Oncologie

Tech Science Press

DOI: 10.32604/oncologie.2022.020993

REVIEW

Progression of Exosome-Mediated Chemotherapy Resistance in Cancer

Haojie Zhang[1], Xiaohong Wang[2,*], Yue Yu[2] and Zhenlin Yang[3,*]

[1]Binzhou Medical University, Yantai, 264003, China

[2]Department of Breast Surgery, Binzhou Medical University Hospital, Binzhou, 256603, China

[3]Department of Thyroid and Breast Surgery, Binzhou Medical University Hospital, Binzhou, 256603, China

[*]Corresponding Authors: Xiaohong Wang. Email: wangxiaohong0607@126.com; Zhenlin Yang. Email: ikb0607@163.com

Received: 22 December 2021 Accepted: 12 April 2022

ABSTRACT

Chemotherapy plays an important role in controlling cancer progression, but the long-term use of chemotherapeutic agents can lead to drug resistance and eventually treatment failure. Therefore, elucidation of the mechanism of drug resistance is the key to solve the problem of chemotherapy resistance. In recent years, exosomes derived from tumor cells have received extensive attention from researchers. In this paper, we reviewed the role and mechanism of exosome-mediated tumor drug resistance in recent years, summarized the related studies of exosome and chemotherapy drug resistance, and focused on several different ways by which exosomes participate in tumor drug resistance. It includes the transporters of non-coding RNAs (ncRNAs), active proteins, stromal cell-derived exosomes and exosomes that directly mediate the efflux of drug molecules. Our review suggests that exosomes can play a role in the treatment of tumor drug resistance by inhibiting the secretion of exosomes, providing a new idea for the prevention and treatment of tumor chemotherapy drug resistance.

KEYWORDS

Exosomes; chemotherapy; drug resistance; tumor microenvironment

1 Introduction

Chemotherapy is one of the main treatments for controlling tumor progression [1–3]. However, the long-term application of chemotherapeutic agents usually results in chemotherapy drug resistance of tumor cells, and eventually treatment failure and disease progression [4–6]. Therefore, elucidating the mechanisms of action for chemotherapy drug resistance is essential for effective cancer prevention, evaluation, or reversal of resistance to chemotherapy. Tumor cell-derived exosomes (TDEs) have been shown to play a role as cargo carriers which mediate the transfer of chemoresistance information between cells.

Extracellular vehicles (EVs) usually refer to vesicles with a lipid bilayer membrane structure that are secreted by cells or shed from the cell membrane. EVs can be classified into exosomes, microvesicles, and apoptotic bodies according to their biogenesis, size, markers and contents. The diameter of exosomes (40–100 nm) is smaller compared to microvesicles (100–1000 nm) and apoptotic bodies (1–4 μm) [7,8]. Exosomes were first discovered by researchers during the transition from reticulocytes to mature red blood cells [9]. At early stage, exosomes were referred to as "garbage bags" to remove unwanted proteins from the body. Various cell types including lymphocytes, epithelial cells, immune cells, mesenchymal

stem cells, nerve cells, and tumor cells can secrete exosomes. Exosomes can be found in body fluids (e.g., blood, saliva, and urine) and enter the circulatory system to reach distant sites, thereby producing remote control effects [10–13]. When exosomes are observed under a transmission electron microscope, they usually appear as "dish-shaped" or "cup-shaped" vesicles with a lipid bimolecular membrane structure [14]. There are a variety of specific proteins on the surface, such as transmembrane proteins CD9, CD63, CD81, CD82, fusion proteins (Flotillin, annexin), and heat shock proteins (Hsc70). Among these proteins, the four transmembrane proteins have been recognized as markers of exosomes to distinguish it from other vesicles [15,16]. Genetic cargo, protein and non-coding RNAs (ncRNAs), carried by exosomes have important biological significance in the development and progression of tumors and drug resistance [17–20].

Exosomes originate from the endolysosomal system which forms early endosomes during endocytosis. Exosomes are formed by cell membrane invagination to form endosomes, then form multivesicular bodies, and finally exosomes are formed in cell multivesicular bodies and are released into the extracellular environment through fusion with cell membranes [21]. Functional molecules such as DNA, ncRNA, mRNA, and protein enter into early endosomes and develop into late endosomes that are rich in intracavity vesicles, namely extracellular vesicles [22–28]. These small spherical vesicles between 40–100 nm in diameter are secreted by various cells types and carry a variety of biologically active small molecules to participate in cell-cell information transmission and the regulation of a variety of malignant biological behaviors of tumor cells in tumor chemotherapy resistance, invasion and metastasis, and immune escape [29–35]. Tumor-derived exosomes (TDE) can enhance or induce drug resistance in sensitive cells through the delivery of ncRNA, proteins, and other biological molecules [29,36–42]. When this transport system is activated, the internal chemotherapeutic drug molecules and their metabolites can be transported to the endosome by MDR-ABC. The endosome further aggregates to form MVBs. MVBs fuse with the cell membrane and release exosomes. The drug will be excreted from the intracellular to the extracellular, causing tumor cells to develop drug resistance [43–46]. This article reviews the role and mechanism of tumor resistance mediated by exosomes, and aims to provide new ideas for the prevention and treatment of tumor chemotherapy resistance.

2 Tumor Drug Resistance Mediated by Exosomes

2.1 Exosomes Participate in the Regulation of Tumor Microenvironment

The tumor microenvironment (TME) is the local pathological environment where tumor occur, develop and metastasize. The TME is mainly composed of tumor cells, immune cells, endothelial cells, fibroblasts, inflammatory cells and extracellular matrix [18,19]. Exosomes mainly participate in the material transportation and information exchange between tumor and non-tumor cells through three ways: 1) Phagocytosis of target cells and receptor-mediated endocytosis. 2) Antigen presentation and receptor-ligand interaction. 3) Direct membrane fusion with target cell. A large number of studies have shown that as a mediator of intercellular communication, exosomes shuttle within the TME and are absorbed by surrounding cancer cells or stromal cells, and can transmit information by releasing their contents to cause tumor cell proliferation, invasion and metastasis, and chemotherapy drug resistance [47,48].

Signal transduction via soluble signaling molecules (cytokines, growth factors, or hormones) by all multicellular organisms occurs through membrane adhesion molecules, gap junctions and nanotubes to maintain necessary homeostasis conditions. Exosomes can change the tumor phenotype through signal transduction between tumor cells or tumor-related stromal cells. TDEs carry a variety of stimulating and inhibiting biomolecules (mRNA, ncRNA, protein) to provide a signaling network for the tumor microenvironment *in vivo* and *in vitro*. These biomolecules regulate cell signaling pathways and influence biological functions [20]. For example, the Ca^{2+} influx induced by TDEs play an important role in the

function of T-regs, and thus, the regulation of T-reg inhibitors by TDE are carried out through a cell signal-dependent mechanism, without the need for recipient cells to internalize exosomes [49].

