Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD26550

Application and Prospect of Exosomes in Tumor Drug Delivery

Xingrong Chen[1], Haodong Fang[2*], Jiayi Hao[3]

[1]*College of Pharmacology, Nanjing Tech University, Nanjing, China*
[2]*College of Food and Health, Zhejiang Agricultural and Forestry University, Harbin, China*
[3]*College of Plant Protection, Northeast Agricultural University, Harbin, China*
**Corresponding Author. Email: fhdzuishuai@stu.zafu.edu.cn*

Abstract. Exosomes have emerged as promising oncology drug delivery vectors due to their natural biocompatibility, low immunogenicity, ability to cross biological barriers, and potential tumor targeting. This article summarizes the biological properties of exosomes, their advantages as drug carriers and the design principles of their delivery systems, and reviews the latest research progress of exosomes in the field of antitumor drug delivery by type of loaded drug. Studies have shown that through engineering transformation, the drug loading efficiency, tumor targeting specificity and therapeutic effect of exosomes have been significantly improved, and breakthroughs have been made in the delivery of chemotherapy drugs, nucleic acid drugs and immunomodulators. However, achieving clinical transformation still faces key challenges such as standardized production, improving targeting accuracy, and promoting industrialization. Although exosome research is still in its early stages, the existing results have fully demonstrated its broad application prospects and provided breakthrough treatment strategies for refractory diseases such as tumors.

Keywords: Exosomes, tumor, drug delivery.

1. Introduction

Tumour is a disease in which cells proliferate abnormally caused by a genetic mutation. Benign tumors grow relatively slowly, usually do not metastasize, and cannot grow back after surgical resection. Malignant tumors (i.e., cancer) have a high lethality rate and are prone to metastasis in the human body. Compared with benign tumors, the symptoms of malignant tumors are more complex, and their treatment often requires a combination of chemotherapy drugs and other means in addition to surgery.

At present, the research and development of tumor drugs is facing multi-dimensional challenges, and the core lies in the complexity and dynamic evolution characteristics of tumors themselves. Researchers must develop highly personalized treatment plans and weigh the high cost of drug development while accurately typing. In addition, drug resistance is another key factor in cancer treatment failure. Today's traditional chemotherapy drugs are less selective, and while killing cancer cells, they can also damage rapidly proliferating normal cells, leading to serious side effects such as bone marrow suppression, nausea and vomiting, and hair loss. Targeted drugs and immunotherapies,

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.LD26550

although more precise, still carry the risk of toxic side effects (e.g., targeted drugs may cause skin toxicity or cardiotoxicity, and immunotherapy may induce immune pneumonia, colitis, hepatitis, etc.).

Therefore, how to accurately deliver sufficient drugs to tumor sites and minimize damage to normal tissues is the key to improving the effectiveness of tumor treatment and reducing toxic side effects. Drug delivery systems (DDS) developed to address these issues and treat tumors already contain a variety of vectors. As a multivesicular vector formed mainly by endogenous lysosomal microparticles, exosomes combine the advantages of cell and nanodrug delivery technology. First, in order to meet the rapid growth of tumor cells, the arrangement of epithelial cells in the nearby capillary plexus is looser than that of normal cells, and the pores are similar in diameter to nanodrugs, so drugs can be enriched between tumor cells. Secondly, the lack of lymphatic vessels in tumor cells hinders lymphatic flow and reduces drug clearance, making it easy to achieve a long cycle of nanodrugs. This is the enhanced permeability and retention effect (EPR) of the human body. For nanoparticles and liposomes, the EPR is important for the administration of tumor sites. Exosomes are usually between 40-100 nm in diameter and can make good use of the EPR in the human body to selectively infiltrate tumors and inflammatory sites. Exosomes not only have the ability to cross biological barriers, but also show great application potential due to their wide distribution in the body and low cytotoxicity, and have become a high-profile research hotspot in the field of cancer treatment.

This article reviews the latest research progress of exosomes in the field of antitumor drug delivery by loading drug type, and looks forward to the challenges and possible solutions faced by exosomes in this regard.

