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# Engineered Stem Cell-Derived Exosomes for Precision Regenerative Medicine: Molecular Targeting, Cargo Optimization, and Therapeutic Applications

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## ABSTRACT

Regenerative medicine has increasingly transitioned from cell-based therapies to cell-free approaches due to the constraints of stem cell transplantation, such as limited engraftment efficiency, immunogenicity, tumorigenic potential, and difficulties in clinical standards. Among novel cell-free methodologies, stem cell-derived exosomes have garnered considerable interest as nanoscale extracellular vesicles that facilitate tissue repair via paracrine signaling. Recent advancements in molecular biology and bioengineering have facilitated the creation of engineered exosomes, permitting precise alterations of surface molecules and bioactive cargo to improve therapeutic specificity and efficacy. This narrative review encapsulates current advancements in synthetic stem cell-derived exosomes for precision regenerative medicine, emphasizing molecular targeting techniques, therapeutic cargo optimization, and applicability across various disease types. Literature pertinent to the years 2020 to 2025 was sourced from PubMed, Scopus, and ScienceDirect and subjected to qualitative analysis. The results demonstrate that engineered exosomes can efficiently regulate critical biological pathways associated with apoptosis, inflammation, angiogenesis, and tissue regeneration. Improved targeting specificity increases tissue accumulation and therapeutic efficacy, while tailored cargo allows for precise modulation of molecular signaling in damaged microenvironments. Despite encouraging preclinical results, challenges related to production standardization, cargo uniformity, dosage optimization, and long-term safety hinder clinical translation. However, ongoing advancements in bioengineering, nanotechnology, and regulatory structures position engineered exosomes as strong contenders for the development of next-generation regenerative therapeutics. Engineered stem cell-derived exosomes are a versatile and unique platform with considerable promise to connect molecular mechanisms and clinical applications in precision regenerative medicine.

**Keywords:** Intermittent hypoxia; MAFLD; Oxidative stress; Hepatic fibrosis; Composite oxidative-fibrotic index.

## INTRODUCTION

Regenerative medicine has progressed swiftly in recent decades, aiming to repair, replace, or regenerate damaged tissues and organs caused by degenerative diseases, injuries, or aging[1]. Initially, stem cell-based therapy seemed promising due to the inherent ability of stem cells to differentiate and support tissue repair. However, an increasing amount of scientific evidence and clinical experience has revealed several significant limitations of cell-based therapies. These limitations include low engraftment efficiency, the risk of immune responses, potential tumorigenicity, and considerable challenges related to large-scale production standardization and long-term storage for clinical use[2–6].

These constraints have led to a significant shift from cell-based therapeutics to methodologies that do not rely on cells[7,8]. Increasing data indicate that the therapeutic effects of stem cells are mostly mediated by paracrine mechanisms involving the production of bioactive substances, rather than just relying on their differentiation capacity[9,10]. Stem cell-derived exosomes play a crucial role as mediators of paracrine actions. These exosomes are nanoscale extracellular vesicles, measuring approximately 30-150 nm in diameter, and are vital for intercellular communication. They facilitate the transfer of various bioactive compounds, including microRNAs, proteins, lipids, and metabolites[11,12].

Stem cell-derived exosomes have been demonstrated to exert significant regenerative effects, including modulation of inflammation, inhibition of apoptosis, stimulation of cell proliferation, promotion of angiogenesis, and regulation of immune responses[11,13,14]. A variety of in vitro and in vivo studies have indicated that exosomes can replicate many of the therapeutic benefits of stem cells while minimizing the inherent biological risks associated with live cell transplantation. As a result, exosomes have emerged as safer, more stable, and more easily scalable options for long-term therapeutic applications [15–17].

Advancements in molecular biology and bioengineering have transformed exosomes from simple byproducts of stem cells into versatile therapeutic platforms that can be precisely engineered[18]. Exosome engineering enables the modification of molecular cargo, such as the enrichment of specific microRNAs or proteins, as well as surface engineering to enhance targeted delivery to specific tissues or cell types[19]. This strategy offers substantial potential for the development of regenerative therapies that are more precise, effective, and tailored to specific pathological conditions[18,19].

Engineered stem cell-derived exosomes are a promising platform in precision regenerative medicine due to their biocompatibility, efficient tissue penetration, and adaptability for molecular engineering[20–22]. Therefore, this review aims to comprehensively summarize recent advances in molecular targeting mechanisms, therapeutic cargo optimization, and the diverse therapeutic applications of engineered exosomes within the context of modern regenerative medicine.

