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Exosome-Based Therapies for Scar-Free Skin Regeneration: Clinical Applications and Emerging Trends

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Abstract

Scar formation remains a significant limitation in conventional wound care, often leading to functional impairment and aesthetic concerns. In recent years, exosome-based therapies have emerged as a novel regenerative strategy capable of accelerating wound healing while reducing fibrosis. Nanosized extracellular vesicles derived from sources such as mesenchymal stem cells, adipose tissue, and platelets, carry bioactive molecules that regulate inflammation, stimulate angiogenesis, and remodel the extracellular matrix. Preclinical and clinical evidence increasingly supports their potential to facilitate scar-free skin regeneration. This review highlights the therapeutic applications, clinical advancements, and emerging trends in exosome-based wound healing strategies. It also examines current challenges – including scalability, regulatory approval, and delivery methods – and proposes future directions to enhance clinical translation.

Keywords: exosomes, skin regeneration, scar-free healing, cell-free therapy, clinical applications, regenerative medicine

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Экзосомальная терапия для безрубцового восстановления кожи: клиническое применение и новые тенденции

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Резюме

Образование рубцовой ткани остается существенным ограничением традиционных методов лечения ран, нередко приводящим к функциональным нарушениям и эстетическим дефектам. В последние годы экзосомальная терапия рассматривается как новая регенеративная стратегия, способная ускорять заживление ран и снижать уровень формирования фиброза. Наночастицы внеклеточных везикул, полученные из мезенхимальных стволовых клеток, жировой ткани и тромбоцитов содержат биологически активные молекулы, регулирующие воспалительные процессы, стимулирующие ангиогенез и способствующие ремоделированию внеклеточного матрикса. Результаты доклинических и клинических исследований все чаще подтверждают потенциал экзосомальной терапии в стимулировании безрубцовой регенерации кожи.

Настоящий обзор направлен на изучение терапевтических применений, клинических достижений и новых тенденций в области экзосомальных технологий кожной регенерации. Также рассматриваются текущие трудности – включая масштабируемость производства, вопросы нормативного регулирования и способы доставки – предлагаются возможные пути для ускорения внедрения в клиническую практику.

Ключевые слова: экзосомы, регенерация кожи, безрубцовое заживление, бесклеточная терапия, клиническое применение, регенеративная медицина

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Introduction

Wound healing is a complex biological process involving coordinated phases: hemostasis, inflammation, proliferation, and remodeling. Although these phases typically restore skin integrity, they often result in fibrotic scar formation that can impair both tissue function and cosmetic appearance.[1,2] Despite advancements in surgical techniques and regenerative biomaterials, current wound care approaches primarily focus on symptom management rather than true tissue regeneration.

One of the most promising frontiers in regenerative medicine is harnessing the therapeutic potential of exosomes—nanosized extracellular vesicles secreted by various cell types. Exosomes carry a diverse cargo of signaling molecules, including microRNAs, growth factors, and proteins, which can modulate cellular communication and reprogram the wound microenvironment.[3] As part of the broader stem cell secretome, exosomes are believed to mediate many of the paracrine regenerative effects previously attributed to stem cells .[4]

Unlike cell-based therapies, exosome-based treatments offer unique advantages: lower immunogenicity, enhanced biocompatibility, and scalability as off-the-shelf products. Preclinical models have demonstrated that exosomes can accelerate wound closure, improve vascularization, reduce inflammation, and significantly minimize scar formation.[5] These findings have fueled growing interest in their clinical application across diverse wound types, including chronic diabetic ulcers, burns, and post-surgical wounds.

This review provides a comprehensive overview of exosome-based therapeutic strategies for scar-free skin regeneration. We examine key sources of exosomes, highlight preclinical and clinical evidence of efficacy, compare their advantages over traditional treatments, and discuss ongoing challenges in clinical translation and regulation.

Methods

Search Strategy

This review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and methodological rigor. A comprehensive literature search was performed across four major databases—PubMed, Scopus, Web of Science, and Google Scholar—to identify recent studies on the clinical and translational application of exosomes in wound healing and scar-free skin regeneration. The search included articles published between January 2021 and March 2025.

Keywords and Medical Subject Headings (MeSH) terms included: “Exosomes”, “Wound Healing”, “Skin Regeneration”, “Extracellular Vesicles”, “Therapeutic Application”, “Stem Cell-Derived Exosomes”, “Platelet-Derived Exosomes”, “Clinical Trials”, and “Scar-Free Healing”. Boolean operators (AND, OR) were applied to ensure comprehensive coverage. Only peer-reviewed articles published in English were included.

