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Exosomal RNA: Interplay and Therapeutic Potential

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Abstract

Exosomal RNA has emerged as a crucial mediator of intercellular communication, enabling the transfer of genetic information between cells. This intricate signaling system holds great promise for unraveling complex cellular processes and advancing therapeutic applications. This review provides an in-depth examination of the current state of knowledge regarding exosomal RNA, emphasizing its role in intercellular signaling and its relevance to various physiological and pathological conditions. Furthermore, we explore the potential therapeutic applications that leverage exosomal RNA, opening new avenues for innovative treatments across diverse medical domains. The nuanced interplay of exosomal RNA presents a fertile ground for further investigation and application, promising advancements in both fundamental biology and clinical interventions.

Keywords: ***Exosomal RNA, Intercellular communication, Therapeutic potential, Vesicles, Cargo.***

Introduction

In recent years, the investigation into exosomes has revealed a dynamic facet of intercellular communication, where small vesicles, known as exosomes, play a crucial role in transporting molecular cargo between cells. Among the diverse molecules encapsulated in exosomes, RNA has emerged as a pivotal mediator, facilitating the exchange of genetic information. This intricate communication system extends its influence across various physiological and pathological contexts, exerting a profound impact on cellular functions and responses. Understanding the nuances of exosomal RNA opens up new avenues for deciphering fundamental biological processes and exploring innovative therapeutic applications. This review aims to present a comprehensive overview of the current state of knowledge concerning exosomal RNA, shedding light on its various roles in intercellular signalling (Li *et al*., 2014). The focus is on exploring the biogenesis and composition of exosomes, emphasizing the packaging and transport of RNA cargo. Additionally, we delve into the regulatory functions of exosomal RNA in physiological processes and its implications in pathological conditions. The growing recognition of the significance of exosomal RNA prompts an exploration of its therapeutic potential, offering novel strategies for intervention across various medical fields.Navigating through the intricate landscape of exosomal RNA, this review synthesizes existing knowledge while underscoring critical gaps in understanding, paving the way for future research directions. The multifaceted interplay of exosomal RNA not only enhances our understanding of cellular communication but also holds the promise of transformative therapeutic applications. Consequently, the exploration of exosomal RNA emerges as a compelling subject for investigation, offering significant opportunities for scientific inquiry and exploration (Narang *et al*., 2022).

Significance and Biogenesis of Exosome and it's RNA

Exosomal RNA encompasses a diverse range of RNA molecules enclosed within exosomes, small extracellular vesicles released by various cell types. These exosomes play a crucial role as mediators of intercellular communication, facilitating the exchange of information between cells. Within exosomes, RNA, along with proteins and lipids, contributes to the modulation of various cellular functions and responses. The RNA cargo within exosomes comprises different types of RNA, including messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA), and other small non-coding RNAs. These molecules are securely enclosed within the lipid bilayer of exosomes, providing protection against degradation and enhancing stability in the extracellular environment. Exosomal RNA is implicated in numerous physiological processes such as immune response regulation, tissue repair, and neuronal signaling. Its involvement in pathological conditions, including cancer, neurodegenerative diseases, and infectious diseases, has also been extensively studied. Transfer of exosomal RNA can influence recipient cells by modulating gene expression, inducing phenotypic changes, or triggering specific cellular responses.

The biogenesis of exosomes occurs through the endosomal pathway, involving the formation of intraluminal vesicles within multivesicular bodies (MVBs), which are then released as exosomes upon fusion with the cell membrane. This process selectively packages specific RNA molecules into exosomes, contributing to the functional diversity of exosomal cargo. Research into exosomal RNA has expanded rapidly, revealing its potential as both a diagnostic tool and therapeutic agent. Exosomes' capacity to deliver functional RNA to target cells has led to investigations exploring their use in drug delivery and as potential biomarkers for various diseases. Understanding the intricate roles of exosomal RNA in intercellular communication holds promise for advancing our knowledge of cellular processes and developing innovative strategies for diagnosing and treating a variety of health conditions.

Mechanism of Exosomal RNA

1. Biogenesis: The journey of exosomal RNA begins within the endosomal pathway. Early endosomes mature into multivesicular bodies (MVBs), which are characterized by the inward budding of the endosomal membrane. This budding leads to the formation of intraluminal vesicles (ILVs) within the MVBs.

