https://doi.org/10.35401/2541-9897-2025-10-3-136-142

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Exosomes in Wound Healing: Biological Roles and Mechanistic Insights

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Received: February 25, 2025. Received in revised form: May 29, 2025. Accepted: June 16, 2025.

Abstract

Wound healing is a dynamic and complex biological process involving hemostasis, inflammation, proliferation, and remodeling. While traditional wound care promotes tissue closure, it often results in fibrosis and scarring. Recent advances have identified exosomes – nanosized extracellular vesicles secreted by various cell types – as critical regulators of intercellular communication during wound healing. These vesicles carry a diverse cargo of proteins, lipids, and nucleic acids that modulate immune responses, stimulate angiogenesis, promote extracellular matrix remodeling, and influence cellular behavior across different healing phases. This review provides a mechanistic overview of how exosomes impact the biology of wound healing, from their biogenesis and molecular composition to their functional roles in cellular crosstalk, with a focus on their therapeutic relevance in enhancing regenerative outcomes.

Keywords: exosomes, wound healing, extracellular vesicles, cell communication, tissue regeneration, molecular mechanisms

Cite this article as: Eskandar K. Exosomes in wound healing: biological roles and mechanistic insights. *Innovative Medicine of Kuban.* 2025;10(3):136–142. https://doi.org/10.35401/2541-9897-2025-10-3-136-142

Роль экзосом в процессе заживления ран: биологические функции и механистические аспекты

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Поступила в редакцию 25 февраля 2025 г. Исправлена 29 мая 2025 г. Принята к печати 16 июня 2025 г.

Резюме

Процесс заживления ран представляет собой динамическую и сложную биологическую последовательность этапов, включающую стадии гемостаза, воспаления, клеточной пролиферации и ремоделирования ткани. Несмотря на эффективность традиционных методов терапии, направленных на закрытие раневой поверхности, такие подходы нередко приводят к формированию фиброза и развитию рубцовых изменений. Современные исследования подчеркнули ключевую роль экзосом – наноразмерных внеклеточных везикул, выделяемых различными типами клеток, в регуляции межклеточных взаимодействий во время репарационных процессов. Экзосомы характеризуются богатым содержанием специфичных белков, липидных молекул и нуклеиновых кислот, что позволяет им регулировать иммунные реакции, активизировать процессы ангиогенеза, способствовать перестройке внеклеточного матрикса и влиять на фенотипическое поведение различных типов клеток на каждом этапе процесса заживления. Настоящий обзор направлен на изучение механизмов воздействия экзосом на различные аспекты биологии раны, начиная от их происхождения и особенностей молекулярного состава до конкретных функций в рамках межклеточной коммуникации, уделяя особое внимание перспективности их применения в качестве новых терапевтических агентов для стимуляции регенеративных процессов.

Ключевые слова: экзосомы, заживление ран, внеклеточные везикулы, межклеточное взаимодействие, регенерация тканей, молекулярные механизмы

Цитировать: Эскандар К. Роль экзосом в процессе заживления ран: биологические функции и механистические аспекты. *Инновационная медицина Кубани.* 2025;10(3):136–142. https://doi.org/10.35401/2541-9897-2025-10-3-136-142

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Introduction

Wound healing is a multifaceted physiological process vital for restoring tissue integrity following injury. It progresses through four well-defined yet overlapping phases: hemostasis, inflammation, proliferation, and remodeling. During hemostasis, vasoconstriction and fibrin clot formation prevent blood loss and provide a provisional matrix for cell migration.[1] The inflammatory phase follows, marked by neutrophil and macrophage infiltration to clear debris and pathogens. In the proliferative phase, cellular activities—including fibroblast proliferation, keratinocyte migration, and angiogenesis—contribute to tissue regeneration.[2] Finally, the remodeling phase involves extracellular matrix (ECM) reorganization and collagen fiber alignment, restoring tensile strength and structure.[3]

Although would healing effectively restores skin continuity, it often results in fibrotic scarring, which compromises both aesthetic and functional outcomes. This scarring primarily arises imbalances in ECM deposition and fibroblast activity.[4] Therefore, understanding the cellular and molecular regulators of each wound healing phase is critical for developing strategies aimed at promoting regenerative, scar-free healing.

