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Fibroblast-derived exosomes in wound healing and regenerative medicine: mechanisms, therapeutic potential, and clinical perspectives

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Skin wound healing is a complex biological process involving coordinated interactions among fibroblasts, immune cells, keratinocytes, endothelial cells, and extracellular matrix (ECM) components. Chronic and diabetic wounds remain significant clinical challenges due to persistent inflammation, oxidative stress, impaired angiogenesis, and defective tissue remodeling. Fibroblast-derived exosomes have recently emerged as promising cell-free therapeutic nanovesicles capable of regulating intercellular communication during tissue repair. These nanosized extracellular vesicles (EVs) carry diverse bioactive cargos, including microRNAs, proteins, lipids, and growth factors, which modulate inflammation, angiogenesis, cell proliferation, migration, and ECM remodeling. Recent studies have demonstrated that fibroblast-derived exosomes can accelerate wound closure, enhance granulation tissue formation, improve epidermal barrier restoration, and reduce oxidative stress in both normal and diabetic wound models. Beyond the intrinsic regenerative properties of these exosomes, increasing attention has focused on their integration with biomaterials, hydrogels, and scaffold-based delivery systems to achieve sustained and localized therapeutic effects. However, challenges such as cargo heterogeneity, isolation standardization, scalability, reproducibility, and biosafety evaluation continue to limit their clinical translation. This review summarizes the biological functions, regenerative mechanisms, and therapeutic applications of fibroblast-derived exosomes in wound healing while emphasizing translational challenges, biomaterial-assisted delivery strategies, and future perspectives for precision regenerative medicine.

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1. Introduction

Fibroblasts are dynamic mesenchymal cells that play a central role in preserving tissue integrity through the synthesis and remodeling of the extracellular matrix (ECM).[1] Under normal conditions, they support structural stability and help regulate stem cell microenvironments.[2,3] Following injury, fibroblasts become activated, proliferate, and differentiate into myofibroblasts to promote tissue repair.[2,4] However, persistent or dysregulated activation contributes to pathological conditions, including fibrosis, tumor progression *via* cancer-associated fibroblasts (CAFs), and chronic inflammatory disorders.[3] The fibroblasts produce key structural components such as collagen, elastin, and glycosaminoglycans (GAGs), which provide mechanical strength and architectural support to tissues.[2,5] Beyond their structural function, fibroblasts actively participate in cellular communication by creating specialized signaling niches that interact with immune cells and stem cells to preserve physiological balance.[3,5] Notably, these cells exhibit significant phenotypic plasticity, enabling them to respond

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dynamically to biochemical cues and mechanical stimuli, thereby modulating their function to meet the changing demands of the tissue microenvironment.[3,5,6] Human dermal fibroblasts and umbilical cord-derived MSCs share similar surface markers, multilineage differentiation potential, and overlapping gene expression and metabolic profiles.[7] Increasing evidence suggests that fibroblasts can also differentiate into adipogenic and osteogenic lineages.[8] Acting as functional MSC-like cells within the skin, dermal fibroblasts are readily harvested in large quantities and are more accessible than many other MSC sources.[7] These advantages, together with over past decades of clinical application in topical therapies,[9] make dermal fibroblasts an attractive and scalable source for the large-scale production of therapeutic secretomes and exosomes.[10]

Pathological conditions can arise when fibroblast activity becomes dysregulated. Persistent activation and excessive matrix deposition contribute to widespread fibrotic disorders, including idiopathic pulmonary fibrosis, liver fibrosis, and systemic sclerosis.[11] In the tumor microenvironment (TME), specialized CAFs support malignant progression by enhancing tumor growth, fostering immunosuppression, and reducing therapeutic responsiveness. Additionally, in autoimmune and chronic inflammatory diseases, fibroblasts can adopt a proinflammatory phenotype, releasing cytokines and chemokines that sustain and amplify inflammatory signaling.[3] Fibroblasts represent a highly heterogeneous cell population rather than a single uniform type, whose functions vary according to the tissue origin and anatomical context. In response to injury or stress, they undergo activation and transition into myofibroblasts, characterized by enhanced extracellular matrix (ECM) production and contractile activity. Aberrant regulation of signaling pathways, such as transforming growth factor (TGF)-β/SMAD and Wnt/β-catenin, is frequently associated with this pathological activation, driving fibroblast-mediated tissue remodeling and disease progression.[5]

