derived from paclitaxel-resistant BC cells. Paclitaxel activates the EZH2/STAT3 axis in BC cells. Activated BC cells secrete chemotherapy-elicited exosomes enriched in miR-378a-3p and miR-378d. These exosomes are absorbed by chemotherapy-surviving BC cells, leading to activation of the WNT and NOTCH stem cell pathways by targeting DKK3 and NUMB [23]. Wnt/β-catenin and Notch signaling can act in a synergistically to regulate cell development and differentiation [36]. Activation of Wnt/β-catenin and Notch signaling is in part responsible for the stemness effects of cancer cells [37], thus resulting in drug resistance.

Ovarian cancer

The mechanisms underlying paclitaxel resistance in ovarian cancer (OC) include P-gp-mediated drug efflux, apoptosis evasion, and cell cycle dysregulation [38,39]. Several exosomal miRNAs participate in these mechanisms and influence paclitaxel resistance in ovarian cancer. For instance, miR-1246 expression is significantly higher in paclitaxel-resistant OC exosomes than in their sensitive counterparts. Exosomal miR-1246 confers chemoresistance by targeting the Cav1/p-gp/M2-type macrophage axis. Overexpression of Cav1, a direct miR-1246 target, and anti-miR-1246 treatment significantly sensitize OC cells to paclitaxel [40]. Additionally, MiR21 expression is increased in exosomes from CAAs and CAFs. Transferred from CAAs or CAFs to cancer cells, miR21 confers paclitaxel resistance by binding to its target, apoptotic peptidase activating factor 1 (APAF1). APAF1 sensitizes OC cells to paclitaxel treatment, and miR21 inhibits APAF1 mRNA expression by binding to the APAF1 coding sequence, thereby inducing paclitaxel resistance [27]. Weiner-Gorzel et al. showed that cells expressing high levels of miR-433 release miR-433 into growth media via exosomes and induce a senescence bystander effect that modulates the tumor microenvironment, ultimately promoting resistance to paclitaxel through the induction of cellular senescence in OC cells. MiR-433-induced inhibition of cellular senescence may be attributed to the loss of CDK6, a critical mediator of cellular transition into the S phase [41]. The induction of cellular senescence and subsequent alterations in cell signaling have been shown to correlate with changes in the epigenome of cells, promoting cancer progression [42], and mediate paclitaxel resistance in OC cells [25]. Although miRNAs can participate in the mechanisms involved in paclitaxel resistance in OC, including intracellular drug inactivation, DNA damage repair, activation of cancer stem cells, and epithelial-mesenchymal transition (EMT) [43,44], the role of exosomal miRNAs in these processes remains unclear.

Gastrointestinal cancers

The complex mechanisms underlying paclitaxel resistance in gastrointestinal (GI) cancers involve the inactivation of apoptotic signaling pathways, loss of cell cycle checkpoint control, accelerated cell proliferation and autophagy flux, enhanced DNA damage repair capacity, diminished uptake and/or increased efflux of drugs, activation of cancer stem cells, and EMT [45-47]. The regulatory effects of exosomal miRNAs on apoptosis and EMT signaling pathways have been confirmed in GI cancer cell lines. The effects of CAF-derived exosomes on the chemoresistance of GI cancer cells are significant [48]. Zhang et al. analyzed CAF-secreted exomirRNAs and found that paclitaxel can promote miR-522 secretion by activating the USP7/hnRNPA1 axis. This leads to arachidonate lipoxygenase 15 (ALOX15) suppression and decreased lipid peroxide (lipid-ROS) accumulation in cancer cells. The decrease in iron-dependent lipid ROS leads to the inhibition of ferroptosis, a novel form of regulated cell death, ultimately resulting in decreased paclitaxel sensitivity [28]. Another study in GI cancer generated a paclitaxel-resistant GI cell line (MGC-803R) and found that MGC-803R-exosomes deliver miR-155-5p into chemosensitive cancer cells, inducing paclitaxel-resistant phenotypes. Exosomal delivery of miR-155-5p may induce chemoresistance by suppressing the expression of GATA-binding protein 3 (GATA3) and tumor protein p53-inducible nuclear protein 1 (TP53INP1). Both of these proteins are associated with the regulation of EMT [49,50], a classical paclitaxel resistance mechanism in GI cancer. Moreover, knockdown of miR-155-5p reversed the chemoresistant phenotypes of MGC-803R cells, potentially via the upregulation of GATA3 and TP53INP1. Targeting miR-155-5p may be a promising strategy to overcome paclitaxel resistance in GI cancer [51]. Future translational studies or clinical trials are warranted to develop exosomal
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miRNA-based therapeutic interventions along with traditional chemotherapy, which may improve the prognosis of patients with GI cancer by overcoming drug resistance.