Study Selection

Inclusion criteria:

- Peer-reviewed studies published in English
- Focus on therapeutic use of exosomes for wound healing and scar-free skin regeneration
- Clinical trials, preclinical studies, translational research, and systematic reviews with therapeutic relevance
- Published between 2021 and 2025

Exclusion criteria:

1. Non-peer-reviewed or opinion-based articles (e.g., editorials, letters, abstracts)
2. Studies focused exclusively on exosome biology without therapeutic application
3. Articles lacking clear methodological details or with unresolved quality concerns
4. Reviews not focused on regenerative skin therapies

Screening Process

From the initial 124 records identified, 94 unique articles remained after duplicates were removed using EndNote and Mendeley. Screening was conducted in two phases:

1. Title and Abstract Screening for therapeutic relevance and quality
2. Full-Text Review against inclusion and exclusion criteria

Following this, 67 studies were included in the final review.

Data Extraction

A standardized data extraction form was used to collect:

- *Study characteristics*: authorship, publication year, design, and geographic origin
- *Exosome sources*: cell types (e.g., MSCs, ASCs, platelets), and isolation techniques
- *Application type*: wound models (e.g., diabetic wounds, burns), delivery methods (topical, injectable, scaffold-based)
- *Therapeutic outcomes*: healing rate, angiogenesis, collagen remodeling scar reduction
- *Challenges and limitations*: immunogenicity, dosage control, scalability, regulatory status

Two independent reviewers extracted and verified the data. Discrepancies were resolved by consensus.

Quality Assessment

The Joanna Briggs Institute (JBI) Critical Appraisal Tools were used to assess study quality. Criteria included methodological clarity, data robustness, risk of bias, and reproducibility. All included studies met high standards of scientific validity.

Data Synthesis

Due to variation in models, exosome types, and delivery methods, a narrative synthesis approach was adopted. Findings were thematically categorized into:

- Sources of therapeutic exosomes

- Preclinical and clinical evidence
- Advantages over traditional wound therapies
- Challenges in translation to clinical use

A PRISMA flowchart (Figure 1) visually outlines the article selection process.

Sources of Exosomes for Wound Healing Therapies

Exosomes are nanoscale extracellular vesicles secreted by various cell types that have attracted significant attention for their potential applications in wound healing therapies. Their ability to transfer bioactive molecules such as proteins, lipids, and nucleic acids to recipient cells positions them as pivotal mediators in tissue regeneration processes.[5] Identifying optimal cellular sources for exosome production is crucial for developing effective therapeutic approaches.

Mesenchymal stem cells (MSCs) are among the most extensively studied sources of exosomes for regenerative medicine. MSCs can be isolated from various tissues, including bone marrow, adipose tissue, and umbilical cord blood.[6] Exosomes derived from MSCs have demonstrated remarkable potential in modulating inflammation, promoting angiogenesis, and enhancing tissue repair. For instance, MSC-derived exosomes contain growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β), which are instrumental in wound healing processes.[7,8] Moreover, these exosomes carry microRNAs that regulate gene expression in recipient cells, thereby influencing cellular behaviors essential for tissue regeneration. The therapeutic efficacy of MSC-derived exosomes has been validated in various preclinical models, highlighting their promise for clinical applications.[9,10]

Adipose-derived stem cells (ADSCs) represent another valuable source of exosomes for wound healing therapies. ADSCs are abundant and easily accessible, making them an attractive option for autologous treatments.[11] Exosomes derived from ADSCs have been shown to enhance collagen synthesis, accelerate re-epithelialization, and improve wound closure rates. The cargo of ASC-derived exosomes contains cytokines and growth factors that synergistically promote tissue repair .[12,13] Additionally, their anti-inflammatory properties contribute to establishing a favorable healing environment, thereby reducing the risk of chronic wound development.[14]

Platelet-derived exosomes have emerged as a promising therapeutic approach in wound management. Platelets are traditionally known for their role in hemostasis, they also secrete exosomes enriched with growth factors like platelet-derived growth factor (PDGF) and insulin-like growth factor-1 (IGF-1).[15] These exosomes promote cellular proliferation, migration, and angiogenesis, all critical components of effective wound healing. Clinical studies have investigated the application of platelet-derived exosomes in treatment of various conditions, including skin rejuvenation and chronic wounds, with promising outcomes.[16] For instance, Rion Aesthetics has developed a platelet-derived exosome serum that has demonstrated improvements in skin texture and redness, suggesting potential applications in wound healing .[17]