In this context, exosomes have emerged as crucial mediators of intercellular communication, influencing a broad spectrum of physiological responses. These nano-sized extracellular vesicles are secreted by numerous cell types and carry a complex cargo of signaling molecules, including proteins, lipids, and microRNAs.[5] Recent research suggests that exosomes are integral to the paracrine actions of stem cells, modulating processes such as cell proliferation, angiogenesis, immune regulation, and tissue remodeling.[6]

This review focuses on the biological and mechanistic aspects of exosome function in wound healing. By elucidating their functions across the different stages of healing, we aim to provide a deeper understanding of how exosomes contribute to tissue regeneration and lay the foundation for future therapeutic applications.

Methods:

Search Strategy

A systematic literature review was conducted in according with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor and transparency. The objective was to identify and synthesize mechanistic and biological insights into the role of exosomes in wound healing. Searches were performed in PubMed, Scopus, Web of Science, and Google Scholar, covering publications from January 2021 to March 2025.

The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms, including: “Exosomes,” “Wound Healing,” “Extracellular Vesicles,” “Cell Signaling,” “Tissue Regeneration,” “Fibroblasts,” “Angiogenesis,” and “Inflammation Modulation.” Boolean operators (AND, OR) were used to combine terms for maximum relevance. Only peer-reviewed articles published in English were considered.

Study Selection

Inclusion criteria:

- Articles published in English
- Studies emphasizing biological roles, cellular mechanisms, or molecular pathways of exosomes in wound healing.
- Original experimental research, mechanistic reviews, and meta-analyses with biological insights.
- Publication from 2021 to2025.

Exclusion criteria:

1. Articles focused primarily on clinical applications or therapeutic delivery.
2. Studies lacking detailed mechanistic or biological data.
3. Non-peer-reviewed sources such as commentaries, editorials, conference abstracts.
4. Studies with insufficient methodological clarity or unresolved quality issue.

Screening Process

The initial search retrieved 92 records. After removing duplicates usingEndNote and Mendeley, 83 unique articles remained. Screening was conducted in two phases:

1. Title and Abstract Review to eliminate irrelevant articles.
2. Full-Text Review for studies meeting the inclusion criteria.

A total of 59 studies were included in the final synthesis for their relevance to biological and mechanistic functions of exosomes in wound healing.

Data Extraction

Data were extracted using a structured template focusing on:

- Study characteristics (authors, year, model systems).
- Exosome origin and isolation methods.
- Mechanisms of exosome action in different wound healing phases (immune modulation, angiogenesis, ECM remodeling).
- Key biomolecules (proteins, miRNAs) involved in signaling.
- Methodological strengths or limitations noted by authors.

Two independent reviewers conducted the extraction; disagreements were resolved through consensus.

Quality Assessment

Study quality was evaluated using the Joanna Briggs Institute Critical Appraisal Tools, focusing on experimental design, reproducibility, and clarity of mechanistic claims. Only high-quality studies were included in the final synthesis.

Data Synthesis

Given the diversity of study designs and mechanistic endpoints, a narrative synthesis approach was used. Findings were thematically organized around:

- Exosome biogenesis and molecular composition
- Phase-specific roles in wound healing biology
- Pathway-specific actions (e.g., TGF-β, VEGF, MMPs)

Quantitative pooling was not performed due to methodological and outcome heterogeneity. A PRISMA flowchart (Figure 1) illustrates the screening and selection process.

Discussion

Biology of Wound Healing

Wound healing is a complex and dynamic process that is essential for restoring tissue integrity following injury. This process is traditionally divided into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling.[7] Each phase involves a coordinated interplay of cellular and molecular mechanisms ensuring effective tissue repair. Recent research has highlighted the significant role of extracellular vesicles, particularly exosomes, in modulating these phases of to facilitate optimal healing outcomes.[8]

The initial phase, hemostasis, occurs immediately after tissue injury and serves to prevent blood loss. Upon vascular disruption, platelets adhere to the exposed ECM components, such as collagen, leading to their activation.[9] Activated platelets release granules containing adenosine diphosphate, thromboxane A_2, and other mediators that promote further platelet aggregation and vasoconstriction. Concurrently, the coagulation cascade is activated, resulting in the conversion of fibrinogen to fibrin, which stabilizes the forming clot and provides a provisional matrix for incoming cells.[10,11]

Following hemostasis, the inflammatory phase ensues, characterized by the recruitment of immune cells to the wound site. Neutrophils are among the first responders, arriving within minutes to hours after injury.[12] They phagocytose debris and pathogens, releasing reactive oxygen species and proteolytic enzymes to combat potential infections. As neutrophils undergo apoptosis, macrophages become the predominant cell type.[13] Macrophages play a dual role: they continue phagocytic activity and secrete cytokines and growth factors, such as transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF), which are crucial for transition to the proliferative phase.[14]