After 30 years of extensive research, it has been confirmed that transcription regulators can activate other signaling pathways during cell development and progression, such as Notch, Hedgehog (HH) family secreted proteins, Wingless/WNT, epidermal growth factor (EGF) and fibroblasts growth factor (FGF) [50]. Pikkarainen et al. [51] found that WNT signaling and Mac-2BP expression in HEK293 cells were significantly up-regulated under the induction of exosomes. In addition, further studies showed that the four domains of the Mac-2BP protein bind to the C-terminal domain of WNT. *In vitro* studies have shown that after human mesenchymal stem cells (MSC) and breast cancer cells MCF-7 are co-cultured with exosomes, the WNT signaling pathway in the cells is up-regulated [52]. Similarly, Lin et al. [53] found that after co-cultivating THP-1 cells, exosomes activate cell signaling pathways by producing IL-1β, TNF-α and IL-6, thereby suppressing the immune system and enhancing resistance to cancer treatment.

2.2 Exosomes Participate in the Regulation of Tumor Local Immune Microenvironment

There are many immune cells in the local immune TME, such as T lymphocytes, B lymphocytes, macrophages, dendritic cells, mast cells, natural killer cells, and neutrophils. Among them, in tumorigenesis, invasion, metastasis and drug resistance of T lymphocytes and tumor-associated macrophages (TAMs) play a very critical role. Exosomes play a very important role in anti-tumor immunity and immune escape between tumor cells and immune cells, and the flow of information [50,54,55]. Evasion of immune surveillance is a crucial step to gain metastatic outgrowth. Many findings revealed that exosomes, using multiple mechanisms, can help cancer cells to exert immunomodulatory activities [56]. Exosomes released by murine mammary carcinoma cells TS/A or 4T1 induced cancer growth in a mouse model, inhibiting natural killer (NK) cell cytotoxic activity *ex vivo* and *in vivo* [57]. Recently, an elegant work of Dhouha and coworkers demonstrated that PDL1-expressing exosomes can inhibit antitumour immune responses [58]. Cancer cells may exploit exosomes to confer transcriptome reprogramming that leads to cancer-associated pathologies such as angiogenesis, immune evasion/modulation, cell fate alteration and metastasis [59].

2.3 The Role and Mechanism of Exosomes in the Occurrence of Tumor Resistance

Researchers discovered that this non-spherical membrane structure of vesicles contains many proteins, lipids, and nucleic acids from parental cells [60,61]. The database shows that more than 1,639 RNAs, 764 microRNA, 4,653 protein, and 194 lipid types can be detected in exosomes from various eukaryotic cells. In the past few years, there has been new evidence that exosomes are involved in the occurrence and development of tumors through the transfer of nucleic acids and proteins between cells [62]. And a line of evidence suggested that the content of exosomes released from tumor cells in biological samples may be associated with the clinical outcomes of cancer patients [63].

Exosomes mediate cell-to-cell communication by transferring mRNAs, miRNAs, DNAs and proteins causing extrinsic therapy resistance. Exosomes mediate cell-to-cell communication by transferring mRNAs, miRNAs, DNAs and proteins causing extrinsic therapy resistance. They transfer therapy resistance by anti-apoptotic signaling, increased DNA-repair or delivering ABC transporters to drug sensitive cells, see Fig. 1 below.

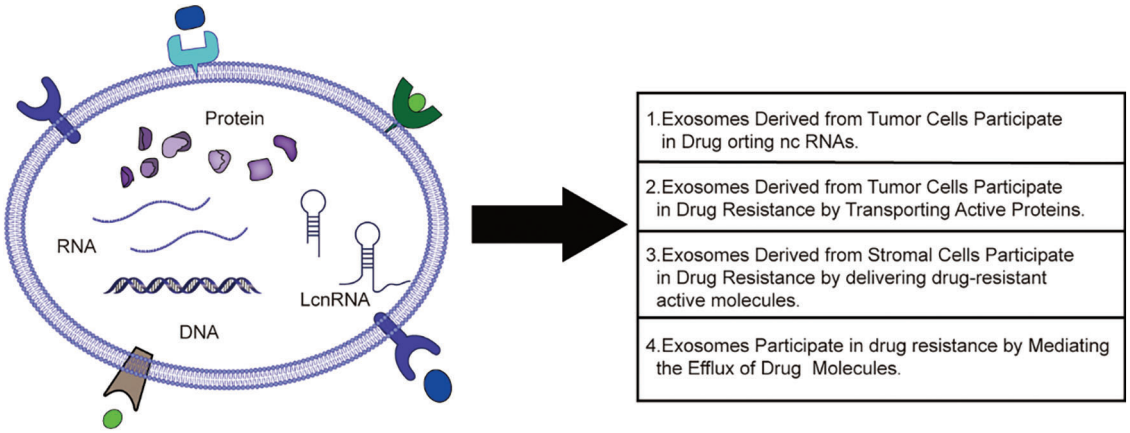

Figure 1: The role of exosomes in drug resistance of tumor

2.3.1 Exosomes Derived from Tumor Cells Participate in Drug Resistance by Transporting ncRNAs

The heterogeneity of tumor cells themself lead to differences of sensitivity of chemotherapy drugs According to this trait, tumor cells can be divided into drug-resistant cells and sensitive cells [64]. For example, exosomes secreted by drug-resistant tumor cells can release proteins and ncRNA (miRNA, lnc RNA) to sensitive cells, thereby acquiring drug resistance [2,65–68].

Non-coding RNA (ncRNA) is a type of small RNA that that does not encode protein. However, they are involved in the process of protein translation. ncRNA can be divided into short-chain (<200 nucleotides) non-coding RNA (sncRNA) such as tRNA and miRNA and long-non-coding RNA (lncRNA > 200 nucleotides) [69]. A large number of studies have shown that ncRNA plays an important role in the chemotherapy resistance of tumors, especially miRNA and lncRNA [70,71].

Liu et al. [72] confirmed that exosomes can target PDCD4 and PTEN in oral squamous cell carcinoma (OSCC) by releasing miR-21 to deliver cisplatin resistance. By using a nude mouse subcutaneous Xenotransplantation model, they injected cisplatin and exosomes derived from oral squamous carcinoma cisplatin-resistant cells HSC-3-R and parental OSCC cells HSC-3 into mice. The exosomes derived from HSC-3-R cell exosomes promoted tumor growth and enhance the resistance of cisplatin [72]. Accumulating studies have found that exosomes can transfer a variety of miRNAs to make cancer sensitive cells resistant to a variety of drugs in many cancers (Table 1).