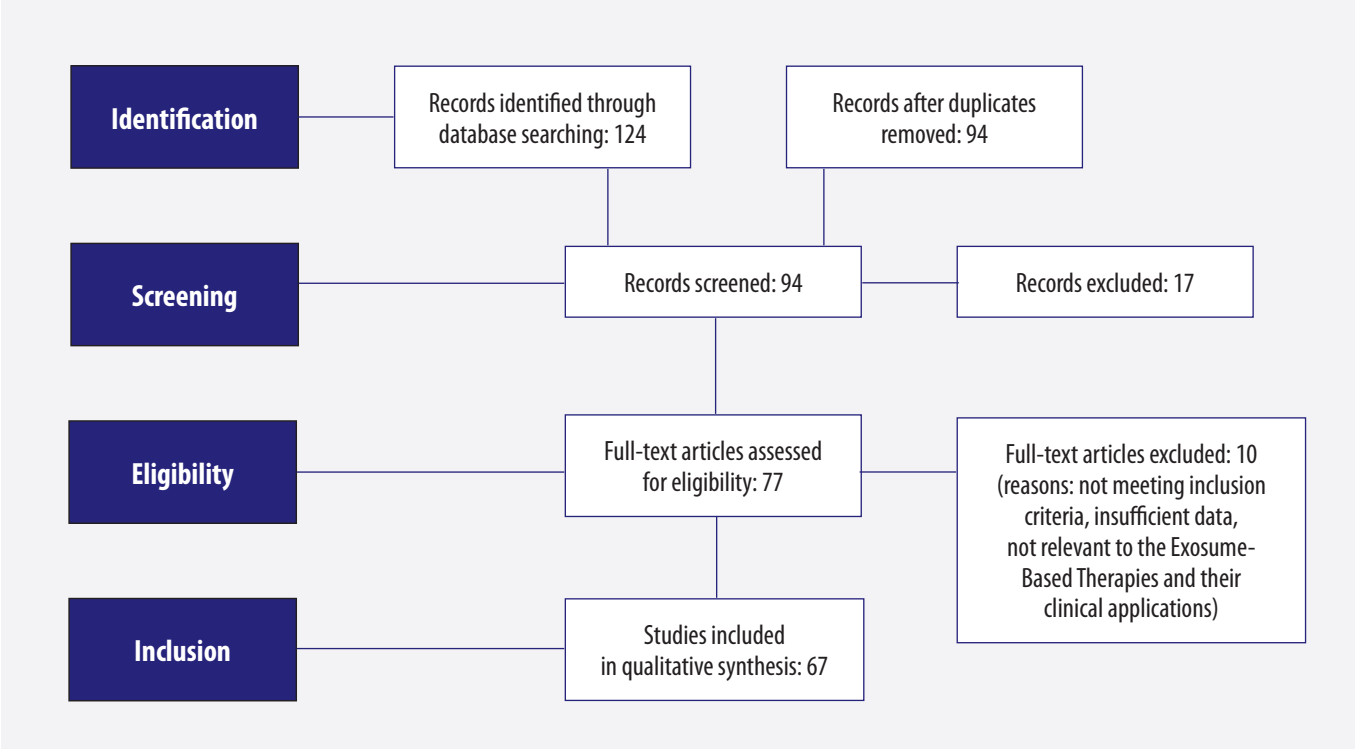

Figure. PRISMA flow diagram
Рисунок. Блок-схема PRISMA

Skin fibroblasts, the primary cells responsible for extracellular matrix production, also serve as a source of exosomes with regenerative potential. Fibroblast-derived exosomes contain matrix metalloproteinases (MMPs) and their inhibitors, which are crucial for balanced matrix remodeling during wound healing.[18,19] By modulating the activity of these enzymes, fibroblast-derived exosomes can influence scar formation and tissue elasticity, contributing to improved healing outcomes.[20] Their role in intercellular communication within the dermal layer highlights their significance in maintaining skin integrity and facilitating repair mechanisms.[21]

Beyond these primary sources, other cell types have been investigated for their exosome production capabilities and therapeutic potential. For instance, exosomes derived from oral keratinocytes have been demonstrated to accelerate wound healing, even when applied across species barriers, such as human exosomes promoting healing in rat models.[22] This finding suggests a conserved mechanism of action and broad applicability in regenerative medicine. Additionally, exosomes from endothelial cells and immune cells, including dendritic cells are being explored for their roles in angiogenesis and immune modulation, respectively, increasing the diversity of exosome sources for therapeutic applications.[22]