2. Characteristic of exosomes

2.1. Biological characteristics of exosomes

Cells actively secrete vesicle-like bodies with a diameter of 40-100 nm, that is, exosome bodies, which are rich in cholesterol and sheath phospholipids. They are released and formed by the fusion of intracellular polyvesicles and cell membranes. They exist in blood, urine, milk and other body fluids and can be secreted by a variety of cells. The identification of exocrine and target cells is specific. It can transfer miRNA to receptor cells. As a signal molecule, miRNA directly conveys genetic information to regulate cell function; the exosome body itself also has immune function. The tumour-source exosome body shows two sides in tumour-related effects. The exosome body carrying tumour antigens can activate dendritic cells to enhance Epidemic response, relevant clinical trials are currently in progress. It will also induce T cell apoptosis, inhibit NK cell toxicity, and thus lead to immune escape, and show the characteristics of low-dose tumour proliferation and high-dose inhibition in terms of dose effect [1].

2.2. The advantages of exosomes as a drug carrier

The exocrine body is released by the fusion of the cell polyvesicle and the membrane, which has many advantages. It has low immunogenicity, and the autologous exocrine body has almost no immune rejection; it has high stability, long circulation time in the blood, and can avoid being removed by the reticular endothelial system; it can also achieve efficient delivery, and the drug is directly released to the cytoplasm through membrane fusion to avoid the degradation of the body; and it has passive targeting, using EPR The effect (enhancing osmotic retention) targets tumours and

DOI: 10.54254/2753-8818/2025.LD26550

inflammatory tissues. This is because the endothelial cells of blood vessels near normal tissue are relatively closely arranged, and the exocrine body will hardly penetrate through blood vessels, while the endothelial cell gap of the blood vessels near the tumour tissue is large, and the exocrine body can penetrate blood vessels through the intercellular gap and stay in the tumour. Tissue, so as to realise the passive targeting effect on the tumour [2].

The key components of exosome body include transmembrane protein (CD9/CD63/CD81), heat shock protein (HSP70), and lipids (cholesterol, sheath phospholipids). As a carrier, it can carry proteins, miRNA, mRNA, siRNA and other biological molecules [2].

2.3. Exosome DDS design principle

At present, the targeted modification strategy of exosomes is mainly divided into two types: cell level modification before secretion and exocrine level modification after secretion. Among them, the cell level modification before secretion adopts the endogenous drug-carrying mother cell transformation method, that is, the exosome body naturally carries drugs through co-incubation of cells and drugs. The advantage of this method is that the exosome body is good, but there is a disadvantage of low drug-carrying efficiency (about 10-20%); and the exosome level modification after secretion The exocrine engineering method of exogenous drug carrier specifically includes electroperforation method, ultrasound/extrusion method and incubation method that is only applicable to hydrophobic drugs. The drug carrier is flexible but the exocrine body is easily damaged [3]. In contrast, the exosome engineering method of postsecretory exogenous drug carrier modification has the advantages of flexible operation, high safety and controllable drug carrier efficiency. It does not need to interfere with mother cells. It is suitable for a variety of exosome bodies and drug types, but it may destroy the exosome structure, the drug carrier has poor sustainability and is difficult to mass produce; while presecretory cells Horizontal modification can retain the structure and targeting of the exosome body in a natural way. The drug has good stability and is suitable for complex cargo, but there is a safety risk of cell modification, complex operation and low drug controllability. That is, the former focusses more on flexibility and safety, while the latter relies more on the natural characteristics of exosomes but is limited by operation and safety issues.

3. Research status

Studies have shown that the drug delivery of exosomes is cell-dependent, and their biodistribution depends on their parent cells. Therefore, when using exosomes to encapsulate drugs, various factors such as the source, purification method, and drug delivery method need to be considered [4,5].

3.1. Delivery of small molecule antitumor drugs

In numerous studies on small molecule chemotherapy drugs, Sun D's team isolated exosomes from mouse bone marrow-derived dendritic cell culture supernatants and encapsulated curcumin in them to form exosome-curcumin (ExoCUR) complexes [6]. In the brain inflammation model, ExoCUR inhibits microglial activation far more effectively than free curcumin at a lower dose, providing a new idea for the treatment of brain inflammatory diseases. This study sets a precedent for exosome delivery of hydrophobic drugs, confirming its potential to enhance efficacy and reduce toxicity, laying the foundation for the treatment of inflammatory diseases.