Table 1: Exosomes derived from tumor cells participate in drug resistance by transporting ncRNAs

Exosomal markers	Tumor	Drug resistance	References
miR-21	Oral squamous carcinoma cisplatin-resistant cells	Enhance cisplatin resistance	[72]
miR-155	Pancreatic ductal cancer	Reduce gemcitabine resistance	[73]
miR-17, miR-30, miR-100, miR-222	Breast cancer sensitive	Enhance the resistance of docetaxel and adriamycin	[74]
miR-433	Ovarian cancer	Promote paclitaxel resistance	[75]
lncARSR	Renal cell carcinoma	Relieve resistant to sunitinib	[76]
lncRNA PART1	Esophageal squamous cell carcinoma	Enhance gefitinib resistance	[77]

(Continued)

Table 1 (continued)

Exosomal markers	Tumor	Drug resistance	References
Lnc-VLDLR	Hepatocellular carcinoma	Relieve resistant to sorafenib	[78,79]
lncRNA ROR	Hepatocellular carcinoma	Reduce sorafenib or adriamycin resistance	[80]
lncRNA RP11838N2.4	Non-small cell lung cancer	Promote erlotinib resistance	[81]
lncRNA UCA1	Bladder cancer	Enhance cisplatin resistance	[82]
lncRNA UCA1	Bladder cancer	Promote tamoxifen resistance	[83]
lncRNA AX747207	Bladder cancer	Promote tamoxifen resistance	[84]

In addition, lncRNA also plays an important role in tumor resistance. In advanced renal cell carcinoma (renal cell carcinoma, RCC), Wang et al. [76] found that exosomes derived from drug-resistant cells can impart sunitinib resistance to sensitive cells by delivering lncARSR, and its mechanism is competitively inhibited with lncARSR. After miR-34/miR-449 promoted the expression of c-Met and AXL, the AXL/c-MET inhibitors or targeted lncARSR treatment of sunitinib-resistant RCC can effectively relieve RCC tumor cells are resistant to sunitinib [76]. LncRNAs are involved in chemotherapy resistance and transfers its resistance to recipient cells in various cancers, including renal cell carcinoma, bladder cancer, breast cancer (Table 1).

2.3.2 Exosomes Derived from Tumor Cells Participate in Drug Resistance by Transporting Active Proteins

TDEs can transfer proteins to recipient cells, so that tumor-sensitive cells can acquire drug resistance. Researchers in a colon cancer study found that after co-cultivating exosomes secreted by the drug-resistant cell line RKO and colon cancer sensitive cell line Coca-2, the drug resistance of Coca-2 increased. Further research found that the mechanism may be due to exosomes derived from the drug-resistant cell line RKO can down-regulate PTEN proteins and increase the level of phosphorylated Akt, thereby inducing Cetuzumab resistance in Coca-2 cells [85]. Lv et al. [86] found that compared with breast cancer sensitive cells MCF-7/S, breast cancer drug-resistant cell lines MCF-7/DOC derived exosomes contain high levels of P-glycoprotein (P-gp). Exosomes derived from these drug-resistant cells MCF-7/DOC can transmit docetaxel resistance to sensitive cells MCF-7/S by delivering P-gp. Ning et al. [87] found that breast cancer drug-resistant cells highly express UCH-L1 protein and release these proteins into the TME through exosomes, thereby transferring chemotherapy resistance to recipient cells. Subsequently, researchers further confirmed that the mechanism of its transmission of drug resistance may be that the highly expressed UCH-L1 activates the MAPK/ERK signaling pathway to up-regulate the expression of P-gp, thereby enhancing breast cancer drug resistance [88].

2.3.3 Exosomes Derived from Stromal Cells Participate in Drug Resistance

Not only can tumor cells exchange information through exosomes, but exosomes released by stromal cells can also mediate drug resistance in tumor cells by delivering drug-resistant active molecules. Studies have found that in pancreatic ductal adenocarcinoma (PDAC), the sensitivity of exosome-release-deficient mice to gemcitabine is significantly higher than that of wild-type mice. In addition, it was confirmed that macrophage-derived exosomes (MDE) can induce PDAC mice to be resistant to gemcitabine by transporting miR-365 [42]. Lobb et al. [89] have shown that exosomes derived from mesenchymal and oncogene-transformed lung cells can transport ZEB1 mRNA to tumor recipient cells, thereby transporting chemoresistance and mesenchymal phenotypes to tumor cells. Exosomes secreted by TAMs can deliver cell signaling molecule miR-21 to gastric cancer tumor cells, thereby enhancing the resistance of gastric cancer to cisplatin. In addition, miR-21 inhibits cell apoptosis and promotes the activation of PI3 K/AKT

signaling pathway by down-regulating PTEN in gastric cancer [90]. Ji et al. [37,91] found that exosomes rich in human mesenchymal stem cells (MSC) can activate calcium/calmodulin-dependent protein kinase (CaMK) and Raf/MEK/ERK pathways, thereby antagonizing 5-fluorouracil-induced tumor cells apoptosis and further enhance the multi-drug resistance (MDR) protein in tumor cells, thereby promoting resistance of gastric cancer cells to 5-fluorouracil. Chi et al. [92] found that the expression level of miR-21 in exosomes derived from cancer-associated adipocytes (CAAs) and fibroblasts (CAFs) was higher than that in exosomes derived from ovarian cancer cells. In-depth studies have shown that miR-21 can transfer from CAAs or CAFs to ovarian cancer cells, thereby inhibiting the apoptosis of ovarian cancer cells and directly binding to its target molecule APAF1 to trigger drug resistance. The above data indicate in the microenvironment of omental tumors, exosomes released from adjacent stromal cells of the tumor can change the malignant biological behavior of metastatic ovarian cancer cells by transporting and inhibiting miR-21 in exosomes. Metastasis is another new way to treat highly metastatic and highly recurring ovarian cancer. Researchers from Wang et al. [93] found that the antagonism of PGE2/EP4 can induce exosome-mediated clearance of tumor stem cells, and this effect can weaken the resistance of MSCs to tumor chemotherapy drugs and enhance the sensitivity of tumor chemotherapy.

2.3.4 Exosomes Directly Mediate the Efflux of Drug Molecules

Exosomes encapsulate anti-cancer drugs in tumor cells and mediate the efflux of drug molecules, thereby reducing the treatment of anti-tumor drugs. Shedden et al. [94] tracked the anti-tumor drug doxorubicin via fluorescent pulse tracking and found that tumor cells can shed the drug by shedding vesicles (exosomes). At the same time, studies have found that many transporters such as multidrug resistance related protein 1 (MRP-1), P-gp, and ATP transport protein (ABCA3), breast cancer resistance protein (BCRP) and other proteins, this type of protein has the same transmembrane domain, also known as MDR-ABC transporter protein.