In this review, the term “engineered exosomes” is used consistently to describe exosomes that have been modified through biological, chemical, or physical approaches to enhance their therapeutic properties. This terminology encompasses what are sometimes referred to as modified or synthetic exosomes in the literature.

## MATERIALS AND METHODS

### *Literature Search Strategy*

This review was conducted through a comprehensive search and critical analysis of relevant scientific literature retrieved from major databases, including PubMed, Scopus, and ScienceDirect. The search focused on studies addressing stem cell–derived exosomes and exosome engineering approaches within the framework of precision regenerative medicine. The keywords used included “stem cell-derived exosomes,” “engineered exosomes,” “extracellular vesicles,” “regenerative medicine,” “molecular targeting,” “cargo optimization,” and “therapeutic applications.”

The included studies were primarily English-language articles published between 2020 and 2025, with emphasis on recent advances in exosome engineering and regenerative therapeutic

strategies. A total of approximately 100 articles were initially identified through database searching. After screening based on relevance, publication year, and study focus, 60 articles were ultimately included in this narrative review. The selection process prioritized studies related to engineered stem cell-derived exosomes, particularly those focusing on molecular targeting strategies, cargo optimization, and therapeutic applications in regenerative medicine.

### *Inclusion and Exclusion Criteria*

This analysis reviewed literature focused on original research articles and review papers that examined stem cell-derived exosomes and methods for enhancing their therapeutic effects. The emphasis was on research related to the alteration of molecular cargo, surface modification of exosomes for targeted delivery, and their therapeutic applications in models of degenerative disorders or tissue damage. This review only included materials directly about stem cell-derived exosomes, research addressing extracellular vesicles with engineering methodologies, case reports including mechanistic analysis, and scientific publications.

### *Data Extraction and Analysis*

Articles meeting the relevance criteria were qualitatively reviewed to extract key information, including stem cell sources, exosome engineering methods, types of optimized therapeutic cargo, molecular targeting strategies, and major outcomes related to regenerative effects and clinical translational potential. The extracted data were then synthesized using a descriptive and thematic approach to identify common patterns, dominant molecular mechanisms, as well as current challenges and emerging opportunities in the development of engineered stem cell–derived exosomes as a platform for precision regenerative therapy. This review was conducted as a narrative literature review and was not intended to be a systematic review or meta-analysis.

## RESULTS

### *The Role of Stem Cell–Derived Exosomes in Tissue Regeneration*

Multiple studies have indicated that exosomes produced from stem cells serve as crucial mediators of paracrine signaling in tissue regeneration processes[17,23,24]. These exosomes carry a wide array of bioactive molecules, including microRNAs, regulatory proteins, lipids, and metabolic factors, which are capable of modulating target cell responses without the direct involvement of viable stem cells[25–28]. Across various in vitro and in vivo models, exosomes have been shown to suppress apoptosis[29–31], attenuate inflammatory[32–34], enhance cell proliferation, and stimulate angiogenesis as well as tissue remodeling[35–37]. These findings reinforce the concept that the therapeutic effects of stem cells are largely mediated by exosomes, thereby supporting the development of cell-free therapeutic strategies in regenerative medicine.

### *Strategies for Exosome Engineering in Molecular Targeting*

Advancements in bioengineering technology have enabled the engineering of exosomes to enhance targeting specificity for particular tissues or cell types. Molecular targeting techniques typically involve modifying exosomal surface molecules, either by genetically engineering donor cells or by chemically altering them after isolation. These approaches include the production or conjugation of specific ligands, targeting peptides, or antibodies on the exosomal membrane, which facilitates the recognition and binding to specific receptors on target cells[38–40]. Engineered exosomes with enhanced targeting capabilities have demonstrated increased accumulation in injured or diseased tissues, such as ischemic tissues, damaged kidneys, post-infarction myocardium, and

neurodegenerative neural tissues. This targeted delivery contributes to improved therapeutic efficacy while reducing systemic off-target effects[41–44]. To facilitate comparison between different engineering strategies, a summary is provided in Table 1.

