

The Role of Exosomes in Cancer Drug Resistance, A Review

*Corresponding Author: [Elham O Mahgoub](#)

Email: ilhamomer@yahoo.com

Elham O Mahgoub*

College of Arts and Sciences, Qatar University, Doha, Qatar.

Abstract

Recent research has revealed that extracellular vesicles (EVs), also known as exosomes, are crucial for cell-to-cell communication because they may transmit a variety of genetic and metabolic signals. Exosomes can eventually change the tumor environment to encourage tumor progression, such as metastasis and multidrug resistance (MDR). Exosomes can be secreted by either tumor cells or stromal cells, including immune cells. The resistance type that transforms using exosomes is acquired drug resistance. Nevertheless, little is known about the mechanisms by which chemoresistance cancers develop therapy resistance. Therefore, exosomes can be informative biomarkers of cancer drug resistance. In this review, we represent the current understanding of the connection between exosomes and tumor therapy resistance, as well as the potential uses of exosomes as diagnostic biomarkers and therapeutic targets.

Introduction

Exosomes are small extracellular membrane vesicles that are secreted by many kinds of tumor cells and exist in most body fluids [1]. Regardless of origin, exosomes have similar protein compositions, which can be categorized into three major groups: natural raft proteins, cytoskeletons-like proteins, and heat shock proteins. Internal vesicles are formed by the inward bud-aiding of cells known as multivesicular endosomes (MVE). The fusion of the MVE with the plasma membrane leads to the release of the internal vesicles known as exosomes[1]. Exosomes could travel to surrounding cells or distant tissues to display functions such as immune stimulation, debris deletion, immune suppression, induction of proliferation and tolerance, and transfer of genetic material[2],[3]. Three exosome-mediated drug resistance mechanisms are commonly described: neutralization of antibody-based drugs, drug export via the exosome pathway, and exosome-mediated transfer of miRNAs. Exosomes contain a substantial amount of RNA that is transferred from one cell to another, thereby contributing to the proliferation and metastasis of cancer and cancer development[4]. However, the involvement of exosomes in regulating the sensitivity of cancer cells to drugs remains investigable.

The first observation of exosome transfer resistance to recipient cells was introduced by [4] when the research group demonstrated that exosomes released from cisplatin-resistant ovarian carcinoma cells and found to contain 2.6 times more cisplatin than exosomes released from cisplatin-sensitive ovarian carcinoma cells in a preclinical study. This finding

Received: Jan 25, 2024

Accepted: Feb 14, 2024

Published Online: Feb 21, 2024

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Keywords: Exosomes; Cancer Drug Resistance; Acquired Drug Resistance.

Cite this article: Mahgoub EO. The Role of Exosomes in Cancer Drug Resistance, A Review . J Clin Med Images Case Rep. 2024; 4(1): 1632.

suggests that cancer cells have been using the endocytic compartment as a drug export vector. All of these results point to an essential role for exosomes in drug resistance across a range of tumor types[5],[6]. Notably, it can be a desirable concept in the field of liquid biopsy research to examine particular exosome groups within the overall population in various bodily fluids. Unfortunately, there is still work to be done in order to effectively separate Tumor-Derived Exosome TDEs from the rest of the exosome population in bodily fluids like blood, particularly in cancer patients[7].

Nonetheless, it appears that the entire exosome population has a high concentration of (TDEs)[7]. In this review, we present the use of exosomes as a biomarker for cancer cells' resistance to drugs. The exosomes change the tumor microenvironment, as appears in Figure (1), by using miRNA and RNA molecules and proteins that change the sensitive recipient cells to the drug and the insensitive recipient.

Exosomes' Role in Transfer RNA and miRNA Exchange

Recent studies [8] showed that the miRNA and RNA expression of the cells would change when extra exosomes were added to the cells. During the last few years, there has been interest in drug resistance by exosome-mediated transfer of miRNAs. Accordingly, the overexpression of exosomes should be increased on the media of treated cancer cells with chemotherapy[9]. Meanwhile, those extra-induced exosomes influence the surrounding cells to decrease sensitivity to the drugs[5], which is the main reason to use exosome numbers