Cancer and chronic wound disorders remain major global healthcare challenges due to delayed diagnoses, limited therapeutic efficacies, prolonged treatment durations, and high costs associated with conventional therapies and novel drug development.[12] In this context, drug repurposing and exosome-based regenerative therapies have emerged as promising alternative strategies for improving therapeutic outcomes. Drug repurposing utilizes established pharmacological and safety profiles of approved or investigational drugs to accelerate clinical translation in diseases such as cancer, neurodegenerative disorders, and infectious conditions.[12,13] Several repurposed agents, including antimalarials, antibiotics, antivirals, anti-inflammatory drugs, and antifungals, have demonstrated significant antiproliferative, pro-apoptotic, immunomodulatory, and antimetastatic effects.[14] Simultaneously, exosomes have gained considerable attention as cell-free therapeutic nano-platforms due to their ability to mediate intercellular communication and regulate angiogenesis, collagen synthesis, ECM remodeling, inflammation, and tissue repair. Their integration with biomaterials and advanced delivery systems has further expanded their applications in regenerative medicine and wound healing.[15] In parallel, advances in immunotoxicogenomics and multi-omics technologies have improved our understanding of how xenobiotics, environmental toxicants, and therapeutic agents influence immune regulation and disease progression at the molecular level.[16] Exosomes have emerged as critical nanoscale mediators of paracrine communication, enabling both short- and long-distance signaling among fibroblasts, cancer cells, immune cells, and endothelial cells.[17] Exosomes are endosome-derived extracellular vesicles that are commonly reported within the small-EV size range; approximately 30–150 nm is frequently observed but is not a defining criterion.[18,19] In fibroblast biology, exosomes help activate quiescent fibroblasts into matrix-producing myofibroblasts and facilitate reciprocal signaling with immune cells that sustains inflammatory and fibrotic responses.[18–21] Within the TME, CAF-derived exosomes promote tumor progression, angiogenesis, and therapeutic resistance through the transfer of signaling molecules and regulatory RNAs that activate pathways such as SMAD and Wnt/β-catenin.[18,20,22] Conversely, in tissue repair, fibroblast-derived exosomes (FB-EXOs, Fig. 1) support wound healing and angiogenesis by delivering growth factors and pro-regenerative miRNAs. At the same time, similar vesicle-mediated crosstalk regulates post-injury remodeling in cardiovascular tissues. Owing to their stability, low immunogenicity, and intrinsic targeting capability, exosomes are increasingly studied as diagnostic biomarkers and as cell-free therapeutic delivery vehicles.[18–20,22–24] However, clinical translation remains challenging due to cargo heterogeneity, the need for standardized isolation and characterization methods, and the risk of excessive fibroblast activation leading to pathological fibrosis.[21]

Although previous reviews summarized the biological functions and regenerative effects of FB-EXOs in wound healing, several critical translational and bioengineering aspects remain insufficiently discussed. In contrast to earlier reviews that primarily focused on mechanistic signaling pathways and general regenerative properties, the present review provides a broader translational perspective by emphasizing biomaterial-assisted delivery systems, hydrogel and scaffold integration, sustained and localized therapeutic release, cargo heterogeneity, manufacturing reproducibility, and scalability challenges associated with clinical translation.[20,25,26] In addition, this review highlights the emerging role of FB-EXOs as precision regenerative nanoplatforms capable of modulating inflammatory balance, oxidative stress, angiogenesis, ECM remodeling, and targeted tissue repair in chronic and complex wounds. Furthermore, unresolved issues including exosome standardization, therapeutic consistency, biosafety evaluation, and regulatory considerations are critically discussed to provide a more clinically and translationally relevant framework for the future development of FB-EXO-based therapies.