2. Packaging of RNA: Within these ILVs, various RNA molecules are selectively packaged. The specific sorting mechanisms remain an area of active research, with studies suggesting the involvement of RNA-binding proteins, lipid interactions, and RNA motifs in this selective packaging.

3. MVB Maturation and Fusion: As MVBs mature, they face two potential fates. They can fuse with lysosomes, resulting in the degradation of their contents, or they can fuse with the cell membrane, leading to the release of ILVs into the extracellular space as exosomes.

4. Exosome Release: Exosomes, now loaded with a diverse cargo including RNA, are released into the extracellular environment. This process can occur constitutively, ensuring a continuous release of exosomes, or it can be triggered in response to various cellular signals, stressors, or activation cues.
5. Exosome Uptake by Recipient Cells: The released exosomes navigate the extracellular space and are internalized by recipient cells. This uptake process is dynamic and can occur through various mechanisms, such as endocytosis, phagocytosis, or direct fusion with the recipient cell membrane.
6. Exosomal RNA Delivery: Once internalized, exosomes fuse with the endosomal membrane of the recipient cell, releasing their contents, including RNA, into the cytoplasm. This transferred RNA cargo becomes available for various intracellular processes.
7. Functional Impact of Exosomal RNA: The exosomal RNA cargo exerts a functional impact on recipient cells. MicroRNAs delivered by exosomes can bind to target mRNAs, leading to their degradation or inhibition of translation. This regulation influences cellular processes, including cell proliferation, differentiation, and apoptosis.
8. Intercellular Communication: The dynamic exchange of exosomal RNA facilitates robust intercellular communication. This communication is not limited to a single cell type or tissue; rather, it spans diverse cell populations, contributing to the orchestration of physiological processes and responses (Qiu *et al*., 2021).

Applications of Exosomal RNA

Exosomal RNA has demonstrated substantial potential across various applications owing to its distinct characteristics and roles in intercellular communication. Several notable uses of exosomal RNA include:

1. Disease Biomarkers
Cancer Detection: The investigation of exosomal RNA profiles, particularly microRNA signatures, stands out as a promising diagnostic biomarker for a diverse spectrum of cancers. Exosomes, carrying distinct microRNA compositions reflective of their cellular origin, present a unique opportunity for precise cancer detection. The unique microRNA profiles within exosomes serve as molecular identifiers, enabling researchers to differentiate between various cancer types. Moreover, these modified expression patterns provide valuable insights into the stage and progression of cancer, equipping clinicians with essential information for informed decision-making. The potential for early detection offered by exosomal microRNA is particularly noteworthy, allowing the identification of subtle changes even in the initial stages of cancer development. Additionally, the prognostic value of exosomal microRNA signatures assists in predicting the likely course of the disease, guiding treatment strategies based on anticipated outcomes. This biomarker approach proves instrumental not only in distinguishing between benign and malignant tumors but also in complementing traditional diagnostic methods. It provides a non-invasive and dynamically monitored option through liquid biopsy applications. Furthermore, the evaluation of exosomal microRNA profiles during treatment offers insights into treatment response and the emergence of resistance, facilitating timely adjustments to therapeutic interventions. In essence, the exploration of exosomal RNA, particularly microRNA signatures, enhances the accuracy and reliability of cancer diagnostics, ushering in a new era of precision medicine (Zhao *et al*., 2021).

Neurodegenerative Diseases: The exploration of exosomal RNA in cerebrospinal fluid and blood has uncovered its significant potential as a biomarker for neurodegenerative disorders, notably Alzheimer's and Parkinson's diseases. The intricate molecular insights provided by exosomes in these biofluids offer a distinct perspective on the pathological processes associated with these debilitating conditions. In the realm of Alzheimer's disease, distinct exosomal RNA signatures have been identified, reflecting specific alterations in neuronal function and integrity characteristic of the disease. These molecular markers not only contribute to early diagnosis but also facilitate the monitoring of disease progression. In the case of Parkinson's disease, exosomal RNA profiles offer valuable insights into neurodegenerative changes and disease dynamics. The recognition of disease-specific RNA patterns allows for precise differentiation between various neurodegenerative disorders, enhancing the accuracy of diagnostic approaches. Moreover, the non-invasive accessibility of exosomal RNA in blood and cerebrospinal fluid proves advantageous for longitudinal studies and repeated assessments, enabling the continuous tracking of disease evolution. As ongoing research delves deeper into the intricacies of exosomal RNA in neurodegenerative diseases, integrating these biomarkers into clinical practice holds great promise for advancing early detection, comprehending disease mechanisms, and ultimately developing targeted therapeutic interventions (Wang *et al*., 2022).