The proliferative phase is marked by tissue formation and typically commences two to three days post-injury, lasting for several weeks. Key processes during this phase include angiogenesis, fibroplasia, granulation tissue formation, epithelialization, and wound contraction.[15] Angiogenesis involves the sprouting of new blood vessels from existing ones, primarily driven by VEGF and fibroblast growth factor-2 (FGF-2). Fibroblasts migrate into the wound site, depositing ECM components like collagen and fibronectin, forming granulation tissue that serves as a scaffold for further tissue regeneration.[16] Keratinocytes at the wound edges proliferate and migrate to re-epithelialize the wound surface, restoring the barrier function of the skin. Myofibroblasts, differentiated from fibroblasts under the influence of TGF-β, facilitate wound contraction by exerting contractile forces that reduce wound size.[17]

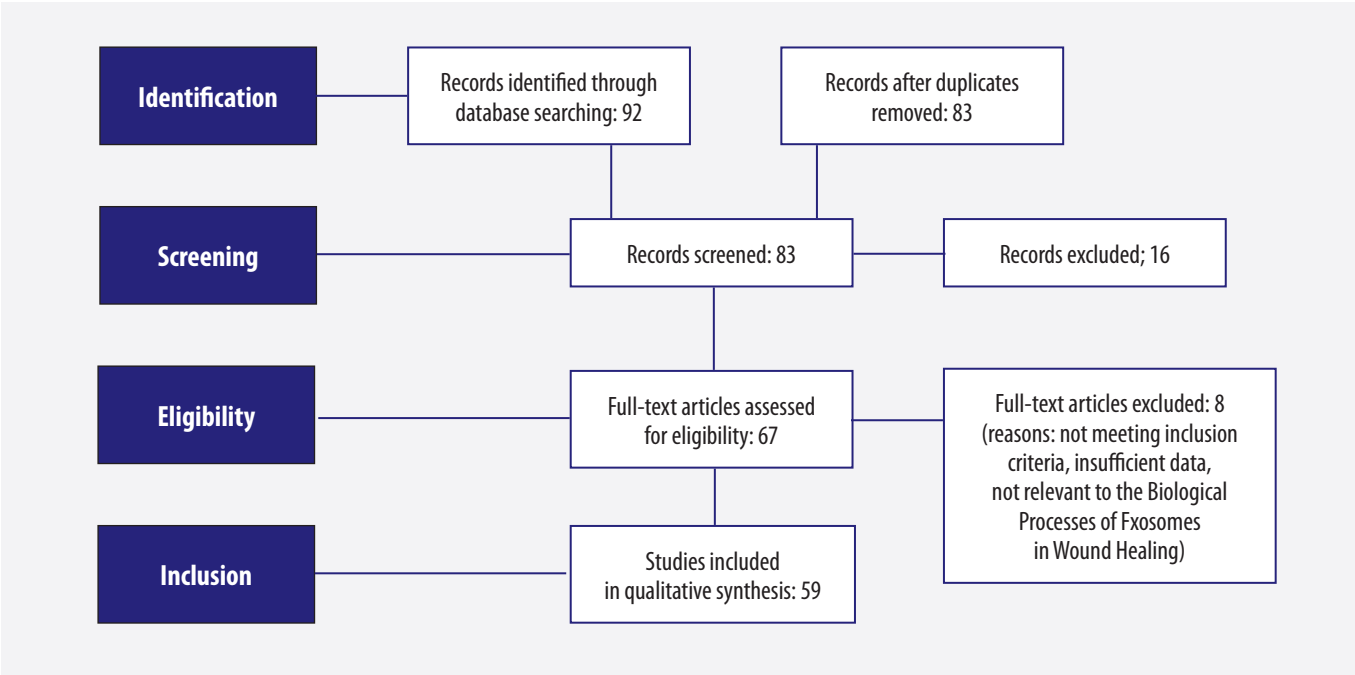

Figure. PRISMA flow diagram
Рисунок. Блок-схема PRISMA

The final phase, remodeling, involves the maturation and reorganization of the ECM to restore tissue tensile strength. This phase can extend from months to years, depending on the wound's severity and location.[18] Type III collagen, initially deposited during the proliferative phase, is gradually replaced by the more robust type I collagen. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) tightly regulate collagen remodeling to ensure proper ECM architecture.[19,20] Fibroblasts and myofibroblasts undergo apoptosis as their roles conclude, leaving a collagen-rich scar that may lack some functional properties of the original tissue.[21]

