





Exosomes in cancer therapy: Advances and current challenges

Rajib Dhar¹ , Arikketh Devi¹ , Shankargouda Patil² , Marcos Roberto Tovani-Palone^{3,4*} 

¹Cancer and Stem Cell Biology Laboratory, Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Tamil Nadu 603203, INDIA

²College of Dental Medicine, Roseman University of Health Sciences, South Jordan, Utah 84095, USA

³Department of Research Analytics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, Tamil Nadu 600077, INDIA

⁴Department of Pharmacy and Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Tamil Nadu 603203, INDIA

*Corresponding Author: marcos_palone@hotmail.com

Citation: Dhar R, Devi A, Patil S, Tovani-Palone MR. Exosomes in cancer therapy: Advances and current challenges. *Electron J Gen Med.* 2023;20(5):em524. <https://doi.org/10.29333/ejgm/13456>

ARTICLE INFO

Received: 18 Mar. 2023

Accepted: 19 Jun. 2023

ABSTRACT

Exosomes are subpopulations of extracellular vesicles (EVs) secreted by cells in normal or pathological conditions. From an oncological point of view, such vesicles are involved in cancer progression and may function as a therapeutic tool (based on EVs source), whose molecular signature plays a significant role in the investigation of cancer biomarkers. Recent research reveals the potential role of exosomes in anticancer drug delivery. In this article, we briefly discuss current theranostics perspectives on exosomes and their future orientation.

Keywords: exosomes, neoplasms, biomarkers, therapeutics, vaccines

Cancer begins as a single cell. The corruption within the fundamental processes of this cell spreads outwards, invading and metastasizing, bringing death and earning cancer the sobriquet “The Emperor of all maladies”. In 2020, one out of six deaths was caused by cancer. Globally, cancer is one of the leading causes of death, second only to cardiovascular diseases [1]. Advances in scientific discovery have led to a dizzying array of tools in our arsenal to combat it. Cancer treatment can extend its reach to the molecular level, tailoring treatment to the unique characteristics of a person’s disease, and targeting specific molecular targets for a tumor type.

Exosomes, in turn, are a promising new avenue of treatment in a long line of scientific advances [2-4]. They are nothing more than extracellular vesicles of endosomal origin that help in intercellular communication [5]. Originally, exosomes were believed to simply be cellular cargo containers carrying deoxyribonucleic acid (DNA), messenger ribonucleic acid (mRNA), micro-ribonucleic acid (miRNA), proteins, and lipids. However recent research has given us dramatic insights into these seemingly unimportant tiny vesicles. Exosomes may serve as intercellular and systemic communicators with their composition unique based on the recipient microenvironment and cells. Exosomes are also produced by tumor cells – referred to as tumor-derived exosomes (TEXs). These may play a critical role in cancer, acting as signaling molecules [6]. In cancer, the signals from exosomes can affect the immune system by inhibiting the function and production of antigen-presenting cells, T cells, and natural killer cells. They may also increase the number of immune suppressor cells providing a fertile ground for the progression of neoplastic lesions [7,8]. TEXs mediate these immune support cancer cells to escape the immune surveillance during cancer development.

TEXs regulate several characteristics of cancers. They promote uncontrolled cell growth (TEXs glycan), angiogenesis (TEXs miRNAs and proteins cargos), metastasis (miRNAs), EMT-epithelial-mesenchymal transition (fibronectin related to extracellular matrix remodeling), organ-specific metastasis (TEXs surface integrins), drug and therapeutic resistance (TEXs miRNA and proteins), and cancer stem cell development (TEXs miRNA and proteins) [7,8].

On the other hand, TEXs could play a critical role in the diagnosis and prognosis of different types of cancer, including liver, gastric, breast, colorectal, ovarian, esophageal, and prostate cancer, etc. [8]. Circulating TEXs may open a new platform for liquid biopsy as they contain molecules characteristic of the parent malignant tissues [8,9]. Isolation of exosomes from body fluids such as urine, serum, plasma, saliva, and lymph are possible through microfluidics-based platforms [10] and innovative mechanisms such as acoustic [11] or electromagnetic isolation [12]. The release of exosomes coincides with the activation of autophagy [13]. They may serve as clinical biomarkers to monitor autophagy during cancer therapy. Exosomal release of proteins involved in the metastasis of cancer may for example be possible candidates for the progression and surveillance of lung [14] and breast cancer [15].