Focusing on exosome–fibroblast interactions provides important insights into mechanisms driving fibrosis, tumor progression, chronic inflammation, and wound healing while also revealing opportunities to modulate these processes through cell-free therapeutic approaches. Accordingly, this review summarizes current advances in understanding how

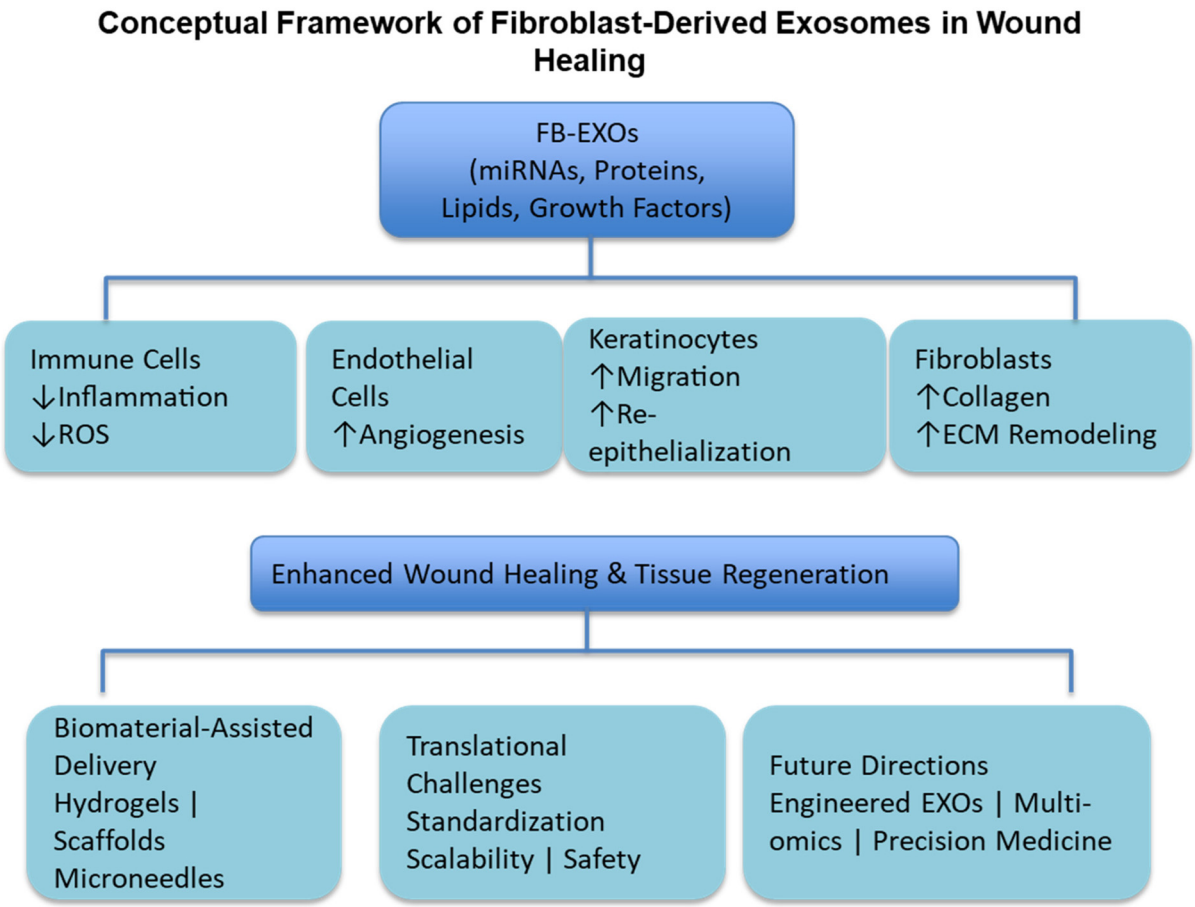

Fig. 1 Conceptual framework of fibroblast-derived exosome (FB-EXO)-mediated wound healing and translational development. FB-EXOs deliver bioactive cargos, including microRNAs, proteins, lipids, growth factors, and mRNAs, to regulate immune cells, endothelial cells, keratinocytes, and fibroblasts, thereby promoting inflammation resolution, angiogenesis, re-epithelialization, extracellular matrix remodeling, and tissue regeneration. Biomaterial-assisted delivery platforms may further enhance therapeutic efficacy, while challenges including cargo heterogeneity, donor variability, manufacturing standardization, scalability, and regulatory requirements remain barriers to clinical translation. Future advances in engineered exosomes, gene editing, and precision regenerative medicine may facilitate clinical application. The image was created using Microsoft PowerPoint.

exosomal cargos regulate fibroblast activation, differentiation, and signaling across diverse disease contexts and evaluates emerging translational applications such as diagnostic biomarkers and engineered exosome-based delivery systems. It also discusses key challenges, including cargo heterogeneity, standardization of isolation and characterization methods, and safety considerations, with the aim of guiding future development of exosome-guided strategies for regenerative medicine and targeted disease interventions.

2. Literature search strategy

This review was prepared as a narrative review by collecting and summarizing relevant studies related to fibroblast-derived exosomes and their applications in wound healing and regenerative medicine. Literature searches were conducted using multiple scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Keywords and search terms included combinations of fibroblast-derived exosomes, secretomes, wound healing, skin regeneration, extracellular vesicles, regenerative