Extracellular vesicles, including exosomes, have emerged as pivotal mediators in intercellular communication during wound healing. Exosomes are nanosized vesicles (30–150 nm) secreted by various cell types, encapsulating bioactive molecules such as proteins, lipids, and nucleic acids.[22] They facilitate the horizontal transfer of these molecules between cells, influencing numerous physiological and pathological processes. In the context of wound healing, exosomes derived from mesenchymal stem cells (MSCs) have been shown to promote angiogenesis, enhance fibroblast proliferation and migration, and modulate immune responses, collectively accelerating the healing process.[23,24]

During the inflammatory phase, exosomes released by immune cells can modulate the immune response, either amplifying or resolving inflammation as needed. For instance, macrophage-derived exosomes containing anti-inflammatory microRNAs can shift the macrophage phenotype from pro-inflammatory (M1) to anti-inflammatory (M2), aiding in inflammation resolution and transition to the proliferative phase.[25,26] In the proliferative phase, exosomes from keratinocytes and fibroblasts contribute to re-epithelialization and ECM formation. Keratinocyte-derived exosomes can stimulate neighboring keratinocytes to proliferate and migrate, accelerating wound closure.[27] Fibroblast-derived exosomes carrying collagen and fibronectin mRNAs promote ECM deposition, providing structural integrity to the healing tissue.[28]

Moreover, exosomes play a role in angiogenesis by transporting proangiogenic factors. For example, MSC-derived exosomes enriched with microRNA-21 have been demonstrated to promote endothelial cell proliferation and neovascularization, essential for supplying nutrients and oxygen to the regenerating tissue.[29] In the remodeling phase, exosomes contribute to ECM remodeling by delivering MMPs or their regulators, ensuring proper collagen organization and preventing excessive scar formation.[30]

Exosomes: Biogenesis, Composition, and Mechanism of Action

Exosomes are nano-sized extracellular vesicles, typically ranging from 30 to 150 nanometers in diameter, that play a pivotal role in intercellular communication and tissue regeneration. They are secreted by various cell types and are involved in numerous physiological and pathological processes.[31] Understanding the biogenesis, composition, and mechanisms of action of exosomes is crucial for harnessing their therapeutic potential in regenerative medicine.

The biogenesis of exosomes begins within the endosomal system of the cell. It starts with the inward budding of the plasma membrane to form early endosomes. These early endosomes undergo maturation into late endosomes, during which their limiting membrane invaginates to create intraluminal vesicles (ILVs) within larger structures known as multivesicular bodies (MVBs).[32] The formation of ILVs is orchestrated by several mechanisms, prominently involving the endosomal sorting complex required for transport (ESCRT) machinery. The ESCRT pathway comprises four main protein complexes—ESCRT-0, -I, -II, and -III—and associated ATPases like Vps4.[33] ESCRT-0 recognizes and sequesters ubiquitinated proteins destined for inclusion in ILVs. Subsequently, ESCRT-I and ESCRT-II facilitate membrane budding, while ESCRT-III mediates vesicle scission, culminating in the formation of ILVs within MVBs.[34] Alternatively, ESCRT-independent pathways, such as those involving tetraspanins or the syndecan–syntenin–ALIX axis, have been identified in exosome biogenesis. Once formed, MVBs can either fuse with lysosomes for degradation or merge with the plasma membrane, releasing ILVs into the extracellular milieu as exosomes.[35]

Exosomes are enriched with a diverse array of bioactive molecules that reflect their cell of origin. Their lipid bilayer membrane is rich in cholesterol, sphingomyelin, and ceramide, contributing to membrane rigidity and stability.[36] The protein cargo of exosomes includes tetraspanins (e.g., CD9, CD63, CD81), heat shock proteins (e.g., HSP70, HSP90), and proteins involved in membrane fusion and transport (e.g., annexins, Rab GTPases).[37] Notably, exosomes carry nucleic acids, particularly various forms of RNA, such as messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA), and other small RNAs. These RNA molecules can be transferred to recipient cells, where they modulate gene expression and influence cellular functions.[38,39]