DOI: 10.54254/2753-8818/2025.LD26550

Kim MS et al. loaded paclitaxel into mouse bone marrow-derived dendritic cell exosomes by electroporation or saponification. This complex (Exosome Paclitaxel, ExoPTX) bypasses the P-glycoprotein efflux pump and is enriched in multidrug-resistant tumor cells, and its intracellular toxicity has been detected to be significantly higher than that of free paclitaxel [7]. In vivo experiments have shown that ExoPTX not only effectively inhibits tumor growth, but also reduces systemic toxicity, attributed to exosome targeting and protective effects on drugs, reducing drug exposure to non-targeted tissues. This undoubtedly provides a very promising strategy for the treatment of drug-resistant tumors.

In addition, studies have confirmed that exosomes have the ability to homing as natural carriers, which helps drug enrichment in tumor tissue. Exosome Doxorubicin (ExoDOX) have also shown advantages in breast and ovarian cancer models. In the same model, ExoDOX showed a stronger tumor growth inhibitory effect than the same dose of free doxorubicin, and mice treated with ExoDOX also had significantly reduced cardiac tissue damage [8].

3.2. Delivery of protein drugs

Compared with other vectors, exosomes have the ability to cross biological barriers due to their rich membrane proteins and special lipid components, and have unique advantages in biological macromolecule drug delivery. Haney et al. compared multiple loading methods and finally selected saponin permeabilization method to load catalase into exosomes as a model therapeutic agent. In vivo and in vitro experiments have confirmed that exosome delivery systems show higher brain delivery efficiency and therapeutic effects compared to free catalase or liposomal-encapsulated catalase [9]. Therefore, the use of exosomes to deliver drugs is expected to be an effective treatment strategy for brain tumors, but the study also points out the direction of further development of exosomes in the future, including large-scale production of standardized exosomes, improving drug loading efficiency and precise control of drug loading.

3.3. Delivery of nucleic acid drugs

Exosomes also show advantages in the field of delivering nucleic acid drugs, and are suitable for nucleic acid molecules such as miRNA and siRNA. Recent studies have shown that exosomes produced by adipose stem cells can effectively deliver miR-138-5p to bladder cancer (BC) cells, inhibiting the migration, invasion, and proliferation of BC cells by regulating multiple target genes and signaling pathways [10]. In terms of siRNA delivery, Kamerkar S et al. designed the Kirsten rat sarcoma viral oncogene homolog (Glycine 12 Aspartic acid) small interfering RNA (KRASG12D siRNA) in the mesenchymal stem cell exosome, which showed improved anti-cancer effects in mouse models and showed a strong synergistic effect in combination with gemcitabine [11]. It was revealed that targeted KRAS can not only directly kill cancer cells, but also indirectly enhance the anti-tumor effect by changing the tumor microenvironment. Zhao L et al. used exosomes to transport siRNA in their studies, which successfully reduced the high recurrence rate of triple-negative breast cancer and effectively controlled postoperative breast cancer metastasis [12].

In addition, exosomes are also used in the delivery of larger molecular weight nucleic acids such as mRNA. Studies have confirmed that exosomes loaded with phosphatase and tensin homolog (PTEN) mRNA significantly inhibit tumor growth when delivered to PTEN-deficient glioma mice [13]. Kim SM et al. used tumor cell-derived exosomes loaded with plasmid DNA to successfully target ovarian cancer cells and knock out the poly (ADP-Ribose) polymerase 1 (PARP-1) gene, inducing apoptosis in ovarian cancer cells and enhancing their sensitivity to cisplatin [14].

DOI: 10.54254/2753-8818/2025.LD26550

3.4. Plant-derived exosomes

Exosomes are extracellular nanovesicles that can be secreted by all cell types. For a long time, relevant research has mainly focused on mammalian origin exosomes. Recently, plant extracellular vesicles have attracted attention because they are expected to overcome the potential toxicity and safety issues of animal exosomes. Nanovesicles isolated from cabbage by You JY et al. exhibit anti-inflammatory and pro-migration activities in human cells, indicating that edible plant-derived nanovesicles are expected to become novel bioactive materials and therapeutic carriers [15].

In short, exosomes, with their characteristics as natural nanocarriers, have shown great advantages in the field of drug delivery, such as precise targeting, enhanced drug efficacy, reduced toxicity, and penetration through the blood-brain barrier. Although it has broad application prospects and provides breakthrough targeted therapies from chemotherapy drugs to gene editing for refractory diseases such as pancreatic cancer and BC, there are still some key challenges to face in the future.

4. Current problems and challenges

Although exosomes have significant advantages as tumor drug delivery carriers, their clinical application still faces multiple challenges.