medicine, angiogenesis, extracellular matrix remodeling, and biomaterials. Both original research articles and recent review articles were considered. Studies were selected based on their relevance to fibroblast-derived exosomes, regenerative mechanisms, translational applications, and wound-healing outcomes. The selected literature was then organized thematically to provide an integrated discussion of biological functions, mechanistic insights, therapeutic strategies, translational challenges, and future perspectives.

3. Skin homeostasis under physiological conditions and following injury

Under normal physiological conditions, dermal fibroblasts are central to preserving the skin's architecture and function. They synthesize key ECM components including structural and

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adhesive proteins as well as GAGs and proteoglycans that provide mechanical strength and hydration.[1,10] In addition to matrix production, fibroblasts regulate skin homeostasis through the secretion of growth factors, cytokines, and exosomes that mediate biochemical and biophysical signaling.[1,10] Epidermal keratinocytes sustain the outer skin barrier by producing keratin, surface lipids, and intercellular junctional molecules[10,27,28] while also contributing to immune defense and wound repair *via* cytokines, neuropeptides, and other regulatory mediators.[10,27] These cells continually differentiate into corneocytes to maintain the integrity of the stratum corneum.[10,29] Immune surveillance is further supported by dermal mast cells and epidermal Langerhans cells, which help regulate the inflammatory balance.[10,30,31]

Following acute skin injury, the earliest response is mediated by platelets and endothelial cells.[10,32] Beyond their role in hemostasis, platelets release signaling molecules that orchestrate the inflammatory and early repair phases of healing.[10,33] Platelet-derived extracts enriched with exosomes may therefore provide an immediate stimulatory effect on tissue repair. During subsequent stages, fibroblasts and keratinocytes drive granulation tissue formation and ECM remodeling to restore structural integrity.[10,34] Platelet-associated extracellular vesicles may contribute to the regenerative effects of PRP.[10]