2. Liquid Biopsy: Exosomal RNA emerges as a revolutionary non-invasive source of genetic material for liquid biopsies, reshaping the landscape of cancer diagnostics and monitoring. This innovative approach transforms our understanding and management of disease progression, treatment responses, and the emergence of resistance in cancer patients, eliminating the necessity for invasive tissue biopsies. The non-invasive characteristic of exosomal RNA in liquid biopsies brings notable advantages, mitigating patient discomfort and associated risks linked to traditional tissue procedures. Accessible in bodily fluids like blood, exosomal RNA allows for dynamic monitoring of disease evolution in real time, providing insights into metastasis and molecular alterations within the tumor. Its capacity to assess treatment responses without subjecting patients to repeated tissue biopsies equips clinicians with a dynamic and minimally invasive tool for evaluating therapeutic intervention efficacy. Significantly, the early detection of resistance mechanisms through continuous monitoring of exosomal RNA profiles empowers healthcare professionals to promptly adapt treatment plans. Offering a more comprehensive representation of tumor heterogeneity and enabling longitudinal studies, exosomal RNA-based liquid biopsies prove versatile across diverse cancer types. In essence, this approach holds the promise of enhancing patient care by delivering timely, accurate, and minimally invasive molecular insights for optimized cancer management (Valencia and Montuenga, 2021).

3. Therapeutic Delivery: Engineered exosomes, serving as natural carriers for therapeutic RNA molecules, stand at the forefront of targeted drug delivery strategies, representing an innovative approach in precision medicine. Laden with cargoes such as small interfering RNA (siRNA), microRNA mimics, or messenger RNA (mRNA), these exosomes offer a sophisticated and adaptable means to enhance the efficacy of RNA-based treatments while minimizing off-target effects. The engineering process involves modifying exosomal membranes to display specific ligands or proteins that facilitate targeted binding to particular cells or tissues. This targeted delivery system holds tremendous promise for precisely addressing the root causes of diseases. The use of small interfering RNA within engineered exosomes allows for the precise silencing of specific genes, offering a potent tool for addressing the underlying mechanisms of diseases, including cancer. MicroRNA mimics, alternatively, enable the modulation of gene expression, contributing to the regulation of intricate cellular processes. The delivery of messenger RNA by engineered exosomes holds potential for inducing the synthesis of therapeutic proteins within target cells, presenting a novel approach for treating genetic disorders or deficiencies (Aslan *et al*., 2021; Lu *et al*., 2023).

4. Immunomodulation : Exosomal RNA, notably microRNAs, plays a pivotal role in regulating immune responses. Leveraging exosomal RNA for immunomodulation holds promise for developing therapies that can enhance or suppress immune reactions in diseases, including cancer. The ability to engineer exosomal microRNAs provides a targeted approach for fine-tuning immune responses, offering potential applications in personalized medicine for conditions marked by dysregulated immune activity, such as autoimmune disorders and inflammatory diseases. This dynamic interplay of exosomal RNA in immune regulation opens new avenues for precision interventions in the quest for more effective treatments (Shan *et al*., 2023).

5. Regenerative Medicine: Exosomal RNA derived from stem cells holds significant promise for tissue repair and regeneration in conditions involving injury and degeneration. These tiny vesicles, containing a unique cargo of genetic material, including microRNAs, modulate gene expression to facilitate crucial cellular responses for healing. The potential of exosomal RNA to influence various tissue activities positions it as a valuable candidate for innovative therapies, extending beyond conventional treatments. Its natural compatibility and ability to navigate biological barriers enhance its appeal for safe and efficient tissue repair applications. Ongoing research aims to unravel specific mechanisms, paving the way for tailored exosomal RNA-based therapies optimized for diverse tissues and diseases, including neurodegenerative disorders and osteoarthritis**. (**Muthu *et al*., 2021**)**

6. Drug Development and Target Identification: Examining exosomal RNA from diseased tissues is a crucial approach for pinpointing potential drug targets, providing insights into altered gene expressions and signaling pathways related to disease progression. This molecular information guides drug development by identifying specific molecular targets pivotal in driving the disease. Disease-specific exosomal RNA profiles enable patient stratification based on molecular subtypes, facilitating the creation of targeted and personalized therapeutic interventions. Beyond target identification, the insights gained from exosomal RNA analysis offer biomarkers for disease progression, treatment response, and potential resistance mechanisms, enhancing the precision and effectiveness of therapeutic strategies. In essence, exosomal RNA analysis stands as a powerful tool in drug discovery, paving the way for more targeted and personalized approaches in developing therapeutic interventions (Kar *et al*., 2023).