The role of exosomes in mediating cell-cell communication is fundamental to their function in tissue regeneration. Upon release into the extracellular space, exosomes can interact with recipient cells through various mechanisms. They may directly fuse with the plasma membrane, resulting in the release of their cargo into the cytoplasm.[40] Alternatively, surface proteins on exosomes can bind to specific receptors on target cells, triggering intracellular signaling pathways without the need for internalization. Additionally, exosomes can be internalized by recipient cells via endocytic pathways such as clathrin-mediated endocytosis, caveolin-dependent endocytosis, or micropinocytosis.[41] Once inside, they fuse

with endosomal membranes, facilitating the delivery of their bioactive contents into the cytosol, where they exert regulatory effects on cellular processes.[42]

Through these mechanisms, exosomes facilitate the horizontal transfer of bioactive molecules, thereby modulating various physiological processes in recipient cells. In the context of tissue regeneration, exosomes derived from mesenchymal stem cells (MSCs) have been shown to promote angiogenesis, enhance fibroblast proliferation and migration, and modulate immune responses, collectively contributing to accelerated wound healing and tissue repair.[43]

Exosomes in Wound Healing: Mechanistic Insights

Exosomes, nano-sized extracellular vesicles secreted by various cell types, have emerged as pivotal mediators in the wound healing process. Their multifaceted roles span the modulation of inflammation, promotion of cellular proliferation, and facilitation of tissue remodeling, ultimately contributing to enhanced and potentially scar-free healing outcomes.[44]

During the inflammatory phase of wound healing, exosomes exert significant influence by modulating immune responses to prevent excessive inflammation, which can impede the healing process.[45] Studies have demonstrated that exosomes derived from mesenchymal stem cells (MSCs) can downregulate pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), while upregulating anti-inflammatory cytokines like interleukin-10 (IL-10).[46,47] This cytokine modulation leads to a balanced immune response conducive to healing. Furthermore, exosomes have been shown to induce macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, further contributing to the resolution of inflammation and promotion of tissue repair.[48]

In the proliferation phase, exosomes play a crucial role in stimulating key cellular activities essential for tissue regeneration. They have been found to promote fibroblast migration and proliferation, which are vital for the formation of granulation tissue.[49] Additionally, exosomes enhance angiogenesis by delivering proangiogenic factors and microRNAs to endothelial cells, thereby facilitating the formation of new blood vessels necessary for supplying nutrients and oxygen to the healing tissue.[50] Keratinocyte activation is also influenced by exosomes, leading to accelerated re-epithelialization and restoration of skin barrier function.[51]

During the remodeling phase, exosomes contribute to the regulation of extracellular matrix (ECM) dynamics, which is critical for achieving functional and aesthetic tissue restoration. They influence the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), ensuring proper ECM deposition and degradation.[52,53] This regulation minimizes excessive fibrosis and scar formation, promoting scarless healing. Furthermore, exosomes have been implicated in the differentiation of myofibroblasts, cells responsible for wound contraction and ECM remodeling, thereby influencing the structural integrity of the healed tissue.[54,55]

Compared to traditional wound care methods, exosome-based therapies offer several advantages. Conventional treatments often focus on symptomatic relief and protection of the wound site but may not actively modulate the underlying biological processes essential for optimal healing.[56] In contrast, exosomes provide targeted delivery of bioactive molecules that can orchestrate the complex cellular interactions required for effective tissue repair. This targeted approach has been associated with improved outcomes, such as enhanced wound closure rates, reduced inflammation, and minimized scarring.[57,58] However, it is important to note that while preclinical studies have shown promising results, the translation of exosome-based therapies into clinical practice requires further investigation to address challenges related to large-scale production, standardization, and regulatory approval.[59]

Conclusions

Exosomes have emerged as essential biological mediators in the wound healing process, influencing cellular behavior across the hemostasis, inflammation, proliferation, and remodeling phases. Their ability to transport bioactive molecules—including proteins, lipids, and nucleic acids—positions them as key regulators of intercellular communication, immune modulation, angiogenesis, and extracellular matrix remodeling. This review highlights the mechanistic underpinnings of how exosomes coordinate the complex events involved in tissue repair. Understanding these biological roles provides a foundational framework for future research and therapeutic exploration. Continued investigation into the molecular signaling pathways and cell-specific functions of exosomes will be critical for advancing regenerative strategies and optimizing scar-free healing outcomes.

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Conflict of interest: *none declared.*

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Конфликт интересов

Автор заявляет об отсутствии конфликта интересов.

Availability of data and material:

Data sharing not applicable to this article as no data-sets were generated or analyzed during the current study