The selection of an appropriate exosome source for wound healing therapies depends on various factors, including specific wound characteristics, patient condition, and scalability of exosome production.[23] Autologous sources, such as patient-derived MSCs or ASDCs, offer the advantages including reduced immunogenicity and potential for personalized treatment approaches. However, allogeneic sources are also under considered, especially when rapid treatment initiation is required and donor cells are readily available.[24,25] Standardization of isolation and purification methods is essential to ensure the consistency, safety, and efficacy of exosome-based therapies.[26]

Preclinical and Clinical Evidence on Exosome-Based Wound Healing

Exosome-based therapies have garnered considerable attention in recent years due to their potential to enhance wound healing process. Extensive preclinical studies have demonstrated that exosomes can positively influence various phases of wound healing by modulating inflammation, promoting angiogenesis, and facilitating tissue regeneration.[27] For instance, exosomes derived from MSCs have been shown to stimulate fibroblast proliferation, migration, and collagen synthesis, which are essential for effective wound repair.[28] Similarly, exosomes from ADSCs have demonstrated pro-angiogenic properties by delivering regulatory factors to endothelial cells.[29] These findings highlight the therapeutic potential of exosomes to modulate key cellular processes involved in tissue regeneration.

In diabetic wound models, which present particular challenges due to impaired healing processes, exosome-based therapies have demonstrated promising results. For example, exosomes derived from induced pluripotent stem cells (iPSCs) have been shown to enhance wound closure by stimulating dermal fibroblast proliferation and migration.[30,20] Similarly, exosomes containing microRNA-221-3p from endothelial progenitor cells promoted skin wound healing in diabetic mice by modulating the AGE-RAGE signaling pathway, regulating the cell cycle, and influencing the p53 pathway.[31]

The application of bioengineered MSC-derived exosomes has also been investigated to enhance therapeutic efficacy. By modifying exosomes or combining them with biomaterials, researchers aim to increase dosage, achieve sustained release, and target specific stages of the healing process.[32] These bioengineering strategies have demonstrated improved regenerative efficiency in skin wound repair and tissue regeneration.

Despite promising preclinical data, translating exosome-based therapies into clinical practice remains challenging. A significant hurdle is the lack of standardized methods for exosome isolation and purification .[33] Variability in these protocols can lead to inconsistencies in exosome preparations, impacting their therapeutic efficacy and safety. Furthermore, the scalability of exosome production remains a concern, as large quantities are required for clinical applications.[34]

Another critical issue is the potential immunogenicity of exosome-based therapies. While autologous exosomes are less likely to trigger immune responses, allogeneic exosomes may carry risks of immunogenicity and pathogen transmission. Therefore, rigorous screening and characterization of exosome preparations are essential to mitigate these risks.[35,36]

The route of administration and delivery methods also influence the therapeutic outcomes of exosome-based treatments. Topical application, subcutaneous injection, and incorporation into biomaterial-based dressings are among the strategies explored.[37] Each method presents its advantages and limitations, and optimizing these delivery systems is crucial to maximize therapeutic efficacy. Regulatory considerations further complicate the clinical translation of exosome therapies.[38] As relatively new therapeutic agents, exosomes face an evolving regulatory landscape. Establishing clear guidelines for their classification, manufacturing, quality control, and clinical application is imperative to ensure patient safety and treatment efficacy.[39]

Advantages of Exosome Therapy Over Conventional Treatments

Exosome therapy has emerged as a cutting-edge approach in regenerative medicine, offering distinct advantages over traditional wound healing treatments such as growth factor therapies and skin grafts.[24] One of the most significant benefits of exosome therapy is its inherent biocompatibility and reduced risk of immune rejection.

Exosomes are naturally occurring extracellular vesicles secreted by various cell types, including MSCs, and play a pivotal role in intercellular communication by transporting bioactive molecules such as proteins, lipids, and nucleic acids.[40,41] Their endogenous origin contributes to high biocompatibility, minimizing the likelihood of eliciting adverse immune responses upon administration. This characteristic is particularly advantageous compared to traditional treatments like allogeneic skin grafts, which often face challenges related to immune compatibility and potential rejection, necessitating immunosuppressive therapy that carries its own risks and complications.[42,43]

Another notable advantage of exosome therapy is its potential for off-the-shelf, personalized treatments. Exosomes can be isolated from various cell sources, including MSCs, and stored for extended periods without significant loss of therapeutic efficacy.[44] This facilitates the development of readily available therapeutic products that can be tailored to individual patient needs, enhancing the precision and effectiveness of wound healing interventions.[45] In contrast, growth factor therapies typically involve the administration of single or limited growth factors, which may not fully replicate the complex signaling required for optimal wound healing.[46] Furthermore, the use of recombinant growth factors is associated with high costs and limited shelf life, posing practical challenges in clinical application.[47]