Exosomes may also serve to track treatment response assessment. It is worth noting here that tumor cells prevent their destruction with a degree of metabolic flexibility against traditional treatments. Tumor-associated exosomes are believed to contribute to this evasion through rising drug resistance in tumor cells [16]. Blocking the exosomal secretion pathway has shown promising results in reducing secretions of chaperone proteins that are high-value oncologic targets in cancer treatment [17]. Exosome-mediated communication can

also be targeted using mechanisms and compounds that inhibit its uptake such as heparin, cytochalasin D, dynasore, or endocytosis inhibitors [18].

Drug delivery in cancer treatment has different limitations (biological barrier crossing, toxicity, and biocompatibility). Exosomes can contribute greatly to successfully circumventing these barriers as useful vectors for drug delivery of anticancer drugs, given that different nanoparticles can be combined with exosomes for targeted delivery to tumor cells [19]. Indeed, extracellular vesicles can function as nanosystems to deliver drugs, nucleic acids, proteins, and viruses, which could slow down the growth of tumor cells [20]. Dendritic cell-derived exosomes have already been previously shown to eradicate murine tumors, acting as a cell-free vaccine by priming cytotoxic T lymphocytes [21].

Exploiting and developing exosomes for delivering therapeutics is an unmet challenge in the fight against cancer. Commercial development of products of exosome research remains at an adolescent stage and invites serious conversation to conceptualize this emerging field in therapeutics. Despite the challenges related to exosome therapy, including difficulties in the production of a heterogeneous population, large-scale production, and the production of a cancer vaccine based on TEXs, important research is ongoing. The use of exosomes for solid tumor therapy and engineered exosomes as drug carriers are currently under clinical trials. Mesenchymal stem cell-derived exosomes, dendritic cell-derived exosomes, and educated immune cell-derived and plant-derived exosomes are being investigated for their effects on tumor cells. The ongoing clinical trials may unlock novel and precise exosome technology [20]. Despite all the barriers, this fascinating field walks side by side with precision cancer medicine, as well as looking towards related vaccine development [22].

In short, exosomes continue to hold great promise for non-invasive early-stage detection of cancer, sensing of the tumor-microenvironment, and intracellular imaging. Such vesicles are an extraordinary opportunity that can further progress previous research success to create sustainable mechanisms that can be translated from the laboratory to the clinic to combat the cancer burden. The next decade is expected to experience a rapid expansion in cancer treatment incorporating advances as our understanding of related biology grows.

Author contributions: RD & AD: conception, design, and writing. **SP & MRT-P:** writing - original draft, critical review, and editing. All authors have sufficiently contributed to the study, and agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Acknowledgements: The authors thank Saveetha Institute of Medical and Technical Sciences and SRM Institute of Science and Technology for supporting this study.

Ethical statement: Authors stated that ethics committee approval was not required for this study.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

REFERENCES

1. World Health Organization. The top 10 causes of death. Available at: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death> (Accessed: 18 June 2023).
2. Basthi Mohan P, Rajpurohit S, Musunuri B, Bhat G, Lochan R, Shetty S. Exosomes in chronic liver disease. *Clin Chim Acta*. 2023;540:117215. <https://doi.org/10.1016/j.cca.2022.117215> PMID:36603656
3. Nian W, Fu C. Exosomes in myocardial infarction: therapeutic potential and clinical application. *J Cardiovasc Transl Res*. 2023;16(1):87-96. <https://doi.org/10.1007/s12265-022-10284-3> PMID:35672604
4. Sharma V, Nikolajeff F, Kumar S. Employing nanoparticle tracking analysis of salivary neuronal exosomes for early detection of neurodegenerative diseases. *Transl Neurodegener*. 2023;12(1):7. <https://doi.org/10.1186/s40035-023-00339-z> PMID:36747288 PMCid:PMC9903484
5. Edgar JR. Q&A: What are exosomes, exactly? *BMC Biol*. 2016;14:46. <https://doi.org/10.1186/s12915-016-0268-z> PMID:27296830 PMCid:PMC4906597
6. Li I, Nabet BY. Exosomes in the tumor microenvironment as mediators of cancer therapy resistance. *Mol Cancer*. 2019; 18(1):32. <https://doi.org/10.1186/s12943-019-0975-5> PMID:30823926 PMCid:PMC6397467
7. Grizzle WE, Zhang H-G. The Effects of Exosomes and related vesicles on cancer development, progression, and dissemination BT - Emerging concepts of tumor exosome-mediated cell-cell communication. In: Zhang H-G, editor. *New York, NY: Springer New York*; 2013. p. 107-29. https://doi.org/10.1007/978-1-4614-3697-3_5
8. Wang X, Tian L, Lu J, Ng IO. Exosomes and cancer - Diagnostic and prognostic biomarkers and therapeutic vehicle. *Oncogenesis*. 2022;11(1):54. <https://doi.org/10.1038/s41389-022-00431-5> PMID:36109501 PMCid:PMC9477829
9. Zhou B, Xu K, Zheng X, Chen T, Wang J, et al. Application of exosomes as liquid biopsy in clinical diagnosis. *Signal Transduct Target Ther*. 2020;5(1):144. <https://doi.org/10.1038/s41392-020-00258-9> PMID:32747657 PMCid:PMC7400738
10. Davies RT, Kim J, Jang SC, Choi EJ, Gho YS, Park J. Microfluidic filtration system to isolate extracellular vesicles from blood. *Lab Chip*. 2012; 12(24):5202-10. <https://doi.org/10.1039/c2lc41006k> PMID:23111789
11. Lee K, Shao H, Weissleder R, Lee H. Acoustic purification of extracellular microvesicles. *ACS Nano*. 2015; 9(3):2321-7. <https://doi.org/10.1021/nn506538f> PMID:25672598 PMCid:PMC4373978
12. Li H, Lin L, Li L, Zhou L, Zhang Y, Hao S, et al. Exosomal small RNA sequencing uncovers the microRNA dose markers for power frequency electromagnetic field exposure. *Biomarkers*. 2018;23(4):315-27. <https://doi.org/10.1080/1354750X.2018.1423707> PMID:29297241
13. Kumar D, Gupta D, Shankar S, Srivastava RK. Biomolecular characterization of exosomes released from cancer stem cells: Possible implications for biomarker and treatment of cancer. *Oncotarget*. 2015;6(5):3280-91. <https://doi.org/10.18632/oncotarget.2462> PMID:25682864 PMCid:PMC4413653