**Prostate cancer**

Given that paclitaxel is commonly used in prostate cancer treatment, extensive research has been conducted on the mechanisms of resistance. Activation of oncogenic pathways such as STAT3, NF-κB, β-catenin, and EH22 contributes to the development of chemotherapy resistance in prostate cancer, while tumor-suppressor factors like PTEN are downregulated [52]. There is limited research on the role of exosomal miRNAs in prostate cancer, and follow-up studies can be initiated from these pathways. Corcoran et al. investigated intracellular and extracellular (exosomal) miRNAs related to docetaxel resistance and found that downregulation of the tumor suppressor gene miR-34a can cause chemoresistance. Exosomal miR-34a has been suggested to be a predictive biomarker for the response to docetaxel because it regulates the anti-apoptotic gene BCL-2 [24]. This is the first time that exosomal miRNAs have been suggested as possible adjuvants to paclitaxel for the treatment of prostate cancer. Recent studies have reported that treatment of prostate cancer with paclitaxel often fails owing to the development of chemoresistance; however, there is limited research on the regulation of paclitaxel resistance in prostate cancer by exosomal miRNAs. Several miRNAs, such as miR-223-3p, miR-323, miR-375, and miR-148a, have been linked to taxane resistance by interfering with apoptosis. Moreover, miR-21 is often overexpressed in cancer and renders prostate cancer resistant to docetaxel by interfering with pro-apoptotic proteins and downstream pathways [53]. Given the significant roles of miRNAs in altering apoptosis-related pathways and influencing the response of prostate cancer cells to paclitaxel, further studies are warranted to investigate the detection of these miRNAs in exosomes and their impact on the sensitivity of target cancer cells to paclitaxel. Moreover, it is crucial to determine whether this effect is caused by interventions in apoptosis-related pathways.

**Other cancers**

Furthermore, exosomal miRNAs modulate the response of other cancer types to paclitaxel, including hepatocellular carcinoma (HCC) and nasopharyngeal carcinoma (NPC). Xu et al. investigated the molecular mechanism of human umbilical cord mesenchymal stem cell (hUCMSC)-derived exosomal miR-451a in HCC and found that hUCMSC-derived exosomal-induced upregulation of miR-451a can downregulate metalloprotease 10 (ADAM10). Inhibition of ADAM10 promotes apoptosis [54] and suppresses paclitaxel resistance of HCC cells [55]. A recent study on NPC suggested that paclitaxel-sensitive cancer cells can transfer exosomal miRNAs to paclitaxel-resistant cancer cells, mediating the reversal of paclitaxel resistance. In this previous study, we elucidated the role of miR-183-5p delivered by extracellular vehicles (EVs).

**Clinical Treatment**

Primary or secondary resistance to paclitaxel presents a challenge in clinical treatment, leading to aggressive cancer behavior and poor outcomes [57,58]. Researchers are constantly attempting to overcome paclitaxel resistance in clinical treatment. Mosca et al. have delineated possible modalities to overcome chemoresistance to taxanes, such as increasing drug solubility, delivery, and pharmacokinetics; overcoming microtubule alterations or mitotic slippage; inhibiting drug efflux pumps or drug metabolism; and targeting redox metabolism, immune response, and other cellular functions [59]. Exosomal miRNAs inhibit drug efflux pumps and target cellular functions (cellular apoptosis, senescence, and ferroptosis). Significant progress has been made in the use of exosomal miRNAs as therapies for paclitaxel resistance and in potential regenerative medicine in preclinical trials. Based on preclinical research, several clinical trials have been planned and conducted. These clinical trials involve various cancer types, including GC (NCT01779583, NCT02662621 and NCT02565264), BC (NCT03262311 and NCT01299038), HCC (NCT05375604), pancreatic cancer (NCT03608631), and lung cancer (NCT01159288 and NCT03108677) [60]. The findings from these clinical trials suggest that EVs can overcome chemoresistance, including paclitaxel vincristine (VCR) and cisplatin [33,61,62]. Xia et al. suggests that exosomal miRNAs derived from paclitaxel-treated BC cells could induce paclitaxel resistance, indicating the possibility of using exosomes to treat paclitaxel resistance [33].

Compared with traditional gene carriers, exosomes offer the following advantages: (1) as endogenous vesicles, exosomes have low immunogenicity; (2) their biocompatible structure facilitates efficient cellular entry, enabling more effective gene delivery; (3) their robust membrane can protect therapeutic miRNAs from degradation; and (4) their ability to avoid phagocytosis and bypass engulfment by lysosomes makes
However, several challenges remain associated with the translation of exosomal miRNA-based therapies from preclinical studies to clinical applications, including issues related to their scalability, delivery, and safety. Regarding the scalable manufacturing of therapeutic exosomal miRNAs, the selection of proper exosome-producing cells, development of efficient cargo-loading technology, and establishment of large-scale production and purification systems should be considered for successful clinical translation. The choice of exosome-producing cells should be carefully considered to minimize the incorporation of unwanted cellular bioactive cargoes and maximize the loading of desired therapeutic miRNAs on a large scale [67]. The delivery of miRNAs with the ability to regulate paclitaxel resistance in patients presents another challenge. Although exosomes confer stability to miRNAs, controlling their destinations remains to be investigated [68]. Anti-cancer therapeutic exosomes could be targeted to cancer cells or tissues passively or actively. Passive targeting occurs when exosomes naturally target tumors based in their cellular origin [69]. However, Smyth et al. suggested that tumor-derived exosomes exhibit tumor targetability only when injected locally into the tumor parenchyma [70]. Jung et al. also showed that hypoxic cancer cell-derived exosomes exhibited increased delivery to hypoxic cancer cells in vitro but not in vivo [71]. Further studies are required to elucidate the mechanisms underlying the targetability of tumor cell-derived exosomes to their parental cells.

