

Exosomes: Small Vesicles with Great Potential

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ISSN: 2576-8816



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Submission: 📅 March 17, 2025

Published: 📅 April 24, 2025

Volume 11 - Issue 5

How to cite this article: Meral Miraloglu*. Exosomes: Small Vesicles with Great Potential. Res Med Eng Sci. 11(5). RMES.000771. 2025. DOI: [10.31031/RMES.2025.11.000771](https://doi.org/10.31031/RMES.2025.11.000771)

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Abstract

Exosomes are nanosized extracellular vesicles, typically ranging between 30 and 150 nanometers, released by a wide variety of cell types. They originate from the inward budding of endosomal membranes, forming multivesicular bodies (MVBs), which subsequently fuse with the plasma membrane to release exosomes into the extracellular space.

These vesicles serve as carriers of a complex cargo composed of proteins, lipids, messenger RNAs, microRNAs, and DNA fragments. Through the horizontal transfer of these biomolecules, exosomes play a fundamental role in modulating gene expression, cellular signaling, and intercellular communication in both nearby and distant target cells.

In physiological contexts, exosomes are involved in numerous critical processes such as immune modulation, tissue regeneration, and neuronal communication. Conversely, in pathological conditions-particularly in cancer-exosomes contribute to tumor progression by enhancing angiogenesis, promoting metastasis, and modulating immune responses in favor of tumor survival.

Due to their stability in biological fluids and their ability to reflect the molecular signature of the originating cells, exosomes have gained increasing attention as promising biomarkers for non-invasive disease diagnosis. Moreover, their natural biocompatibility and targeting properties make them suitable candidates for the development of innovative drug delivery systems, particularly in the fields of oncology, neurology, and regenerative medicine.

Exosomes can be isolated from accessible biological fluids such as blood, urine, and saliva, providing a minimally invasive method for disease monitoring and therapeutic targeting. As research in exosome biology advances, their application in precision medicine is expected to expand significantly.

In conclusion, exosomes represent a novel and powerful platform for both diagnostics and therapeutics, holding great potential to transform current approaches to patient care.

Introduction to the Problem

Exosomes are nanoscale vesicles, ranging in size from 30 to 150nm, surrounded by a membrane and secreted by various cells. They play a crucial role in intercellular communication by carrying biomolecules such as proteins, lipids, and RNA. Exosomes are involved in regulating immune responses, cell proliferation, and apoptosis, making them significant in both normal physiological processes and disease-related conditions. In recent years, the potential of exosomes in biomedical research and clinical applications has been increasingly recognized (Théry et al. 2006).

Exosome biogenesis

Exosomes originate from intracellular endosomal pathways and are formed through three key stages:

Endosomal pathway: Early endosomes form by incorporating materials from the cell membrane and subsequently mature into late endosomes, giving rise to multivesicular bodies (MVBs).

Vesicle formation: Intraluminal vesicles (ILVs) are generated within MVBs. This process is regulated by the Endosomal Sorting Complex Required for Transport (ESCRT) protein complex and ESCRT-independent mechanisms [1].

Exocytosis: Multivesicular bodies (MVBs) either undergo lysosomal degradation or fuse with the cell membrane to release exosomes into the extracellular environment (Kowal et al., 2014). Recent studies suggest that Rab GTPases play a critical role in regulating exosome secretion, influencing cellular communication and disease pathogenesis [2].

Exosome structure

Exosomes are enclosed by a lipid bilayer membrane and contain diverse biomolecules depending on their cellular origin. Their main structural components include:

Membrane proteins: Tetraspanins (CD9, CD63, CD81), Rab proteins, and integrins facilitate exosome recognition and binding to target cells [3].

Lipid components: Cholesterol, sphingomyelin, and phospholipids contribute to exosome stability and biological activity [4].

Genetic material: Exosomes carry mRNA, microRNA (miRNA), long non-coding RNAs (lncRNA), and even DNA, making them important for gene regulation and cellular reprogramming [5]. Recent evidence highlights the role of exosomal circular RNAs (circRNAs) in gene regulation and cancer progression [6].

Cytoplasmic content: Enzymes and signaling proteins within exosomes can modulate biochemical pathways in recipient cells [7].