**Table 1.** Comparison of Engineering Strategies for Stem Cell-Derived Exosomes

| Engineering Strategy | Method | Key Advantage | Limitation |
|---|---|---|---|
| Surface modification | Ligand conjugation, receptor targeting, antibody attachment | Enhances targeting specificity and tissue accumulation | Complex modification process and potential immunogenicity |
| Genetic engineering of donor cells | Overexpression of specific miRNAs or proteins | Stable and efficient cargo loading | Technically demanding and time-consuming |
| Direct cargo loading | Electroporation, incubation, sonication | Simple and rapid loading of therapeutic molecules | May affect exosome integrity and cause heterogeneous cargo distribution |
| Hybrid engineering approaches | Combination of surface and cargo modification | Synergistic improvement of targeting and therapeutic efficacy | Increased production complexity and cost |

## *Optimization of Exosomal Therapeutic Cargo*

In addition to molecular targeting, cargo optimization represents a critical aspect in the development of engineered exosomes. Multiple strategies have been employed to enrich therapeutic cargo, including the overexpression of specific microRNAs or proteins in donor stem cells, as well as direct loading techniques such as electroporation, passive incubation, and sonication-based methods[18,45,46].

Exosomes enriched with anti-apoptotic microRNAs, cell cycle regulators, or pro-angiogenic factors have demonstrated significantly enhanced regenerative capacity compared with non-engineered exosomes. Moreover, accurate regulation of exosomal cargo facilitates the management of distinct molecular pathways, such as inflammatory signaling, oxidative stress responses, and cell survival pathways, thereby yielding more targeted and consistent therapeutic outcomes[36,47–49].

Mechanistically, the therapeutic effects of engineered exosomes are largely mediated through the modulation of specific intracellular signaling pathways. For example, exosomal miR-21 has been reported to inhibit apoptosis by targeting the PTEN/AKT pathway, thereby enhancing cell survival under stress conditions. Similarly, miR-146a plays a critical role in suppressing inflammation through downregulation of the TRAF6/NF-κB signaling axis. In the context of angiogenesis, exosomal cargo such as pro-angiogenic miRNAs can activate VEGF-related pathways, promoting endothelial cell proliferation and neovascularization. These findings highlight that the functional benefits of engineered exosomes are not merely associative but are driven by well-defined molecular mechanisms[30,35,36,48].

### *Therapeutic Applications of Engineered Exosomes in Diverse Disease Models*

Engineered stem cell-derived exosomes have been widely applied across various models of degenerative diseases and tissue injury. In cardiovascular disease models, engineered exosomes have been shown to enhance cardiomyocyte viability, reduce fibrotic area, and improve cardiac function following ischemic injury. In models of acute and chronic kidney injury, exosomes exert protective effects by reducing tubular cell apoptosis, modulating inflammatory responses, and stimulating renal epithelial cell proliferation[50–52].

In addition, within the nervous system, engineered exosomes play a crucial role in enhancing neuroprotection, restoring synaptic function, and suppressing neuroinflammatory processes in models of neurodegenerative diseases. These findings underscore that exosome engineering not only improves therapeutic efficacy but also expands the spectrum of exosome applications in precision regenerative medicine[53,54].

### *Challenges in Clinical Translation*

Despite promising preclinical outcomes, several challenges remain in the clinical translation of engineered exosomes. Major obstacles include the standardization of exosome isolation and characterization methods, consistency of therapeutic cargo, stability during storage, and the determination of optimal dosing regimens and routes of administration. In addition, long-term safety concerns and regulatory frameworks for large-scale clinical-grade exosome production require further investigation before widespread clinical implementation can be achieved[55–58].

Beyond these general challenges, several specific translational barriers have been identified in recent studies. One major issue is batch-to-batch variability in exosome production, which can lead to inconsistencies in therapeutic efficacy. Additionally, the lack of standardized potency assays makes it difficult to reliably evaluate and compare the biological activity of engineered exosomes across studies. From a regulatory perspective, uncertainty remains regarding whether engineered exosomes should be classified as biologics, drug delivery systems, or advanced therapy medicinal products, which complicates approval pathways. Furthermore, large-scale manufacturing under Good Manufacturing Practice (GMP) conditions remains technically demanding and costly, limiting their widespread clinical application. Addressing these issues will be essential for successful translation of engineered exosomes into routine clinical practice[55–58].

## DISCUSSION

### *Engineered Exosomes as an Evolution in Precision Regenerative Therapy*

The development of engineered stem cell–derived exosomes represents a fundamental shift in regenerative medicine toward more controllable and cell-free therapeutic systems. Compared with conventional stem cell-based approaches, exosome-based strategies offer improved safety and stability, as widely reported in previous studies. Rather than reiterating these established advantages, this review emphasizes how engineering strategies further enhance exosomal functionality, particularly through improved targeting specificity and optimized therapeutic cargo, thereby strengthening their role in precision regenerative medicine[2–4,6].