First, the technical bottlenecks related to exosomes need to be broken through urgently. The isolation and purification of exosomes is the primary technical link for their clinical transformation as drug delivery carriers. At present, there is no standardized operating procedure in this field, and different methods vary significantly in extraction efficiency, product purity, and practicality, which seriously restricts the large-scale application of exosomes. The most commonly used isolation and purification method currently is ultracentrifugation. Its core principle is to achieve separation by utilizing the density difference between exosomes and other cellular components through multiple gradient centrifugations (usually after pretreatment at 2000×g and 10000×g, ultracentrifugation at 100000×g is performed). However, this method has obvious limitations: on the one hand, the extraction efficiency is relatively low. Due to the fact that some exosomes may be lost by adsorbing on the inner wall of the centrifuge tube or co-precipitating with protein aggregates during centrifugation, the overall recovery rate is usually less than 50%. On the other hand, the product purity is limited, and it is easy to be mixed with impurities such as microvesicles and protein complexes, with exosomes accounting for only 30%-50% of the separated products. More importantly, the mechanical shear force generated by high rotation speed may damage the integrity of the exosome membrane structure, leading to the leakage of bioactive molecules (such as miRNA and proteins) carried by them, which further reduces the proportion of effective exosomes [4]. As an emerging technology, microfluidic technology provides a new idea for efficient isolation of exosomes. This technology uses a micron-scale chip as the core carrier, and realizes precise separation by designing microchannels with specific structures, combined with the physical properties (40-100 nm in diameter) or biomarkers (such as transmembrane proteins CD9, CD63, CD81) of exosomes. Its separation mechanisms mainly include two categories: one is size-dependent, which retains exosomes through nano-scale filtration structures in the channel and excludes larger extracellular vesicles; the other is immunoaffinity-based, which modifies exosome-specific antibodies on the channel surface and specifically captures target exosomes through antigen-antibody interaction. Compared with ultracentrifugation, the extraction efficiency of microfluidic technology is significantly improved, with exosome purity reaching more than 80% and recovery rate stably at 60%-70%. Moreover, the operation process is gentle, which can maximize the

DOI: 10.54254/2753-8818/2025.LD26550

structural integrity of exosomes [4]. Therefore, developing isolation and purification technologies with high efficiency, low cost, and large-scale potential is a key breakthrough for exosomes to move from laboratory research to clinical application. There is a lack of standardized methods for the isolation and purification of exosomes. Currently, the commonly used ultracentrifugation method has low efficiency and may damage the integrity of exosomes, while the emerging microfluidic technology, although able to improve purity, is costly and difficult to apply on a large scale [4]. In addition, low drug loading efficiency (e.g., only 10-20% for the incubation method) and drug leakage also limit the therapeutic effect [3].

Second is the issue of optimizing the targeting of exosomes. Although exosomes can passively target tumors through the EPR effect, their active targeting ability still needs to be improved. For example, strategies to enhance specificity by modifying exosomal surface proteins may trigger immunogenicity [2]. At the same time, the heterogeneity of the tumor microenvironment further increases the difficulty of precise delivery [5].

Finally, researchers also face the challenge of large-scale production and regulatory barriers. Large-scale production of exosomes has problems such as high cost of cell culture and low yield, and there is a lack of unified quality control standards [8]. At the regulatory level, the framework for evaluating the safety and effectiveness of exosome drugs has not been clarified, which has delayed their clinical transformation process [11]. In conclusion, overcoming these challenges requires multidisciplinary collaboration to promote technological standardization and industrialization, so as to facilitate the wide application of exosomes in tumor treatment.

5. Conclusion

As a new type of DDS, exosomes show advantages such as low immunogenicity, high stability, and passive targeting compared with traditional DDS. Numerous studies on exosomes have not only revealed the mechanisms of tumor proliferation and migration, providing new strategies for the treatment of various types of tumors, but also continue to develop their engineering transformation technology, bringing new breakthroughs in the fields of immunotherapy, tissue repair and regenerative medicine. At present, the research on exosomes has moved from the exploration of basic mechanisms to the stage of clinical transformation, however, due to the immature large-scale production technology of exosomes, the output obtained from experiments is far from meeting clinical needs. To achieve its clinical transformation and widespread application, it is urgent to make breakthroughs in the three core challenges of standardized production, targeting accuracy improvement and industrialization promotion.