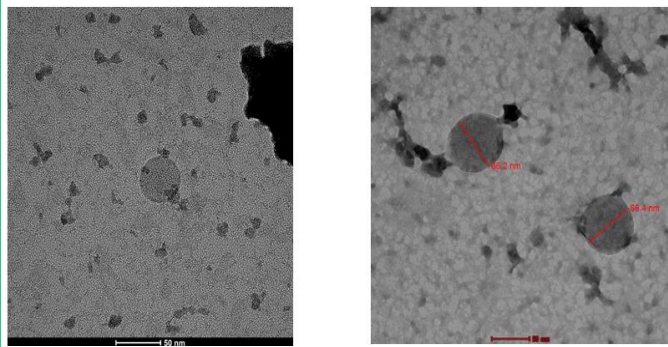


Figure 1: Exosomes in non-small lung cancer cell (1975) microenvironment.

as the main factor in cancer cells decreasing sensitivity towards drugs. Similar occurrences have been reported in several tumor situations, including liver, breast, and lung malignancies[10],[11],[12].

On the contrary, donor-resistant cells produce exosomes with low levels of miRNA miR-100-5p, which facilitates the transfer of cisplatin resistance in lung cancer[5]. This enhanced expression of the mammalian target of Rapamycin (mTOR) protein and chemoresistance in the recipient cells follow[13]. In advanced studies, the expression of particular target genes, such as Sprouty2 (targeted by miR-23a), PTEN (targeted by the major player of miR-222), APC4 (targeted by miR-452), and p27 (targeted by miR-24), can be altered by miRNA packed in exosomes from drug-resistant cells in breast cancer. The modulates chemoresistance in recipient cells that incorporate these exosomes[8]. Even though, miR-221/222's silencing blocks resistance from spreading[10],[14]. However, in lung cancer (NSLCC), exosomes produced from cells chemo-resistant to gemcitabine transfer malignant phenotypes by delivering miRNA-222-3p[15],[16]. Besides, in glioblastoma, exosome transfer of long noncoding RNA SBF2-AS1 increases chemoresistance to temozolomide [17],[18]. Furthermore, exosomal lncRNAs are induced from the breast cancer cells involved in classification, pathways, and medication resistance[19].

Moreover, obtained in ovarian cancer preclinical studies, it was demonstrated that a cisplatin-resistant ovarian cancer cell line transfers the resistance to sensitive cells by the exosomal Exchange of biologically active miR-21-3p, which targeted the NAV3 gene[3],[5]. Moreover, Exosomes produced by human ovarian cancer cells can export cisplatin[4], even though the Role of exosomal miRNAs in drug resistance mediated by the cross-talk with the tumor microenvironment in neuroblastoma (NBL) was investigated [4],[20]. Additionally, research was done on the function of exosomal miRNAs in neuroblastoma (NBL) medication resistance, which is mediated by cross-talk with the tumor microenvironment. Challagundla and colleagues[21] showed that exosomes generated from the NBL cell line were able to transfer the oncomiR-21 to human monocytes in preclinical research. Monocytes transcribed oncomiR-155 through an NF- κ B-dependent pathway as a result of this genetic information exchange.

Interestingly, monocytes also produced exosomes containing miR-155, which were subsequently absorbed by NBL cells. TERF1, a telomerase inhibitor, is one of miR-155's known targets. By silencing TERF1 mRNAs, telomerase activity was mutated, which may boost resistance to cisplatin-induced DNA damage[22],[23].

Exosome's Role in Multidrug Resistance (MDR)

Studies have demonstrated that sensitive cells become resistant to Adriamycin when exposed to GSTP1 exosomal mRNA from resistant breast cancer cells[24]. Crucially, in patients with breast cancer receiving Adriamycin, the presence of GSTP1 in RNA exosomes from peripheral blood [24],[25]. Furthermore, through their attachment to chemotherapeutic medicines, exosomes can have countertherapeutic effects. Evidently, exosomes that overexpress HER-2 in breast cancer are able to resist trastuzumab's therapeutic effects. Trastuzumab can attach to exosomes released by SK-BR-3 and br-474 breast cancer cells that overexpress HER2. Exosomes extracted from patients with breast cancer in its early stages have a lower binding level than those from people with the disease in its later stages[26],[7],[27].