### *Integration of Molecular Targeting and Cargo Optimization*

The central discussion arising from current evidence indicates that the therapeutic efficacy of exosomes is highly dependent on two key components: molecular targeting capability and the composition of bioactive cargo. Engineering of exosomal surface molecules enhances the specificity of interactions with target cells, thereby significantly improving tissue distribution and therapeutic efficiency. This strategy reduces non-specific accumulation and minimizes potential systemic side effects, which are common limitations of nanomaterial-based therapies[38,40,59].

The optimization of exosomal cargo allows for more precise regulation of biological responses by modulating specific molecular pathways, such as inflammation, apoptosis, cell proliferation, and angiogenesis. Consequently, engineered exosomes are not just passive carriers of therapeutic molecules; they also actively regulate the damaged tissue microenvironment. The combination of molecular targeting and cargo optimization represents a therapeutic approach that aligns with the principles of precision medicine, where interventions are customized to meet the specific biological needs of distinct tissues or disease states[31,36,47,48,60].

While both molecular targeting and cargo optimization significantly enhance exosome-based therapies, their relative contributions differ depending on the therapeutic context. Surface engineering strategies, such as ligand or receptor-mediated targeting, primarily improve delivery efficiency and tissue specificity but may not directly influence intracellular signaling. In contrast, cargo optimization approaches, including miRNA enrichment or protein loading, exert more direct and sustained effects on cellular pathways involved in regeneration. However, cargo loading techniques such as electroporation may compromise exosome integrity or result in heterogeneous cargo distribution, whereas genetic modification of donor cells offers higher stability but introduces complexity in production. Therefore, current evidence suggests that a combinatorial strategy integrating both targeting and cargo optimization may provide synergistic benefits and represents a more effective approach for precision regenerative therapy[45,46].

### *Relevance of Molecular Mechanisms to Regenerative Effects*

Mechanistic evidence suggests that the regenerative actions of exosomes result from the concurrent regulation of various cellular signaling pathways rather than a singular mechanism. Exosomes can inhibit excessive apoptosis, diminish oxidative stress, and modulate the equilibrium between inflammation and tissue regeneration. This intricate mechanism of action is especially pertinent in chronic degenerative illnesses, where tissue destruction is frequently associated with complex and enduring dysregulation of molecular signaling networks[32,33,35,37]. Furthermore, the ability of engineered exosomes to deliver cargo that specifically targets defined molecular pathways provides a distinct advantage over conventional therapies, which are often non-specific in nature[27,28,36]. By precisely controlling cargo composition, exosomes can be directed to support tissue regeneration without inducing abnormal proliferation or undesirable immune responses, thereby improving the therapeutic benefit–risk ratio[17,34].

### *Challenges in Clinical Translation and Standardization*

Despite the highly promising therapeutic potential of engineered exosomes, several challenges remain central to their clinical translation. One of the most significant obstacles is the standardization of exosome isolation, characterization, and large-scale production for clinical applications. Variability in stem cell sources, culture conditions, and engineering methods can influence cargo consistency and biological activity, ultimately affecting the reproducibility of clinical outcomes[55–57]. In addition, the determination of optimal dosing, routes of administration, and treatment frequency requires systematic evaluation through well-controlled preclinical and clinical

studies[58]. Long-term safety considerations also represent a critical concern, particularly with regard to potential off-target effects or exosome accumulation in specific tissues. Therefore, the establishment of robust regulatory guidelines and stringent quality control standards is a fundamental prerequisite before engineered exosomes can be widely adopted in clinical practice.

### *Future Perspectives in Precision Regenerative Medicine*

Looking ahead, the integration of engineered exosomes with complementary technologies such as genetic engineering, smart biomaterials, and nanotechnology-based delivery systems has the potential to further expand the scope of regenerative therapeutic applications[18,22,26]. Beyond serving as standalone therapeutic agents, exosomes may also be developed as highly precise delivery platforms for drugs, therapeutic RNAs, and other bioactive molecules. Overall, this results highlights that engineered stem cell–derived exosomes represent an innovative strategy that bridges molecular mechanistic insights with clinical application. By addressing existing translational challenges, this approach has the potential to become a central pillar in the future development of precision regenerative therapies[20,21].