Furthermore, exosomes have demonstrated superior therapeutic properties compared to traditional methods. They facilitate angiogenesis, enhance cell proliferation, and modulate inflammatory responses, all of which are essential processes for effective wound healing.[48] These multifaceted capabilities enable exosomes to address various phases of the healing process simultaneously, potentially resulting in faster and more complete recovery.[49] In contrast, skin grafts, while effective in providing coverage for extensive wounds, present certain limitations. Autologous grafts require the harvesting skin from the patient, which can lead to additional wounds and potential donor site morbidity.[50] Allogeneic grafts carry risks of immune rejection and disease transmission. Exosome therapy eliminates these concerns by offering a cell-free alternative that harnesses the regenerative potential of stem cells without necessitating direct cell transplantation.[51]

Moreover, exosome therapy has demonstrated promise in enhancing the healing of chronic wounds, which are often refractory to conventional treatments. By modulating the wound microenvironment and promoting tissue regeneration, exosomes offer a novel approach to managing these challenging cases.[52] The versatility of exosomes is additionally demonstrated by their exploration as vaccine platforms, particularly for infectious diseases such as COVID-19.

Challenges and future directions

The therapeutic potential of exosomes in regenerative medicine and targeted drug delivery has garnered significant attention in recent years. However, several challenges must be addressed to fully realize their clinical applications.[53] One primary concern is the standardization of exosome production and purification methods. Exosomes are small extracellular vesicles secreted by various cell types that play crucial roles in intercellular communication by transporting biomolecules such as proteins, lipids, and nucleic acids.[54] Their inherent properties, including biocompatibility and the ability to cross biological barriers, make them attractive candidates for therapeutic applications.[55] However, due to their small size (30-150 nm) and presence in various biological fluids, challenges related to isolation, purification, and drug loading efficiency persist.[56] To overcome these challenges, researchers are exploring the development of exosome-like nanovesicles (ELNs) or artificial exosomes, which can be engineered to enhance stability, targeting ability, and therapeutic payload capacity.[57]

Scalability and cost-effectiveness are additional considerations in the development of exosome-based treatments. The complexity of exosome isolation and purification processes can impede large-scale production, limiting the feasibility of widespread clinical application.[58] Advancements in bioengineering have facilitated the development of synthetic exosomes or exosome-mimetic nanovesicles, which can be tailored to possess specific properties and functionalities.[59] These engineered vesicles offer advantages, including enhanced stability, targeted delivery, and the ability to carry a higher therapeutic payload. By customizing the content and surface characteristics of these vesicles, researchers aim to enhance the precision and efficacy of treatments for range of medical conditions, including cancer and neurodegenerative diseases.[60,61]

Regulatory and safety considerations are paramount when translating exosome-based therapies into clinical settings. The inherent biocompatibility of exosomes, attributed to their natural occurrence in the human body, suggests a lower risk of eliciting adverse immune responses.[62] Nonetheless, comprehensive evaluations of their safety are essential to identify potential risks associated with their clinical use. Clinical trials investigating exosome-based therapies for conditions such as low back pain have demonstrated promising results, but further studies are required to validate their efficacy and safety.[63,64]

Looking ahead, the development of bioengineered or synthetic exosomes holds promise for enhancing therapeutic efficacy. By manipulating the structure and content of exosomes, researchers can design vesicles with improved targeting capabilities and therapeutic potential.[65] For instance, exosomes can be engineered to express specific proteins or peptides on their surface, facilitating targeted delivery to particular cell types or tissues. Moreover, loading exosomes with therapeutic agents such

as drugs, RNA, or proteins can enhance their ability to modulate disease processes.[66,67] These advancements may pave the way for more effective treatments across the range of diseases, including cancer, where targeted delivery of chemotherapeutic agents remains a crucial therapeutic objective.

Conclusions

Exosome-based therapies represent a promising frontier in regenerative medicine, offering a cell-free approach to enhance wound healing and achieve scar-free skin regeneration. Through their ability to modulate inflammation, stimulate angiogenesis, and remodel tissue by means of targeted delivery of bioactive molecules, exosomes have demonstrated superior efficacy compared to conventional treatments in both preclinical and early clinical studies. Nonetheless, the successful translation of these findings into widespread clinical application requires overcoming challenges related to standardization, scalability, delivery strategies, and regulatory approval. A combination of ongoing bioengineering progress, cross-disciplinary collaboration, and rigorous clinical validation will be crucial to realize the full therapeutic potential of exosomes in modern wound healing.

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