3 The Role of Exosomes in the Treatment of Tumor Resistance

Exosomes play an important role in the treatment of tumor resistance. Exosomes derived from tumor cells and stromal cells can transmit drug resistance, which reduces the efficacy of chemotherapy. Therefore, the drug resistance of tumor cells can be reversed by inhibiting the secretion of exosomes or using nanoparticles to deliver anti-miRNA and changing the composition of exosomes to improve the therapeutic effect. Studies have shown that rapamycin and U18666A can inhibit the release of exosomes by interfering with the synthesis of MVBs and the participation of cholesterol in the formation of cell membranes, respectively, thereby increasing the sensitivity of B lymphoma to rituximab [95]. At the same time, there are reports that exosomes can act as nanoparticles to encapsulate miRNA-214 and deliver it to cisplatin-resistant gastric cancer cells to reverse the resistance of gastric cancer to cisplatin [96]. Some researchers have also found that β-elemeneact on the target genes of drug-resistant breast cancer cell lines, thereby affecting the content of related drug-resistant miRNAs rich in exosomes, and thereby reducing the amount of external drug resistance transmission efficiency [97]. In addition, it has been reported that exosomal miR-567 is associated with inhibition of autophagy related 5 (ATG5) protein and reversal of resistance to trastuzumab in breast cancer [98]. Recently, a drug nanocarrier for targeted chemotherapy of liver cancer has been developed [99]. This novel strategy utilized homotypic HepG2 cell membrane as cloak and polylactic acid glycolic acid (PLGA) nanoparticles as core to prepare nano-carrier hepm PLGA, which is then to be used as carrier of doxorubicin. Their study has shown high release efficiency and significant therapeutic effect *in vivo* and *in vitro* for this strategy, highlighting the the promising role of this strategy for drug-resistant HCC. In 2021, it has been reported that iRGD-modified (iRGD: a 9-amino acid cyclic peptide) exosomes with siCPT1A, which is a key enzyme in the process of fatty acid oxidation (FAO), could specifically transport siCPT1A into colorectal cancer cells to suppress FAO. Given the crucial role of FAO in drug resistance of colorectal cancer cells, iRGD-modified

exosomes can significantly suppress the expression of CPT1A in colorectal cancer cells and therefore reversed the resistance to oxaliplatin resistance by inhibiting FAO [100]. Moreover, Lima et al. [101] have suggested that accumulation of CCL2-modified exosomes will lead to the change in the immune environment of affected organs, thereby mediating the chemoresistance the chancer cells. Based on these above results, it is reasonable to believe application of exosomes can be considered as a novel strategy to overcome chemoresistance in cancer cells.

4 Prospects and Challenges

Exosomes are a communication tool for transporting substances and transmitting information between cells, and they play an important role in the progression of TME. Exosomes and their contents (miRNAs, lncRNAs, and proteins) are closely related to the occurrence of tumor resistance. They activate signal pathways in cells by fusion with target cells, antigen presentation, and receptor-ligand interactions. However, the physiological and pathological roles of exosomes in the TME need to be further explored.

The number and heterogeneity of exosomes in body fluids may be their shortcomings as biomarkers, that may lead to false negatives or positives in tumor diagnosis. To overcome these obstacles, the precise regulatory mechanism of exosomes in tumor progression needed to be well understood in assisting with cancer diagnosis and cancer prognosis. It is expected that in the near future, exosomes can be used as liquid biopsy and non-invasive biomarkers for early detection of tumors. In addition, exosomes as drug carriers to treat tumors will also become an effective treatment strategy. The review of exosomes-mediated tumor chemotherapy resistance provides insight to reveal the molecular mechanism of tumor resistance and motivation for the search for drug resistance markers and new treatment methods for tumors.

Author Contributions: Haojie Zhang and Xiaohong Wang conceived and designed the study. Yue Yu was responsible for materials. Haojie Zhang and Xiaohong Wang drafted the article. Xiaohong Wang and Zhenlin Yang revised the article critically. All authors had final approval of the submitted versions.

Ethic Approval and Informed Consent Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of Data and Materials: All data generated or analysed during this study are included in this published article. And all the data is real and available.

Funding Statement: This work was supported by National Natural Science Foundation of China [Nos. 81902702, 31801085], Natural Science Foundation of Shandong Province [Nos. ZR2017LH072, ZR2017MH033], Projects of Binzhou Technology Development Program [No. 2015ZC0301], National Key Research and Development Project [No. 2018YFC0114705], Scientific Research Staring Foundation of Binzhou Medical University [Nos. BY2014KYQD36, BY2014KJ36, BY2017KJ01], Science and Technology Program of Universities in Shandong Province [No. J15LL51]. The Special Funds for the Qilu Health and Health Leading Talents Cultivation Project (Wang xiaohong).

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

References

1. Takenaka, M., Köbel, M., Garsed, D. W., Fereday, S., Pandey, A. et al. (2019). Survival following chemotherapy in ovarian clear cell carcinoma is not associated with pathological misclassification of tumor histotype. *Clinical Cancer Research, 25(13),* 3962–3973. DOI 10.1158/1078-0432.CCR-18-3691.