14. Li L, Li W, Chen N, Zhao H, Xu G, Zhao Y, et al. FLI1 exonic circular RNAs as a novel oncogenic driver to promote tumor metastasis in small cell lung cancer. *Clin Cancer Res.* 2019; 25(4):1302-17. <https://doi.org/10.1158/1078-0432.CCR-18-1447> PMID:30429198
15. Tiedemann K, Sadvakassova G, Mikolajewicz N, Juhas M, Sabirova Z, Tabariès S, et al. Exosomal release of L-plastin by breast cancer cells facilitates metastatic bone osteolysis. *Transl Oncol.* 2019;12(3):462-74. <https://doi.org/10.1016/j.tranon.2018.11.014> PMID:30583289 PMCID:PMC6305809
16. Whiteside TL. Tumour-derived exosomes or microvesicles: another mechanism of tumour escape from the host immune system? *Br J Cancer.* 2005;92(2):209-11. <https://doi.org/10.1038/sj.bjc.6602360> PMID:15702078 PMCID:PMC2361845
17. Zhang H, Lu J, Liu J, Zhang G, Lu A. Advances in the discovery of exosome inhibitors in cancer. *J Enzyme Inhib Med Chem.* 2020;35(1):1322-30. <https://doi.org/10.1080/14756366.2020.1754814> PMID:32543905 PMCID:PMC7717571
18. Bastos N, Ruivo CF, da Silva S, Melo SA. Exosomes in cancer: Use them or target them? In: *Seminars in cell & developmental biology.* Elsevier; 2018. p. 13–21. <https://doi.org/10.1016/j.semcd.2017.08.009> PMID:28803894
19. Kar R, Dhar R, Mukherjee S, Nag S, Gorai S, Mukerjee N, et al. Exosome-based smart drug delivery tool for cancer theranostics. *ACS Biomater Sci Eng.* 2023;9(2):577-94. <https://doi.org/10.1021/acsbomaterials.2c01329> PMID:36621949 PMCID:PMC9930096
20. Raguraman R, Bhavsar D, Kim D, Ren X, Sikavitsas V, et al. Tumor-targeted exosomes for delivery of anticancer drugs. *Cancer Lett.* 2023;558:216093. <https://doi.org/10.1016/j.canlet.2023.216093> PMID:36822543
21. Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, et al. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell-derived exosomes. *Nat Med.* 1998;4(5):594-600. <https://doi.org/10.1038/nm0598-594> PMID:9585234
22. Dhar R, Bhattacharya B, Mandal D, Devi A, Thorat ND. Exosome-based cancer vaccine: a cutting-edge approach - Correspondence. *Int J Surg.* 2022;108:106993. <https://doi.org/10.1016/j.ijso.2022.106993> PMID:36356827