## CONCLUSION

In conclusion, engineered stem cell–derived exosomes represent a promising precision regenerative therapeutic approach by combining the safety of cell-free therapies with the versatility of molecular engineering. Through specific targeting and optimization of bioactive cargo, engineered exosomes can more effectively and controllably modulate key pathways involved in apoptosis, inflammation, and tissue regeneration. Although challenges in clinical translation remain, including production standardization, cargo consistency, and long-term safety evaluation, rapid advances in bioengineering and molecular biology position engineered exosomes as strong candidates for next-generation regenerative therapies. This approach has the potential to bridge fundamental research and clinical application in the advancement of precision regenerative medicine.

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### Authors' contributions

All authors contributed equally to this research, including conceptualization, data acquisition and analysis, literature review, manuscript preparation, and revision.

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### Conflict of interest

The authors declare that there are no conflicts of interest related to this work.

## REFERENCES

1. Lee JY, Kim HS. Extracellular Vesicles in Regenerative Medicine: Potentials and Challenges. *Tissue Eng Regen Med*. 2021;18(4):479-484. doi:10.1007/s13770-021-00365-w
2. Petrus-Reurer S, Romano M, Howlett S, Jones JL, Lombardi G, Saeb-Parsy K. Immunological considerations and challenges for regenerative cellular therapies. *Commun Biol*. 2021;4(1):798. doi:10.1038/s42003-021-02237-4
3. Hussen BM, Taheri M, Yashooa RK, et al. Revolutionizing medicine: recent developments and future prospects in stem-cell therapy. *Int J Surg*. 2024;110(12):8002-8024. doi:10.1097/JS9.0000000000002109
4. Chang SH, Park CG. Comparing the Benefits and Drawbacks of Stem Cell Therapy Based on the Cell Origin or Manipulation Process: Addressing Immunogenicity. *Immune Netw*. 2023;23(6). doi:10.4110/in.2023.23.e44
5. Xu Y, Song Y, Zhang C, et al. Mesenchymal stem cells-derived miR-143–3p attenuate acute kidney injury by suppressing TAK1-Driven necroptosis. *Biochem Biophys Res Commun*. 2025;778:152339. doi:10.1016/j.bbrc.2025.152339
6. Wong RSY, Tan EW, Goh BH. Mesenchymal Stem Cell-Based Therapies: Challenges and Enhancement Strategies. *Cell Biochem Biophys*. Published online September 26, 2025. doi:10.1007/s12013-025-01895-z
7. Deng S, Cao H, Cui X, Fan Y, Wang Q, Zhang X. Optimization of exosome-based cell-free strategies to enhance endogenous cell functions in tissue regeneration. *Acta Biomater*. 2023;171:68-84. doi:10.1016/j.actbio.2023.09.023
8. Chou Y, Alfarafisa N, Ikezawa M, Khairani A. Progress in the Development of Stem Cell-Derived Cell-Free Therapies for Skin Aging. *Clin Cosmet Investig Dermatol*. 2023;Volume 16:3383-3406. doi:10.2147/CCID.S434439
9. Gwam C, Mohammed N, Ma X. Stem cell secretome, regeneration, and clinical translation: a narrative review. *Ann Transl Med*. 2021;9(1):70-70. doi:10.21037/atm-20-5030
10. Trigo CM, Rodrigues JS, Camões SP, Solá S, Miranda JP. Mesenchymal stem cell secretome for regenerative medicine: Where do we stand? *J Adv Res*. 2025;70:103-124. doi:10.1016/j.jare.2024.05.004
11. Kalluri R, LeBleu VS. The biology , function , and biomedical applications of exosomes. *Science (80- )*. 2020;367(6478). doi:10.1126/science.aau6977
12. Chen YF, Luh F, Ho YS, Yen Y. Exosomes: a review of biologic function, diagnostic and targeted therapy applications, and clinical trials. *J Biomed Sci*. 2024;31(1):67. doi:10.1186/s12929-024-01055-0
13. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. *Signal Transduct Target Ther*. 2024;9(1):17. doi:10.1038/s41392-023-01704-0
14. Thakur A, Shah D, Rai D, et al. Therapeutic Values of Exosomes in Cosmetics, Skin Care, Tissue Regeneration, and Dermatological Diseases. *Cosmetics*. 2023;10(2):65. doi:10.3390/cosmetics10020065
15. Roszkowski S. Therapeutic potential of mesenchymal stem cell-derived exosomes for regenerative medicine applications. *Clin Exp Med*. 2024;24(1):46. doi:10.1007/s10238-023-01282-z
16. Jo C, Choi YJ, Lee TJ. Therapeutic Potential of Stem Cell-Derived Exosomes in Skin Wound Healing. *Biomimetics*. 2025;10(8):546. doi:10.3390/biomimetics10080546
17. Huang D, Shen H, Xie F, et al. Role of mesenchymal stem cell-derived exosomes in the regeneration of different tissues. *J Biol Eng*. 2024;18(1):36. doi:10.1186/s13036-024-00431-6