Challenges

The exploration of challenges in the domain of exosomal RNA encounters several considerations essential for unlocking its full potential. Ensuring standardization and reproducibility in the isolation, characterization, and analysis of exosomes and their RNA cargo remains a critical concern, demanding uniform protocols across diverse studies and laboratories. The accurate quantification and characterization of exosomal RNA pose challenges due to the diminutive size of exosomes and potential contamination, emphasizing the need for precise measurement techniques. Addressing the functional heterogeneity of exosomes derived from various cell types and tissues is paramount for targeted therapeutic development. Achieving specificity in delivering exosomal RNA to precise cells or tissues presents a challenge but is imperative for optimizing therapeutic efficacy while minimizing off-target effects. Overcoming biological barriers, such as the blood-brain barrier, is pivotal for expanding the applications of exosomal RNA-based therapies. Establishing ethical considerations and clear regulatory frameworks is essential for guiding the responsible development and implementation of exosomal RNA therapies. Transitioning from preclinical to clinical applications involves tackling safety concerns, optimizing dosage, and subjecting therapeutic strategies to rigorous validation in human subjects. Additionally, addressing the cost and scalability of exosome production for therapeutic purposes is crucial to ensure widespread clinical utility. Effectively navigating these challenges will necessitate interdisciplinary collaboration, technological advancements, and a more profound understanding of exosomal biology as research in this field advances.

Future Prospect

The future for exosomal RNA research and applications presents exciting possibilities, paving the way for transformative advancements across various domains. As our comprehension of the intricate roles played by exosomal RNA in intercellular communication deepens, there is a growing anticipation of innovative diagnostic and therapeutic applications. In diagnostics, the use of exosomal RNA profiles as potent biomarkers holds the potential for early disease detection and precise health monitoring, offering a non-invasive and highly specific means of assessing various medical conditions. The prospect of utilizing exosomes, loaded with therapeutic RNA cargo, as targeted drug delivery vehicles signals a transformative shift in precision medicine. This is particularly significant in cancer therapeutics, where engineered exosomes could deliver therapeutic payloads with unparalleled precision, minimizing side effects and maximizing treatment efficacy. The individualized nature of exosomal RNA, mirroring the distinctive molecular signatures of each patient, suggests a future where tailored therapeutic strategies based on exosomal RNA analysis become standard practice. Additionally, the exploration of exosomal RNA in regenerative medicine and tissue engineering hints at its potential role in augmenting tissue repair and regeneration. The integration of exosomal RNA into these burgeoning fields has the potential to revolutionize treatment approaches, offering more effective and targeted solutions for a diverse range of diseases. While challenges persist, the trajectory of exosomal RNA research seems poised to open new frontiers in diagnostics, therapeutics, and regenerative medicine, ultimately contributing to the advancement of personalized and precision healthcare.

Conclusion

In summary, the exploration of exosomal RNA represents a dynamic frontier in biomedical research, providing profound insights into intercellular communication and holding transformative potential across various domains. As we navigate the intricate landscape of exosomal RNA, significant progress has been achieved in understanding its roles in disease diagnostics, therapeutic interventions, and regenerative medicine. The identification of exosomal RNA as potent biomarkers for diverse diseases offers a non-invasive and highly specific approach to early detection and monitoring. Additionally, the use of exosomes as natural carriers for therapeutic RNA cargo presents a promising avenue for precision medicine, particularly in cancer therapeutics, where targeted drug delivery can enhance treatment efficacy while minimizing adverse effects. Looking ahead, the individualized nature of exosomal RNA suggests a future where personalized therapeutic strategies, based on the unique molecular signatures of patients, become integral to healthcare practices. The ongoing exploration of exosomal RNA in regenerative medicine hints at its potential to revolutionize tissue repair and regeneration, opening new possibilities for addressing a range of diseases.