2. Greenbaum, A., Martin, D. R., Bocklage, T., Lee, J. H., Ness, S. A. et al. (2019). Tumor heterogeneity as a predictor of response to neoadjuvant chemotherapy in locally advanced rectal cancer. *Clinical Colorectal Cancer, 18(2),* 102–109. DOI 10.1016/j.carolcarrollLCC2019.02.003.
3. Yoshida, Y., Beppu, T., Kinoshita, K., Sato, N., Akahoshi, S. et al. (2019). Five-year recurrence-free survival after surgery followed by oral chemotherapy for gastric cancer with portal vein tumor thrombosis. *Anticancer Research, 39(4),* 2233–2238. DOI 10.21873/anticanres.13339.
4. He, W., Hou, M., Zhang, H., Zeng, C., He, S. et al. (2019). Clinical significance of circulating tumor cells in predicting disease progression and chemotherapy resistance in patients with gestational choriocarcinoma. *International Journal of Cancer, 144(6),* 1421–1431. DOI 10.1002/ijc.31742.
5. Blanas, A., Sahasrabudhe, N. M., Rodríguez, E., van Kooyk, Y., van Vliet, S. J. (2018). Corrigendum: Fucosylated antigens in cancer: An alliance toward tumor progression, metastasis, and resistance to chemotherapy. *Frontiers in Oncology, 8150,* 1–14. DOI 10.3389/fonc.2018.00150.
6. Wang, R., Yang, L. (2017). Research progress of multidrug resistance in tumor chemotherapy. *Shandong Chemical Industry, 46(9),* 44–49. DOI 10.3969/j.issn.1008-021X.2017.09.016.
7. Mathivanan, S., Ji, H., Simpson, R. J. (2010). Exosomes: Extracellular organelles important in intercellular communication. *Journal of Proteomics, 73(10),* 1907–1920. DOI 10.1016/j.jprot.2010.06.006.
8. Yu, D., Wu, Y., Shen, H., Lv, M., Chen, W. et al. (2015). Exosomes in development, metastasis and drug resistance of breast cancer. *Cancer Science, 106(8),* 959–964. DOI 10.1111/cas.12715.
9. Pan, B. T., Teng, K., Wu, C., Adam, M., Johnstone, R. M. (1985). Electron microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. *The Journal of Cell Biology, 101(3),* 942–948. DOI 10.1083/jcb.101.3.942.
10. Chevillet, J. R., Kang, Q., Ruf, I. K., Briggs, H. A., Vojtech, L. N. et al. (2014). Quantitative and stoichiometric analysis of the microrna content of exosomes. *Proceedings of the National Academy of Sciences, 111(41),* 14888–14893. DOI 10.1073/pnas.1408301111.
11. Admyre, C., Johansson, S. M., Qazi, K. R., Filén, J. J., Lahesmaa, R. et al. (2007). Exosomes with immune modulatory features are present in human breast milk. *The Journal of Immunology, 179(3),* 1969–1978. DOI 10.4049/jimmunol.179.3.1969.
12. Shi, R., Wang, P. Y., Li, X. Y., Chen, J. X., Li, Y. et al. (2015). Exosomal levels of miRNA-21 from cerebrospinal fluids associated with poor prognosis and tumor recurrence of glioma patients. *Oncotarget, 6(29),* 26971–26981. DOI 10.18632/oncotarget.4699.
13. Caby, M. P., Lankar, D., Vincendeau-Scherrer, C., Raposo, G., Bonnerot, C. (2005). Exosomal-like vesicles are present in human blood plasma. *International Immunology, 17(7),* 879–887. DOI 10.1093/intimm/dxh267.
14. Stranford, D. M., Leonard, J. N. (2017). Delivery of biomolecules via extracellular vesicles: A budding therapeutic strategy. *Advances in Genetics, 98,* 155–175. DOI 10.1016/bs.adgen.2017.08.002.
15. Blanchard, N., Lankar, D., Faure, F., Regnault, A., Dumont, C. et al. (2002). TCR activation of human T cells induces the production of exosomes bearing the TCR/CD3/ζ complex. *The Journal of Immunology, 168(7),* 3235–3241. DOI 10.4049/jimmunol.168.7.3235.
16. Poliakov, A., Spilman, M., Dokland, T., Amling, C. L., Mobley, J. A. (2009). Structural heterogeneity and protein composition of exosome-like vesicles (prostasomes) in human semen. *The Prostate, 69(2),* 159–167. DOI 10.1002/pros.20860.
17. Vyas, N., Dhawan, J. (2017). Exosomes: Mobile platforms for targeted and synergistic signaling across cell boundaries. *Cellular and Molecular Life Sciences, 74(9),* 1567–1576. DOI 10.1007/s00018-016-2413-9.
18. Hanahan, D., Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell, 144(5),* 646–674. DOI 10.1016/j.cell.2011.02.013.
19. Hede, K. (2004). Environmental protection: Studies highlight importance of tumor microenvironment. *Journal of the National Cancer Institute, 96(15),* 1120–1121. DOI 10.1093/jnci/96.15.1120.
20. Valadi, H., Ekström, K., Bossios, A., Sjöstrand, M., Lee, J. J. et al. (2007). Exosome-mediated transfer of mRNAs and mRNAs is a novel mechanism of genetic exchange between cells. *Nature Cell Biology, 9(6),* 654–659. DOI 10.1038/ncb1596.

21. Zhuo, X., Chang, A., Huang, C., Yang, L., Xiang, Z. et al. (2015). Expression and clinical significance of microvessel density and its association with twist in nasopharyngeal carcinoma. *International Journal of Clinical Experimental Medicine, 8(1),* 1265–1270.
22. Fu, M., Gu, J., Jiang, P., Qian, H., Xu, W. et al. (2019). Exosomes in gastric cancer: Roles, mechanisms, and applications. *Molecular Cancer, 18(1),* 1–12. DOI 10.1186/s12943-019-1001-7.
23. Xu, R., Greening, D. W., Chen, M., Rai, A., Ji, H. et al. (2019). Surfaceome of exosomes secreted from the colorectal cancer cell line SW480: Peripheral and integral membrane proteins analyzed by proteolysis and TX114. *Proteomics, 19(8),* 1700453. DOI 10.1002/pmic.201700453e1700453.
24. Sun, X. H., Wang, X., Zhang, Y., Hui, J. (2019). Exosomes of bone-marrow stromal cells inhibit cardiomyocyte apoptosis under ischemic and hypoxic conditions via miR-486-5p targeting the PTEN/PI3K/AKT signaling pathway. *Thrombosis Research, 177,* 23–32. DOI 10.1016/j.thromres.2019.02.002.
25. Bai, X., Guo, Y., Shi, Y., Lin, J., Tarique, I. et al. (2019). *In vivo* multivesicular bodies and their exosomes in the absorptive cells of the zebrafish (*Danio Rerio*) gut. *Fish & Shellfish Immunology, 88,* 578–586. DOI 10.1016/j.fsi.2019.03.030.
26. Deng, L., Jiang, W., Wang, X., Merz, A., Hiet, M. S. et al. (2019). Syntenin regulates hepatitis C virus sensitivity to neutralizing antibody by promoting E2 secretion through exosomes. *Journal of Hepatology, 71(1),* 52–61. DOI 10.1016/j.jhep.2019.03.006.
27. Chew, J. R. J., Chuah, S. J., Teo, K. Y. W., Zhang, S., Lai, R. C. et al. (2019). Mesenchymal stem cell exosomes enhance periodontal ligament cell functions and promote periodontal regeneration. *Acta Biomaterialia, 89,* 252–264. DOI 10.1016/j.actbio.2019.03.021.
28. Zhou, W., Woodson, M., Sherman, M. B., Neelakanta, G., Sultana, H. (2019). Exosomes mediate zika virus transmission through SMPD3 neutral sphingomyelinase in cortical neurons. *Emerging Microbes & Infections, 8(1),* 307–326. DOI 10.1080/22221751.2019.1578188.
29. Song, L., Wang, L., Wang, J. (2018). Research progress on the role of exosomes in tumor invasion and metastasis. *Life Science Research Institute Investigate, 22(4),* 326–331. DOI 10.16605/j.cnki.1007-7847.2018.04.010.
30. Del Re, M., Marconcini, R., Pasquini, G., Rofi, E., Vivaldi, C. et al. (2018). PD-L1 mRNA expression in plasma-derived exosomes is associated with response to anti-PD-1 antibodies in melanoma and NSCLC. *British Journal of Cancer, 118(6),* 820–824. DOI 10.1038/bjc.2018.9.
31. Camacho, L., Guerrero, P., Marchetti, D. (2013). Microrna and protein profiling of brain metastasis competent cell-derived exosomes. *PLoS One, 8(9),* e73790. DOI 10.1371/journal.pone.0073790.
32. Xiao, D., Ohlendorf, J., Chen, Y., Taylor, D. D., Rai, S. N. et al. (2012). Identifying mRNA, MicroRNA and protein profiles of melanoma exosomes. *PLoS One, 7(10),* e46874. DOI 10.1371/journal.pone.0046874.
33. Mathivanan, S., Lim, J. W., Tauro, B. J., Ji, H., Moritz, R. L. et al. (2010). Proteomics analysis of A33 immunoaffinity-purified exosomes released from the human colon tumor cell line LIM1215 reveals a tissue-specific protein signature. *Molecular & Cellular Proteomics, 9(2),* 197–208. DOI 10.1074/mcp.M900152-MCP200.
34. Ragusa, M., Barbagallo, C., Statello, L., Caltabiano, R., Russo, A. et al. (2015). Mirna profiling in vitreous humor, vitreal exosomes and serum from uveal melanoma patients: Pathological and diagnostic implications. *Cancer Biology & Therapy, 16(9),* 1387–1396. DOI 10.1080/15384047.2015.1046021.
35. Que, R., Lin, C., Ding, G., Wu, Z., Cao, L. (2016). Increasing the immune activity of exosomes: The effect of mirna-depleted exosome proteins on activating dendritic cell/cytokine-induced killer cells against pancreatic cancer. *Journal of Zhejiang University–Science B, 17(5),* 352–360. DOI 10.1631/jzus.B1500305.
36. Azmi, A. S., Bao, B., Sarkar, F. H. (2013). Exosomes in cancer development, metastasis, and drug resistance: A comprehensive review. *Cancer and Metastasis Reviews, 32(3),* 623–642. DOI 10.1007/s10555-013-9441-9.
37. Ji, R., Zhang, B., Zhang, X., Xue, J., Yuan, X. et al. (2015). Exosomes derived from human mesenchymal stem cells confer drug resistance in gastric cancer. *Cell Cycle, 14(15),* 2473–2483. DOI 10.1080/15384101.2015.1005530.
38. Yu, D., Wu, Y., Zhang, X., Lv, M., Chen, W. et al. (2016). Exosomes from Adriamycin-resistant breast cancer cells transmit drug resistance partly by delivering miR-222. *Tumor Biology, 37(3),* 3227–3235. DOI 10.1007/s13277-015-4161-0.