Currently, several studies indicate that TDEs also function as a genetic exchange vector in the tumor microenvironment. Several in vitro studies suggest that breast cancer cells resistant to different drugs (docetaxel–Adriamycin–tamoxifen) may transfer the resistance to sensitive breast cancer cells in part by exosome miRNA exchange [28]. Also, it was demonstrated in prostate cancer that exosome transfer of multidrug resistance proteins such as multidrug resistance protein 1 (MDR-1/P-gp) could be related to docetaxel resistance. Interestingly, an exosome-mediated transfer of MDR-1 from nonsensitive to sensitive breast cancer cells to docetaxel was observed, transferring docetaxel drug resistance to sensitive cells[2]. Through a variety of processes, including the delivery of multidrug resistance (MDR) proteins and the secretion of chemotherapeutic medicines, exosomes generated from tumor cells can enhance the resistance of tumor cells to chemotherapy medications[29],[18]. Exosomes can transfer drug resistance to recipient cells through the secretion of MDR proteins[30]. Exosomes produced from 5T33 bone marrow stromal cells stimulate multiple myeloma cell growth and create resistance to bortezomib in these cells[30].

Exosomes have been demonstrated in multiple studies to have pro-tumorigenic effects, but they have also been proven to transfer chemoresistance, which facilitates tumor-tumor communication. Ever since Corcoran and associates discovered that prostate cancer patients' docetaxel resistance can be transferred via exosomes, drug resistance in cancer caused by exosomes has been well recognized [31],[32]. In terms of cross-resistance, morphology, proliferation, motility, invasion, anoikis, colony formation, exosome secretion, and functional relevance, docetaxel-resistant variants of DU145 and 22Rv1 were identified and described[31],[33]. Exosomes from pertinent serum samples were also subjected to a preliminary analysis[33]. The development of acquired docetaxel resistance resulted in changes to motility, invasion, proliferation, and anchorage-independent growth, as well as cross-resistance to doxorubicin[34]. Furthermore, By transferring P-glycoprotein, exosomes released by prostate cancer cells resistant to cetaxel can give docetaxel resistance to prostate cancer cells that are susceptible to the drug[31].

Exosomes' Role in transfers Insensitive proteins in Vitro

A different study identifies the function of exosomes in drug-resistant cells that transfer the drug-sensitive MCF-7/S cell line into the same plates that contain the docetaxel-resistant MCF-7/DOC cell line. When MCF-7/S were exposed to exosomes taken

from the MCF-7/DOC supernatant (DOC/exo), the recipient cells absorbed the stained exosomes. The recipient cells developed drug resistance; however, MCF-7/S treated to their exosomes (S/exo) did not change the sensitivity to the drugs. Meanwhile, exosome P-gp expression patterns matched those of the original cells[35].

Exosomes' Role in Stimulating CSCs

Exosomes can stimulate cancer stem cells (CSCs), which in turn mediates treatment resistance in breast cancer. Furthermore, the same study demonstrated exosomes can spread the resistance through expressing glutathione S-transferase P1 (GSTP1) in breast cancer cells. GSTP1 can conjugate with glutathione to detoxify medications used in chemotherapy and make the drugs unaffected [36],[37]. In different solid tumors such as colorectal cancer, the study revealed that cancer-associated fibroblast (CAF)-derived exosomes promote the chemoresistance of colorectal cancer cells by stimulating CSCs[38].

Exosomes' Role in the Communication of Tumor Microenvironment and Innate Immunity leads to chemoresistance.

Since cancers primarily use exosomes obtained from tumors to generate a suitable environment that is conducive to their growth, macrophages, in the M1 and M2 stages, use exosomes derived from macrophages to enhance anti-tumor immunity or induce tumor growth [39],[40]. Exosomes produced from macrophages develop aerobic glycolysis and chemoresistance in lung cancer by stabilizing C-Myc through the suppression of NEDD4L expression [41]. Furthermore, Castration-resistant prostate cancer growth is facilitated by exosomes produced from myeloid-derived suppressor cells via S100A9/circMID1/miR-506-3p/MID1[42].

In conclusion, in advanced studies to overcome exosomes' effect on cancer drug resistance, investigators proposed PTX, which is an anti-mitotic medication that overcomes cancer cells' resistance to drugs that are transferred by exosomes[43]. PTX is used for malignant tumors like glioblastoma multiforme and breast cancer. PTX-encapsulated Cancer-Derived Exosomes (CDE) specifically target drug-resistant cancer stem cells. PTX enhances CDE cytotoxicity against autologous cancer cells. PTX-load exosomes, which demonstrated potent anti-cancer actions in human pancreatic adenocarcinoma, were produced by mesenchymal stromal cells that were pre-treated with PTX [44]. Finally, by secreting oncogenic enriched exosomes, cells change the tumor microenvironment to encourage tumor resistance to therapy. Therefore, exosomes in human serum could be a potential diagnostic marker for different types of cancer that are chemoresistance to therapy.

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