Classification of exosomes: Exosomes can be classified based on different criteria:

Source-based classification

- A. Biologically derived exosomes: Secreted by cells in vivo to regulate naturally functions.
- B. Synthetic exosomes: Engineered in laboratories for specific therapeutic and diagnostic applications (Taylor & Gercel-Taylor, 2011).

Content-based classification

- A. Protein-enriched exosomes: Contain proteins specific to their cell of origin, enabling functional specialization.
- B. RNA-enriched exosomes: Carry genetic materials such as mRNA and microRNA, influencing gene expression in recipient cells.

Functional classification

- A. Intercellular communication exosomes: Facilitate metabolic and genetic information transfer between cells.
- B. Waste-disposal exosomes: Assist in removing toxic and metabolic waste products from cells.

Exosome isolation techniques

The isolation of exosomes is a crucial step for their characterization and utilization in therapeutic and diagnostic applications. The selection of an appropriate isolation technique significantly influences the purity, yield, and bioactivity of the isolated vesicles. Different isolation techniques vary based on application needs and cell sources [8]. Recent advances in microfluidic-based exosome isolation have improved yield and purity, offering a promising alternative to traditional methods. Below is an overview of the primary exosome isolation methods, their advantages, limitations, and applications.

Exosome analysis

Comprehensive analysis is essential for understanding the biological functions and therapeutic potential of exosomes. Commonly used exosome characterization techniques include:

- a. Nanoparticle Tracking Analysis (NTA): Measures size distribution and concentration of exosomes.
- b. Electron Microscopy (EM): Provides high-resolution imaging to examine exosome morphology and surface features.
- c. Western Blot and ELISA: Used to confirm exosomal surface and internal protein components.
- d. Flow Cytometry: Detects exosomal surface proteins and differentiates various exosome subtypes [9].
- e. Mass Spectrometry and Proteomic Analysis: Identifies proteins and other biomolecules present in exosomes.
- f. RNA Sequencing: Profiles exosome-derived RNA to determine the role of different RNA species in gene regulation. Single-cell RNA sequencing has recently been applied to exosomal RNA to better understand their heterogeneity and disease relevance (Zhang et al., 2023).

Biomedical applications of exosomes

Exosomes are being increasingly explored for their potential in biomedical applications, including:

Cancer research: Exosomes derived from tumor cells serve as crucial biomarkers for cancer diagnosis, prognosis, and therapeutic monitoring. The use of exosomes as delivery vehicles contributes to the realization of gene and biological therapies in oncology. Exosomes provide significant advantages for improving the therapeutic index of cancer treatment because they have the potential to target cells for intracellular delivery of their contents [10].

Disease diagnosis: Exosomal cargo, including RNA and proteins, has been implicated in the diagnosis of various diseases, including neurodegenerative and infectious diseases.

Neurodegenerative Diseases: Exosomal biomarkers have been identified for Alzheimer's and Parkinson's disease, providing new avenues for early diagnosis and targeted therapy [11].

Drug delivery: Exosomes offer a promising avenue for targeted drug delivery, potentially improving therapeutic outcomes while minimizing systemic toxicity. Engineered exosomes have been developed as drug carriers for targeted therapy, minimizing side effects while improving drug efficacy [12].

Stem cell research: Studies suggest exosomes play a pivotal role in stem cell differentiation and tissue regeneration, making them a valuable tool in regenerative medicine.

Vaccine development: Exosomes are being explored as carriers for vaccine antigens, particularly in cancer immunotherapy and infectious disease prevention.

Regenerative medicine: Stem cell-derived exosomes are being investigated for their regenerative potential in treating cardiovascular and musculoskeletal diseases [13,14].

Conclusion

Exosomes play a crucial role in intercellular communication and hold great promise for medical applications. Future research in exosome isolation and characterization will enhance their clinical translation, leading to advancements in personalized medicine. Exosome-based drug delivery, disease diagnosis, and immune regulation represent exciting frontiers in medical research. The ability of exosomes to signal specific recipient cells or tissues by coating them with a wide range of contents, including lipids, RNAs, and proteins, makes them a promising diagnostic biomarker and therapeutic tool for the treatment of cancers and other pathologies. The clinical application of exosomes is still in its infancy; further research will contribute to the discovery of cost-effective and time-effective nanotechnologies for large-scale production of exosomes.

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