39. André, M. R., Pedro, A., Lyden, D. (2016). Cancer exosomes as mediators of drug resistance. *Methods in Molecular Biology, 139,* 5229–5239. DOI 10.1007/978-1-4939-3347-1_13.
40. Zhong, S., Chen, X., Wang, D., Zhang, X., Shen, H. et al. (2016). MicroRNA expression profiles of drug-resistance breast cancer cells and their exosomes. *Oncotarget, 7(15),* 19601–19609. DOI 10.18632/oncotarget.7481.
41. Bach, D. H., Hong, J. Y., Park, H. J., Lee, S. K. (2017). The role of exosomes and miRNAs in drug-resistance of cancer cells. *International Journal of Cancer, 141(2),* 220–230. DOI 10.1002/ijc.30669.
42. Binenbaum, Y., Fridman, E., Yaari, Z., Milman, N., Schroeder, A. et al. (2018). Transfer of miRNA in macrophage-derived exosomes induces drug resistance in pancreatic adenocarcinoma. *Cancer Research, 78(18),* 5287–5299. DOI 10.1158/0008-5472.CAN-18-0124.
43. Sharma, A. (2017). Chemoresistance in cancer cells: Exosomes as potential regulators of therapeutic tumor heterogeneity. *Nanomedicine, 12(17),* 2137–2148. DOI 10.2217/nnm-2017-0184.
44. Chapuy, B., Koch, R., Radunski, U., Corsham, S., Cheong, N. et al. (2008). Intracellular ABC transporter A3 confers multidrug resistance in leukemia cells by lysosomal drug sequestration. *Leukemia, 22(8),* 1576–1586. DOI 10.1038/leu.2008.103.
45. Koch, R., Aung, T., Vogel, D., Chapuy, B., Wenzel, D. et al. (2016). Nuclear trapping through inhibition of exosomal export by indomethacin increases cytostatic efficacy of doxorubicin and pixantrone. *Clinical Cancer Research, 22(2),* 395–404. DOI 10.1158/1078-0432.CCR-15-0577.
46. Chen, F., Zhang, W. (2016). The influence of exosomes derived from tumor cells and stromal cells on tumor drug resistance. *Chinese Journal of Cancer Biotherapy, 23(3),* 432–436. DOI 10.3872/j.issn.1007-385X.2016.03.025.
47. Chowdhury, R., Webber, J. P., Gurney, M., Mason, M. D., Tabi, Z. et al. (2015). Cancer exosomes trigger mesenchymal stem cell differentiation into pro-angiogenic and pro-invasive myofibroblasts. *Oncotarget, 6(2),* 715–731. DOI 10.18632/oncotarget.2711.
48. Cho, J. A., Park, H., Lim, E. H., Kim, K. H., Choi, J. S. et al. (2011). Exosomes from ovarian cancer cells induce adipose tissue-derived mesenchymal stem cells to acquire the physical and functional characteristics of tumor-supporting myofibroblasts. *Gynecologic Oncology, 123(2),* 379–386. DOI 10.1016/j.ygyno.2011.08.005.
49. Rak, J. (2013). Extracellular vesicles–biomarkers and effectors of the cellular interactome in cancer. *Frontiers in Pharmacology, 421,* 1–14. DOI 10.3389/fphar.2013.00021.
50. Perrimon, N., Pitsouli, C., Shilo, B. Z. (2012). Signaling mechanisms controlling cell fate and embryonic patterning. *Cold Spring Harbor Perspectives in Biology, 4(8),* a005975. DOI 10.1101/cshperspect.a005975.
51. Pikkarainen, T., Nurmi, T., Sasaki, T., Bergmann, U., Vainio, S. (2017). Role of the extracellular matrix-located Mac-2 binding protein as an interactor of the Wnt proteins. *Biochemical and Biophysical Research Communications, 491(4),* 953–957. DOI 10.1016/j.bbrc.2017.07.141.
52. Gross, J. C., Chaudhary, V., Bartscherer, K., Boutros, M. (2012). Active Wnt proteins are secreted on exosomes. *Nature Cell Biology, 14(10),* 1036–1045. DOI 10.1038/ncb2574.
53. Lin, R., Wang, S., Zhao, R. C. (2013). Exosomes from human adipose-derived mesenchymal stem cells promote migration through wnt signaling pathway in a breast cancer cell model. *Molecular and Cellular Biochemistry, 383(1),* 13–20. DOI 10.1007/s11010-013-1746-z.
54. Lundholm, M., Schröder, M., Nagaeva, O., Baranov, V., Widmark, A. et al. (2014). Prostate tumor-derived exosomes down-regulate NKG2D expression on natural killer cells and $CD8^+$ T cells: Mechanism of immune evasion. *PLoS One, 9(9),* e108925. DOI 10.1371/journal.pone.0108925.
55. Whiteside, T. L. (2015). Re: Effect of nasopharyngeal carcinoma-derived exosomes on human regulatory T cells. *JNCI: Journal of the National Cancer Institute, 107(12),* djv276. DOI 10.1093/jnci/djv276.
56. Giordano, C., La Camera, G., Gelsomino, L., Barone, I., Bonofiglio, D. et al. (2020). The biology of exosomes in breast cancer progression: Dissemination, immune evasion and metastatic colonization. *Cancers, 12(8),* 2179. DOI 10.3390/cancers12082179.
57. Liu, C., Yu, S., Zinn, K., Wang, J., Zhang, L. et al. (2006). Murine mammary carcinoma exosomes promote tumor growth by suppression of NK cell function. *The Journal of Immunology, 176(3),* 1375–1385. DOI 10.4049/jimmunol.176.3.1375.