18. Bahadorani M, Nasiri M, Dellinger K, Aravamudhan S, Zadegan R. Engineering Exosomes for Therapeutic Applications: Decoding Biogenesis, Content Modification, and Cargo Loading Strategies. *Int J Nanomedicine*. 2024;Volume 19:7137-7164. doi:10.2147/IJN.S464249

19. Li L, Wang F, Zhu D, Hu S, Cheng K, Li Z. Engineering exosomes and exosome-like nanovesicles for improving tissue targeting and retention. *Fundam Res*. 2025;5(2):851-867. doi:10.1016/j.fmre.2024.03.025

20. Deng K, Chen Z, Zhang X, et al. Harnessing engineered exosomes for transformative therapy of cardiovascular and cerebrovascular disorders: Opportunities and challenges. *Mater Des*. 2025;256:114243. doi:10.1016/j.matdes.2025.114243

21. Serrano DR, Juste F, Anaya BJ, et al. Exosome-Based Drug Delivery: A Next-Generation Platform for Cancer, Infection, Neurological and Immunological Diseases, Gene Therapy and Regenerative Medicine. *Pharmaceutics*. 2025;17(10):1336. doi:10.3390/pharmaceutics17101336

22. Mendonca SR, Bangera PD, Keerikkadu M, Tippavajhala VK, Rathnanand M. Multifunctional Engineering of Exosomes for Precision Therapeutics: Strategies for Targeted Delivery, Barrier Evasion, and Clinical Translation. *Pharm Res*. 2025;42(11):1931-1952. doi:10.1007/s11095-025-03961-w

23. Zhou C, Zhang B, Yang Y, et al. Stem cell-derived exosomes: emerging therapeutic opportunities for wound healing. *Stem Cell Res Ther*. 2023;14(1):107. doi:10.1186/s13287-023-03345-0

24. Arun M, Rajasingh S, Madasamy P, Rajasingh J. Immunomodulatory and Regenerative Functions of MSC-Derived Exosomes in Bone Repair. *Bioengineering*. 2025;12(8):844. doi:10.3390/bioengineering12080844

25. Foo JB, Looi QH, How CW, et al. Mesenchymal Stem Cell-Derived Exosomes and MicroRNAs in Cartilage Regeneration: Biogenesis, Efficacy, miRNA Enrichment and Delivery. *Pharmaceuticals*. 2021;14(11):1093. doi:10.3390/ph14111093

26. Li Q, Gao H, Ma X, Wang Z, Zhao L, Xiao W. Exosome-mediated crosstalk between the cardiovascular and musculoskeletal systems: Mechanisms and therapeutic potential (Review). *Int J Mol Med*. 2025;56(3):1-23. doi:10.3892/ijmm.2025.5570

27. Xiao Y, Yuan Y, Hu D, Wang H. Exosome-Derived microRNA: Potential Target for Diagnosis and Treatment of Sepsis. Batra L, ed. *J Immunol Res*. 2024;2024(1). doi:10.1155/2024/4481452

28. Chimal-Vega B, Maldonado-Arvizu JE, Hernández Avalos AD, Díaz-Villanueva JF, Avila-Barrientos LP, García González VG. Inter-Tissue Communication Mechanisms via Exosomes and Their Implications in Metabolic Diseases: Opportunities for Pharmacological Regulation. *Futur Pharmacol*. 2025;5(1):11. doi:10.3390/futurepharmacol5010011

29. Zhao G, Liu F, Liu Z, et al. MSC-derived exosomes attenuate cell death through suppressing AIF nucleus translocation and enhance cutaneous wound healing. *Stem Cell Res Ther*. 2020;11(1):174. doi:10.1186/s13287-020-01616-8