While challenges such as standardization, specificity in targeting, and clinical translation persist, collaborative efforts across disciplines continue to propel exosomal RNA research forward. As technology advances and our understanding deepens, the future promises a landscape where exosomal RNA plays a pivotal role in advancing personalized and precision healthcare. The ongoing pursuit of solutions to current challenges ensures that exosomal RNA remains at the forefront of scientific innovation, with the potential to redefine diagnostics and therapeutics in the years to come.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Author Contribution

Data collection and analysis for this project were skillfully carried out by a team comprising Sayantani Chakraborty, Sampanna Roy, Aayushee Chatterjee, Falguni Pal, Ritu Das and Puja Sadhu. The conceptualization, design, and comprehensive refinement of the article were led by Suranjana Sarkar, Dr. Semanti Ghosh, Bidisha Ghosh, and Dr. Subhasis Sarkar.

Reference

1. Aslan, C., Kiaie, S. H., Zolbanin, N. M., Lotfinejad, P., Ramezani, R., Kashanchi, F., & Jafari, R. (2021). Exosomes for mRNA delivery: a novel biotherapeutic strategy with hurdles and hope. *BMC biotechnology*, *21*(1), 20. https://doi.org/10.1186/s12896-021-00683-w
2. Kar, R., Dhar, R., Mukherjee, S., Nag, S., Gorai, S., Mukerjee, N., Mukherjee, D., Vatsa, R., Chandrakanth Jadhav, M., Ghosh, A., Devi, A., Krishnan, A., & Thorat, N. D. (2023). Exosome-Based Smart Drug Delivery Tool for Cancer Theranostics. *ACS biomaterials science & engineering*, *9*(2), 577–594. https://doi.org/10.1021/acsbiomaterials.2c01329
3. Li, M., Zeringer, E., Barta, T., Schageman, J., Cheng, A., & Vlassov, A. V. (2014). Analysis of the RNA content of the exosomes derived from blood serum and urine and its potential as biomarkers. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *369*(1652), 20130502. https://doi.org/10.1098/rstb.2013.0502
4. Lu, Y., Huang, W., Li, M., & Zheng, A. (2023). Exosome-Based Carrier for RNA Delivery: Progress and Challenges. *Pharmaceutics*, *15*(2), 598. https://doi.org/10.3390/pharmaceutics15020598
5. Muthu, S., Bapat, A., Jain, R., Jeyaraman, N., & Jeyaraman, M. (2021). Exosomal therapy-a new frontier in regenerative medicine. *Stem cell investigation*, *8*, 7. https://doi.org/10.21037/sci-2020-037
6. Narang, P., Shah, M., & Beljanski, V. (2022). Exosomal RNAs in diagnosis and therapies. *Non-coding RNA research*, *7*(1), 7–15. https://doi.org/10.1016/j.ncrna.2022.01.001
7. Qiu, Y., Li, P., Zhang, Z., & Wu, M. (2021). Insights Into Exosomal Non-Coding RNAs Sorting Mechanism and Clinical Application. *Frontiers in oncology*, *11*, 664904. https://doi.org/10.3389/fonc.2021.664904
8. Shan, X. Q., Luo, Y. Y., Chang, J., Song, J. J., Hao, N., & Zhao, L. (2023). Immunomodulation: The next target of mesenchymal stem cell-derived exosomes in the context of ischemic stroke. *World journal of stem cells*, *15*(3), 52–70. https://doi.org/10.4252/wjsc.v15.i3.52
9. Valencia, K., & Montuenga, L. M. (2021). Exosomes in Liquid Biopsy: The Nanometric World in the Pursuit of Precision Oncology. *Cancers*, *13*(9), 2147. https://doi.org/10.3390/cancers13092147
10. Wang, J., Yue, B. L., Huang, Y. Z., Lan, X. Y., Liu, W. J., & Chen, H. (2022). Exosomal RNAs: Novel Potential Biomarkers for Diseases-A Review. *International journal of molecular sciences*, *23*(5), 2461. https://doi.org/10.3390/ijms23052461
11. Zhao, G., Zhou, A., Li, X., Zhu, S., Wang, Y., Zhang, S., & Li, P. (2021). The Significance of Exosomal RNAs in the Development, Diagnosis, and Treatment of Gastric Cancer. *Genes*, *12*(1), 73. https://doi.org/10.3390/genes12010073