Active targeting of anti-cancer therapeutic exosomes to cancer cells or tissues can be achieved through two main strategies: a non-genetic approach that directly engineers the surface of exosomes via diverse exogenous methods and a genetic approach that non-directly engineers exosomes by genetically modifying exosome-producing cells. Indirect engineering of exosomes expresses specific cancer-targeting moieties on the surface of exosomes by conjugation with exosomal membrane-associated domains, such as the GPI, C1C2 domain, Lamp2b, and tetraspanins, which could serve as a promising strategy for the active targeting of anti-cancer therapeutic exosomes to cancer cells and tissues [72]. This indicates that the delivery problem may be resolved through active targeting, achieved by targeted exosome engineering. Additionally, tumor-derived exosomes may raise safety concerns in terms of delivering tumorigenic factors to non-tumorigenic cells, which could promote tumor metastasis by inducing the formation of a pre-metastatic niche at potential metastatic sites [73-75]. Therefore, careful consideration is required when using tumor-derived exosomes as delivery vehicles for anti-cancer agents. The use of toxic chemicals for exosomal surface engineering requires caution when applied in clinical settings [67].

**Discussion**

Paclitaxel is a chemotherapeutic agent extensively used for treating human cancers. Resistance to this drug is regarded as a major problem in clinical settings. The dysregulation of exosome-derived miRNA shuttling from paclitaxel-resistant cancer cells to paclitaxel-sensitive cells has been implicated in this problem. Moreover, further studies are needed to determine whether exosomal miRNAs derived from paclitaxel-sensitive cells can fulfill their role after being transported to paclitaxel-resistant cells. Therefore, the insights gained from these studies offer novel avenues for promoting the efficacy of paclitaxel treatment. Considering that ovarian, breast, and gastrointestinal cancers are commonly treated with paclitaxel, these cancer types have been extensively studied regarding the role of exosomal miRNAs in conferring resistance to this drug. Stem cell pathways (Wnt/β-catenin and NOTCH), P-gp axis, and pathways related to cellular apoptosis, senescence, and ferroptosis are among the pathways involved in the modulation of paclitaxel sensitivity by exosomal miRNAs. Other classical apoptotic pathways such as PKC, p53, and ErbB2 also play roles in exosomal miRNA-mediated resistance to paclitaxel. Considering the significant role of exosomal miRNAs in altering the response of cancer cells to paclitaxel, targeted therapies against these transcripts represent putative treatment modalities for combating paclitaxel resistance and enhancing patient survival. Exosome-mediated delivery of miRNAs for gene therapy presents a novel clinical approach to reverse paclitaxel resistance. Moreover, certain exosomal miRNAs provide insights into the cell type from which they are derived, the target, and the cellular state, including therapy resistance. This enables the monitoring and regulation of tumor resistance for personalized therapy. However, this review has several limitations. Current research has yet to elucidate the role of exosomal miRNAs derived from other cells in the tumor microenvironment. Moreover, while in vivo studies support the feasibility of exosomal miRNA therapy in animal models, these modalities have not undergone clinical evaluation. In terms of clinical use, paclitaxel is a first-line drug for late-stage non-small cell lung cancer; however, the role of exosomal miRNAs in modulating the response of lung cells to paclitaxel treatment is still unclear, which could provide valuable insights for future clinical trials benefiting patients with lung cancer.

**Conclusion**

Exosomal miRNAs play a pivotal role in modulating cancer cell response to paclitaxel. Several classic miRNAs have been identified as functional miRNAs in this regard. For instance, miR-433 and miR-21 in OC [25,27] and miR-34a in prostate cancer [24] are functional miRNAs that exert regulatory effects on cancer cell responses to paclitaxel through exosomes. Given the significant role of exosomal miRNAs in altering cancer cell response to paclitaxel, targeted therapies against...
these transcripts represent potential treatment modalities to combat paclitaxel resistance. Although in vivo studies support the feasibility of exosomal miRNA-based therapies in animal models, these modalities have not been examined in clinical settings.

Cancer treatment remains a significant challenge. Paclitaxel has been widely used to treat various types of cancers and has shown good therapeutic effects. Nevertheless, most patients eventually acquire drug resistance, leading to a poor prognosis. Therefore, understanding the mechanism underlying paclitaxel resistance and identifying strategies to reverse it are urgently required. Exosomal miRNAs offer promising targets for therapies against paclitaxel resistance, which may benefit patients with cancer.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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