30. Chen J, Chen J, Cheng Y, et al. Mesenchymal stem cell-derived exosomes protect beta cells against hypoxia-induced apoptosis via miR-21 by alleviating ER stress and inhibiting p38 MAPK phosphorylation. *Stem Cell Res Ther*. 2020;11(1):97. doi:10.1186/s13287-020-01610-0

31. Li J, Huang Y, Sun H, Yang L. Mechanism of mesenchymal stem cells and exosomes in the treatment of age-related diseases. *Front Immunol*. 2023;14. doi:10.3389/fimmu.2023.1181308

32. Zhang Y, Zhang Y, Chopp M, Zhang ZG, Mahmood A, Xiong Y. Mesenchymal Stem Cell–Derived Exosomes Improve Functional Recovery in Rats After Traumatic Brain Injury: A Dose-Response and Therapeutic Window Study. *Neurorehabil Neural Repair*. 2020;34(7):616-626. doi:10.1177/1545968320926164

33. Jing S, Li H, Xu H. Mesenchymal Stem Cell Derived Exosomes Therapy in Diabetic Wound Repair. *Int J Nanomedicine*. 2023;Volume 18:2707-2720. doi:10.2147/IJN.S411562

34. Zubair M, Abouelnazar FA, Iqbal MA, et al. Mesenchymal stem cell-derived exosomes as a plausible immunomodulatory therapeutic tool for inflammatory diseases. *Front Cell Dev Biol*. 2025;13. doi:10.3389/fcell.2025.1563427

35. Song Y, Zhang T, Shi P, Gao Y, Pang X. Exosomes derived from human amniotic mesenchymal stem cells promotes angiogenesis in hUVECs by delivering novel miRNA N-194. *Mol Med*. 2025;31(1):173. doi:10.1186/s10020-025-01192-8

36. Jian X, Han J, Liu X, et al. Exosome-carried miR-1248 from adipose-derived stem cells improves angiogenesis in diabetes-associated wounds. *Int J Biol Macromol*. 2025;297:139822. doi:10.1016/j.ijbiomac.2025.139822

37. Qu Q, Liu L, Wang L, et al. Exosomes derived from hypoxic mesenchymal stem cells restore ovarian function by enhancing angiogenesis. *Stem Cell Res Ther*. 2024;15(1):496. doi:10.1186/s13287-024-04111-6

38. Kang C, Han P, Lee JS, Lee D, Kim D. Anchor, Spacer, and Ligand-Modified Engineered Exosomes for Trackable Targeted Therapy. *Bioconjug Chem*. 2020;31(11):2541-2552. doi:10.1021/acs.bioconjchem.0c00483

39. Wang X, Soh KG, Samsudin S, et al. Effects of high-intensity training on jumping performance among athletes: a systematic review with meta-analysis. *Sci Rep*. 2025;15(1):1763. doi:10.1038/s41598-024-83161-5

40. Chen Y, Hou S. Targeted treatment of rat AKI induced by rhabdomyolysis using BMSC derived magnetic exosomes and its mechanism. *Nanoscale Adv*. 2024;6(16):4180-4195. doi:10.1039/D4NA00334A

41. Li JK, Yang C, Su Y, et al. Mesenchymal Stem Cell-Derived Extracellular Vesicles: A Potential Therapeutic Strategy for Acute Kidney Injury. *Front Immunol*. 2021;12. doi:10.3389/fimmu.2021.684496

42. Thongboonkerd V. Roles for exosome in various kidney diseases and disorders. *Front Pharmacol*. 2020;10(January):1-14. doi:10.3389/fphar.2019.01655

43. Sepehri M, Rabbani S, Ai J, et al. Therapeutic potential of exosomes derived from human endometrial mesenchymal stem cells for heart tissue regeneration after myocardial infarction. *Regen Ther*. 2025;28:451-461. doi:10.1016/j.reth.2025.01.007

44. Zhu L, Zhang X, Yuan R, Chai Y. Y-shaped walker with abundant recognition domians mediated ultrasensitive electrochemical biosensor for miRNA-21 detection. *Sensors Actuators B Chem*. 2023;375:132901. doi:10.1016/j.snb.2022.132901

45. Chen Z, Xiong M, Tian J, Song D, Duan S, Zhang L. Encapsulation and assessment of therapeutic cargo in engineered exosomes: a systematic review. *J Nanobiotechnology*. 2024;22(1):18. doi:10.1186/s12951-023-02259-6