58. Daassi, D., Mahoney, K. M., Freeman, G. J. (2020). The importance of exosomal PDL1 in tumour immune evasion. *Nature Reviews Immunology, 20(4),* 209–215. DOI 10.1038/s41577-019-0264-y.
59. Qadir, F., Aziz, M. A., Sari, C. P., Ma, H., Dai, H. et al. (2018). Transcriptome reprogramming by cancer exosomes: Identification of novel molecular targets in matrix and immune modulation. *Molecular Cancer, 17(1),* 1–16. DOI 10.1186/s12943-018-0846-5.
60. Mathivanan, S., Fahner, C. J., Reid, G. E., Simpson, R. J. (2012). ExoCarta 2012: Database of exosomal proteins, RNA and lipids. *Nucleic Acids Research, 40,* D1241–D1244. DOI 10.1093/nar/gkr828.
61. Hannafon, B. N., Ding, W. Q. (2013). Intercellular communication by exosome-derived microRNAs in cancer. *International Journal of Molecular Sciences, 14(7),* 14240–14269. DOI 10.3390/ijms140714240.
62. Bang, C., Thum, T. (2012). Exosomes: New players in cell–cell communication. *The International Journal of Biochemistry & Cell Biology, 44(11),* 2060–2064. DOI 10.1016/j.biocel.2012.08.007.
63. Mostafazadeh, M., Samadi, N., Kahroba, H., Baradaran, B., Haiaty, S. et al. (2021). Potential roles and prognostic significance of exosomes in cancer drug resistance. *Cell & Bioscience, 11(1),* 1–15. DOI 10.1186/s13578-020-00515-y.
64. He, Q. (2016). Tumor heterogeneity and drug resistance of targeted antitumor agents. *Acta Pharmaceutica Sinica, 51(2),* 197–201. DOI 10.16438/j.0513-4870.2015-1029.
65. Saleem, S. N., Abdel-Mageed, A. B. (2015). Tumor-derived exosomes in oncogenic reprogramming and cancer progression. *Cellular and Molecular Life Sciences, 72(1),* 1–10. DOI 10.1007/s00018-014-1710-4.
66. Kibria, G., Hatakeyama, H., Harashima, H. (2014). Cancer multidrug resistance: Mechanisms involved and strategies for circumvention using a drug delivery system. *Archives of Pharmacal Research, 37(1),* 4–15. DOI 10.1007/s12272-013-0276-2.
67. Fan, Q., Yang, L., Zhang, X., Peng, X., Wei, S. et al. (2018). The emerging role of exosome-derived non-coding RNAs in cancer biology. *Cancer Letters, 414,* 107–115. DOI 10.1016/j.canlet.2017.10.040.
68. Deng, H., Zhang, J., Shi, J., Guo, Z., He, C. et al. (2016). Role of long non-coding RNA in tumor drug resistance. *Tumor Biology, 37(9),* 11623–11631. DOI 10.1007/s13277-016-5125-8.
69. Liu, H., Li, Z., Wang, C., Feng, L., Huang, H. et al. (2016). Expression of long non-coding RNA-HOTAIR in oral squamous cell carcinoma Tca8113 cells and its associated biological behavior. *American Journal of Translational Research, 8(11),* 4726–4734.
70. Yan, J., Cheng, Y., Chen, J. (2016). Chemoresistance and non-coding RNA. *Chinese Journal of Pathology, 45(7),* 498–500. DOI 10.3760/cma.j.issn.0529-5807.2016.07.021.
71. Wang, Y., Zhang, L., Zheng, X., Zhong, W., Tian, X. et al. (2016). Long non-coding RNA *LINC00161* sensitises osteosarcoma cells to cisplatin-induced apoptosis by regulating the *miR-645-IFIT2* axis. *Cancer Letters, 382(2),* 137–146. DOI 10.1016/j.canlet.2016.08.024.
72. Liu, T., Chen, G., Sun, D., Lei, M., Li, Y. et al. (2017). Exosomes containing miR-21 transfer the characteristic of cisplatin resistance by targeting PTEN and PTEN in oral squamous cell carcinoma. *Acta Biochimica et Biophysica Sinica, 49(9),* 808–816. DOI 10.1093/abbs/gmx078.
73. Szedlak, A., Smith, N., Liu, L., Paternostro, G., Piermarocchi, C. (2016). Evolutionary and topological properties of genes and community structures in human gene regulatory networks. *PLoS Computational Biology, 12(6),* e1005009. DOI 10.1371/journal.pcbi.1005009.
74. Mikamori, M., Yamada, D., Eguchi, H., Hasegawa, S., Kishimoto, T. et al. (2017). MicroRNA-155 controls exosome synthesis and promotes gemcitabine resistance in pancreatic ductal adenocarcinoma. *Scientific Reports, 7(1),* 1–14. DOI 10.1038/srep42339.
75. Chen, W., Liu, X., Lv, M., Chen, L., Zhao, J. et al. (2014). Exosomes from drug-resistant breast cancer cells transmit chemoresistance by a horizontal transfer of micrornas. *PLoS One, 9(4),* e95240. DOI 10.1371/journal.pone.0095240.
76. Qu, L., Ding, J., Chen, C., Wu, Z. J., Liu, B. et al. (2016). Exosome-transmitted lncARSR promotes sunitinib resistance in renal cancer by acting as a competing endogenous RNA. *Cancer Cell, 29(5),* 653–668. DOI 10.1016/j.ccell.2016.03.004.

77. Kang, M., Ren, M., Li, Y., Fu, Y., Deng, M. et al. (2018). Exosome-mediated transfer of lncRNA PART1 induces gefitinib resistance in esophageal squamous cell carcinoma via functioning as a competing endogenous RNA. *Journal of Experimental & Clinical Cancer Research, 37(1),* 1–16. DOI 10.1186/s13046-018-0845-9.

78. Kunej, T., Obsteter, J., Pogacar, Z., Horvat, S., Calin, G. A. (2014). The decalog of long non-coding rna involvement in cancer diagnosis and monitoring. *Critical Reviews in Clinical Laboratory Sciences, 51(6),* 344–357. DOI 10.3109/10408363.2014.944299.

79. Takahashi, K., Yan, I. K., Wood, J., Haga, H., Patel, T. (2014). Involvement of extracellular vesicle long noncoding RNA (linc-VLDLR) in tumor cell responses to chemotherapy. *Molecular Cancer Research, 12(10),* 1377–1387. DOI 10.1158/1541-7786.MCR-13-0636.