Although only a small number of exosome-based therapies have now entered the clinic, it is gratifying that researchers have not stopped on this path. With the deep cross-integration of multidisciplinary technologies such as bioengineering, nanotechnology, and microfluidics, exosomes are expected to become key delivery vectors in tumor targeted therapy in the future, benefiting more patients.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

References

[1] Wan Lu, Renqiang Yang and Ling Wang. (2013) Research Progress on Exosomes. The Science of Life, 33, 438-442.

DOI: 10.54254/2753-8818/2025.LD26550

[2] Sidi Li, Xin Hou, Hongzhao Qi, Jin Zhao and Xubo Yuan. (2016) Exosomes: Provide Natural Endogenous Nanocarriers for Efficient Drug Delivery Strategies. Chemical Process, 28, 353-362.
[3] Haonan Xing, Mei Lu, Yingqi Liu, Yuhan Dong and Aiping Zheng. (2022) Research Progress on Targeted Delivery of Anti-tumor Drugs Based on Exosomes. Acta Pharmaceutica Sinica, 57, 150-158.
[4] Johnsen, K.B., Gudbergsson, J.M., Skov, M.N., Pilgaard, L., Moos, T. and Duroux, M. (2014) A Comprehensive Overview of Exosomes as Drug Delivery Vehicles-endogenous Nanocarriers for Targeted Cancer Therapy. Biochim Biophys Acta, 1846(1), 75-87.
[5] Wiklander, O.P., Nordin, J.Z., O'Loughlin, A., Gustafsson, Y., Corso, G., Mager, I., et al. (2015) Extracellular Vesicle in Vivo Biodistribution is Determined By Cell Source, Route of Administration and Targeting. J Extracell Vesicles, 4, 26316.
[6] Sun, D., Zhuang, X., Xiang, X., Liu, Y., Zhang, S., Liu, C., et al. (2010) A Novel Nanoparticle Drug Delivery System: the Anti-inflammatory Activity of Curcumin is Enhanced when Encapsulated in Exosomes. Mol Ther, 18(9), 1606-14.
[7] Kim, M.S., Haney, M.J., Zhao, Y., Mahajan , V., Deygen, I., Klyachko, N.L., et al. (2016) Development of Exosome-encapsulated Paclitaxel to Overcome MDR in Cancer Cells. Nanomedicine, 12(3), 655-64.
[8] Kar, R., Dhar, R., Mukherjee, S., Nag, S., Gorai, S., Mukerjee, N., et al. (2023) Exosome-based Smart Drug Delivery Tool for Cancer Theranostics. ACS Biomaterials Sci Eng, 9(2), 577–94.
[9] Haney, M.J., Klyachko, N.L., Zhao, Y., Gupta, R., Plotnikova, E.G., He, Z., et al. (2015) Exosomes as Drug Delivery Vehicles for Parkinson's Disease Therapy. J Control Release, 207, 18-30.
[10] Tianyao Liu, Tianhang Li, Yufeng Zheng, et al. (2022) Evaluating Adipose-derived Stem Cell Exosomes as miRNA Drug Delivery Systems for the Treatment of Bladder Cancer. Cancer Medicine, 11, 3687–3699.
[11] Kamerkar, S., LeBleu, V.S., Sugimoto, H., Yang, S., Ruivo, C.F., Melo, S.A., et al. (2017) Exosomes Facilitate Therapeutic Targeting of Oncogenic KRAS in Pancreatic Cancer. Nature, 546(7659), 498–503.
[12] Zhao, L., Gu, C., Gan, Y., Shao, L., Chen, H. and Zhu, H. (2020) Exosome-mediated siRNA Delivery to Suppress Postoperative Breast Cancer Metastasis. J Contr Release, 318, 1–15.
[13] Yang, Z., Shi, J., Xie, J., et al. (2020) Large-scale Generation of Functional Mrna-encapsulating Exosomes Via Cellular Nanoporation. Nat Biomed Eng, 4, 69-83.
[14] Kim, S.M., Yang, Y., Oh, S.J., et al. (2017) Cancer-derived Exosomes as a Delivery Platform of CRISPR/Cas9 Confer Cancer Cell Tropism-dependent Targeting. J Control Release, 266, 8-16.
[15] You, J.Y., Kang, S.J. and Rhee, W.J. (2021) Isolation of Cabbage Exosomelike Nanovesicles and Investigation of Their Biological Activities in Human Cells. Bioact Mater, 6, 4321–32.