46. de Abreu RC, Ramos C V., Becher C, et al. Exogenous loading of miRNAs into small extracellular vesicles. *J Extracell Vesicles*. 2021;10(10). doi:10.1002/jev2.12111

47. Tang L, Yang Y, Yang M, et al. miR-21-loaded bone marrow mesenchymal stem cell-derived exosomes inhibit pyroptosis by targeting MALT1 to repair chemotherapy-induced premature ovarian insufficiency. *Cell Biol Toxicol*. 2024;41(1):3. doi:10.1007/s10565-024-09946-6

48. Lv Q, Wang Y, Tian W, et al. Exosomal miR-146a-5p derived from human umbilical cord mesenchymal stem cells can alleviate antiphospholipid antibody-induced trophoblast injury and placental dysfunction by regulating the TRAF6/NF-κB axis. *J Nanobiotechnology*. 2023;21(1):419. doi:10.1186/s12951-023-02179-5

49. Wang T, Jian Z, Baskys A, et al. MSC-derived exosomes protect against oxidative stress-induced skin injury via adaptive regulation of the NRF2 defense system. *Biomaterials*. 2020;257:120264. doi:10.1016/j.biomaterials.2020.120264

50. Cao JY, Wang B, Tang TT, et al. Exosomal miR-125b-5p deriving from mesenchymal stem cells promotes tubular repair by suppression of p53 in ischemic acute kidney injury. *Theranostics*. 2021;11(11):5248-5266. doi:10.7150/thno.54550

51. Huang J, Cao H, Cui B, et al. Mesenchymal Stem Cells-Derived Exosomes Ameliorate Ischemia/Reperfusion Induced Acute Kidney Injury in a Porcine Model. *Front Cell Dev Biol*. 2022;10(May):1-17. doi:10.3389/fcell.2022.899869

52. Ji X, Nie S, Li X, Liu H, Du X, Fan L. <scp>MSC</scp> -Derived Exosomal MiR-127-3p Alleviates Acute Kidney Ischemia–Reperfusion Injury via Suppressing <scp>ATG5</scp> / <scp>ATG7</scp> -Mediated Autophagy. *Nephrology*. 2025;30(6). doi:10.1111/nep.70054

53. He S, Wang Q, Chen L, He YJ, Wang X, Qu S. miR-100a-5p-enriched exosomes derived from mesenchymal stem cells enhance the anti-oxidant effect in a Parkinson's disease model via regulation of Nox4/ROS/Nrf2 signaling. *J Transl Med*. 2023;21(1):747. doi:10.1186/s12967-023-04638-x

54. Ye J, Sun X, Jiang Q, et al. Umbilical cord blood-derived exosomes attenuate dopaminergic neuron damage of Parkinson's disease mouse model. *J Nanobiotechnology*. 2024;22(1):567. doi:10.1186/s12951-024-02773-1

55. Butreddy A, Kommineni N, Dudhipala N. Exosomes as Naturally Occurring Vehicles for Delivery of Biopharmaceuticals: Insights from Drug Delivery to Clinical Perspectives. *Nanomaterials*. 2021;11(6):1481. doi:10.3390/nano11061481

56. Rezaie J, Feghhi M, Etemadi T. A review on exosomes application in clinical trials: perspective, questions, and challenges. *Cell Commun Signal*. 2022;20(1):145. doi:10.1186/s12964-022-00959-4

57. Palakurthi SS, Shah B, Kapre S, et al. A comprehensive review of challenges and advances in exosome-based drug delivery systems. *Nanoscale Adv*. 2024;6(23):5803-5826. doi:10.1039/D4NA00501E

58. Wang Y, Zhu J, Ma Q, et al. Trends in mesenchymal stem cell-derived extracellular vesicles clinical trials 2014–2024: is efficacy optimal in a narrow dose range? *Front Med*. 2025;12. doi:10.3389/fmed.2025.1625787

59. Wang AYL, Kao HK, Liu YY, Loh CYY. Engineered extracellular vesicles derived from pluripotent stem cells: a cell-free approach to regenerative medicine. *Burn Trauma*. 2025;13. doi:10.1093/burnst/tkaf013

60. Zhao Y, Zhu X, Zhang L, et al. Mesenchymal Stem/Stromal Cells and their Extracellular Vesicle Progeny Decrease Injury in Poststenotic Swine Kidney Through Different Mechanisms. *Stem Cells Dev*. 2020;29(18):1190-1200. doi:10.1089/scd.2020.0030