80. Takahashi, K., Yan, I. K., Kogure, T., Haga, H., Patel, T. (2014). Extracellular vesicle-mediated transfer of long non-coding RNA ROR modulates chemosensitivity in human hepatocellular cancer. *FEBS Open Bio, 4,* 458–467. DOI 10.1016/j.fob.2014.04.007.

81. Zhang, W., Cai, X., Yu, J., Lu, X., Qian, Q. et al. (2018). Exosome-mediated transfer of lncrna lncRNA RP11-838N2.4 promotes erlotinib resistance in non-small cell lung cancer. *International Journal of Oncology, 53(2),* 527–538. DOI 10.3892/ijo.2018.4412.

82. Fan, Y., Shen, B., Tan, M., Mu, X., Qin, Y. et al. (2014). Long non-coding RNA UCA1 increases chemoresistance of bladder cancer cells by regulating Wnt signaling. *The FEBS Journal, 281(7),* 1750–1758. DOI 10.1111/febs.12737.

83. Xu, C., Yang, M., Ren, Y., Wu, C., Wang, L. (2016). Exosomes mediated transfer of lncRNA UCA1 results in increased tamoxifen resistance in breast cancer cells. *European Review for Medical and Pharmacological Sciences, 20,* 4362–4368.

84. Huang, L., Zeng, L., Chu, J., Xu, P., Lv, M. et al. (2019). Chemoresistance-related long non-coding RNA expression profiles in human breast cancer cells. *Molecular Medicine Reports, 19(5),* 3956–3957. DOI 10.3892/mmr.

85. Zhang, S., Zhang, Y., Qu, J., Che, X., Fan, Y. et al. (2017). Exosomes promote cetuximab resistance via the PTEN/Akt pathway in colon cancer cells. *Brazilian Journal of Medical and Biological Research, 51,* e6472. DOI 10.1590/1414-431X20176472.

86. Lv, M., Zhu, X., Chen, W., Zhong, S., Hu, Q. et al. (2014). Exosomes mediate drug resistance transfer in MCF-7 breast cancer cells and a probable mechanism is delivery of P-glycoprotein. *Tumor Biology, 35(11),* 10773–10779. DOI 10.1007/s13277-014-2377-z.

87. Ning, K., Wang, T., Sun, X., Zhang, P., Chen, Y. et al. (2017). Uch-l1-containing exosomes mediate chemotherapeutic resistance transfer in breast cancer. *Journal of Surgical Oncology, 115(8),* 932–940. DOI 10.1002/jso.24614.

88. Wang, W., Zou, L., Zhou, D., Zhou, Z., Tang, F. et al. (2016). Overexpression of ubiquitin carboxyl terminal hydrolase-l1 enhances multidrug resistance and invasion/metastasis in breast cancer by activating the MAPK/Erk signaling pathway. *Molecular Carcinogenesis, 55(9),* 1329–1342. DOI 10.1002/mc.22376.

89. Lobb, R. J., van Amerongen, R., Wiegmans, A., Ham, S., Larsen, J. E. et al. (2017). Exosomes derived from mesenchymal non-small cell lung cancer cells promote chemoresistance. *International Journal of Cancer, 141(3),* 614–620. DOI 10.1002/ijc.30752.

90. Zheng, P., Chen, L., Yuan, X., Luo, Q., Liu, Y. et al. (2017). Exosomal transfer of tumor-associated macrophage-derived miR-21 confers cisplatin resistance in gastric cancer cells. *Journal of Experimental & Clinical Cancer Research, 36(1),* 1–13. DOI 10.1186/s13046-017-0528-y.

91. Wang, S., Kong, X., Du, L. (2017). Research on exosomes and drug resistance to tumorization therapy is advanced. *Swelling Lump, 37(2),* 184–187. DOI 10.3781/j.issn.1000-7431.2017.55.719.

92. Yeung, C. L. A., Co, N. N., Tsuruga, T., Yeung, T. L., Kwan, S. Y. et al. (2016). Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1. *Nature Communications, 7(1),* 1–14. DOI 10.1038/ncomms11150.

93. Wang, J., Zhang, L., Kang, D., Yang, D., Tang, Y. (2018). Activation of PGE2/EP2 and PGE2/EP4 signaling pathways positively regulate the level of PD-1 in infiltrating $CD8^+$ T cells in patients with lung cancer. *Oncology Letters, 15(1),* 552–558. DOI 10.3892/ol.2017.7279.

94. Shedden, K., Xie, X. T., Chandaroy, P., Chang, Y. T., Rosania, G. R. (2003). Expulsion of small molecules in vesicles shed by cancer cells: Association with gene expression and chemosensitivity profiles. *Cancer Research, 63(15),* 4331–4337.
95. Aung, T., Chapuy, B., Vogel, D., Wenzel, D., Oppermann, M. et al. (2011). Exosomal evasion of humoral immunotherapy in aggressive B-cell lymphoma modulated by ATP-binding cassette transporter A3. *Proceedings of the National Academy of Sciences, 108(37),* 15336–15341. DOI 10.1073/pnas.1102855108.
96. Wang, X., Zhang, H., Bai, M., Ning, T., Ge, S. et al. (2018). Exosomes serve as nanoparticles to deliver anti-miR-214 to reverse chemoresistance to cisplatin in gastric cancer. *Molecular Therapy, 26(3),* 774–783. DOI 10.1016/j.ymthe.2018.01.001.
97. Zhang, J., Yao, Y. F., Zhong, S. L., Zhao, J. H., Tang, J. H. (2015). B-elemene reverses chemoresistance of breast cancer cells by reducing resistance transmission via exosomes. *Cellular Physiology and Biochemistry, 36(6),* 2274–2286. DOI 10.1159/000430191.
98. Han, M., Hu, J., Lu, P., Cao, H., Yu, C. et al. (2020). Exosome-transmitted miR-567 reverses trastuzumab resistance by inhibiting ATG5 in breast cancer. *Cell Death & Disease, 11(1),* 1–15. DOI 10.1038/s41419-020-2250-5.
99. Liu, X., Sun, Y., Xu, S., Gao, X., Kong, F. et al. (2019). Homotypic cell membrane-cloaked biomimetic nanocarrier for the targeted chemotherapy of hepatocellular carcinoma. *Theranostics, 9(20),* 5828–5838. DOI 10.7150/thno.34837.
100. Lin, D., Zhang, H., Liu, R., Deng, T., Ning, T. et al. (2021). iRGD-modified exosomes effectively deliver *CPT1A siRNA* to colon cancer cells, reversing oxaliplatin resistance by regulating fatty acid oxidation. *Molecular Oncology, 15(12),* 3430–3446. DOI 10.1002/1878-0261.13052.
101. Lima, L. G., Ham, S., Shin, H., Chai, E. P., Lek, E. S. et al. (2021). Tumor microenvironmental cytokines bound to cancer exosomes determine uptake by cytokine receptor-expressing cells and biodistribution. *Nature Communications, 12(1),* 1–12. DOI 10.1038/s41467-021-23946-8.