Exosome- and secretome-based preparations from various mesenchymal stem cell (MSC) sources have also demonstrated promise in skin rejuvenation. Clinical studies using topical application, often combined with microneedling or energy-based treatments, have reported improvements in signs of skin aging.[10,35] However, many currently available formulations rely on conditioned media rather than rigorously isolated and well-characterized exosomes, highlighting the need for standardized purification and validation approaches.[10]

4. Exosomes: biogenesis, composition, and biological functions

4.1. Exosome biogenesis

Exosome formation begins with the internalization of molecular cargo through endocytosis. This process generates early endosomes, which arise from the inward budding of the plasma membrane and serve as the primary sorting stations within the endosomal trafficking system, determining the fate of the internalized material.[36,37] From the early endosome, cargo can follow three distinct routes. Components destined for reuse are directed to peripheral tubular regions, where they are transported back to the Golgi apparatus or returned to the plasma membrane *via* recycling endosomes. In contrast, non-recyclable cargo accumulates within the central vacuolar domain and progresses through the maturation pathway to form late endosomes. These late endosomes ultimately undergo either lysosomal fusion for degradation or fusion with the plasma membrane to release exosomes.[36,38]

Endosomal maturation is accompanied by dynamic alterations in the membrane composition and structure. During early-to-late endosome maturation, Rab5 is progressively replaced by Rab7, whereas Rab11 mainly regulates recycling endosome trafficking.[38–40] Concurrently, portions of the endosomal membrane invaginate inward, forming intraluminal vesicles (ILVs) that encapsulate selected cargoes. The accumulation of these ILVs gives late endosomes their characteristic multivesicular morphology, known as multivesicular bodies (MVBs).[38,41,42] When MVBs fuse with lysosomes, their contents are degraded; however, fusion with the cell surface results in the extracellular release of ILVs, which are then recognized as exosomes (Fig. 2).[38,43] Although the core endosomal machinery of exosome biogenesis is broadly conserved, MSC- and fibroblast-derived exosomes can differ substantially in cargo composition and functional profiles. Both the cell types utilize MVBs for exosome formation and cargo packaging; MSC-derived exosomes are primarily enriched with regenerative and immunomodulatory molecules, including growth factors, anti-inflammatory cytokines, and regulatory miRNAs.[20] In contrast, FB-EXOs are more specifically involved in maintaining the tissue architecture and ECM remodeling by carrying matrix-remodeling enzymes such as matrix metalloproteinases (MMPs), collagen-associated factors, pro-collagen messenger (m)RNAs, and fibroblast-related regulatory miRNAs. These differences contribute to distinct therapeutic roles during wound healing. Sequential delivery of EV populations with complementary immunomodulatory and matrix-remodeling activities could be explored in future regenerative strategies.[20,25,44,45] Consequently, FB-EXOs may be especially advantageous for chronic wounds, diabetic ulcers, and conditions requiring enhanced tissue reconstruction. Emerging regenerative approaches are also investigating sequential or combinational exosome therapies, in which stem cell-derived exosomes are initially administered to control inflammation, followed by FB-EXOs to promote collagen deposition and matrix remodeling.[46,47]

4.2. Biological characteristics of FB-EXOs

Fibroblasts play a central role in wound healing and are among the primary cell types responsible for tissue regeneration. During the proliferative phase of repair, they synthesize and deposit ECM components such as collagen and fibronectin, which are essential for restoring the architecture and functionality of damaged tissues.[48] In addition to this structural role, fibroblasts actively mediate intercellular communication by releasing exosomes, which function as signaling vesicles that influence the repair microenvironment. These FB-EXOs are enriched with diverse bioactive cargos, including proteins, mRNAs, miRNAs, and lipids, that regulate recipient cell activity and contribute to coordinated healing responses.[2048]

Fibroblasts display multifaceted functions during tissue repair. By producing type I and type III collagen, they reestablish tissue integrity and mechanical stability.[20,49] Moreover, in the early stages of healing, fibroblasts can transition into myofibroblasts, specialized contractile cells that drive wound con-

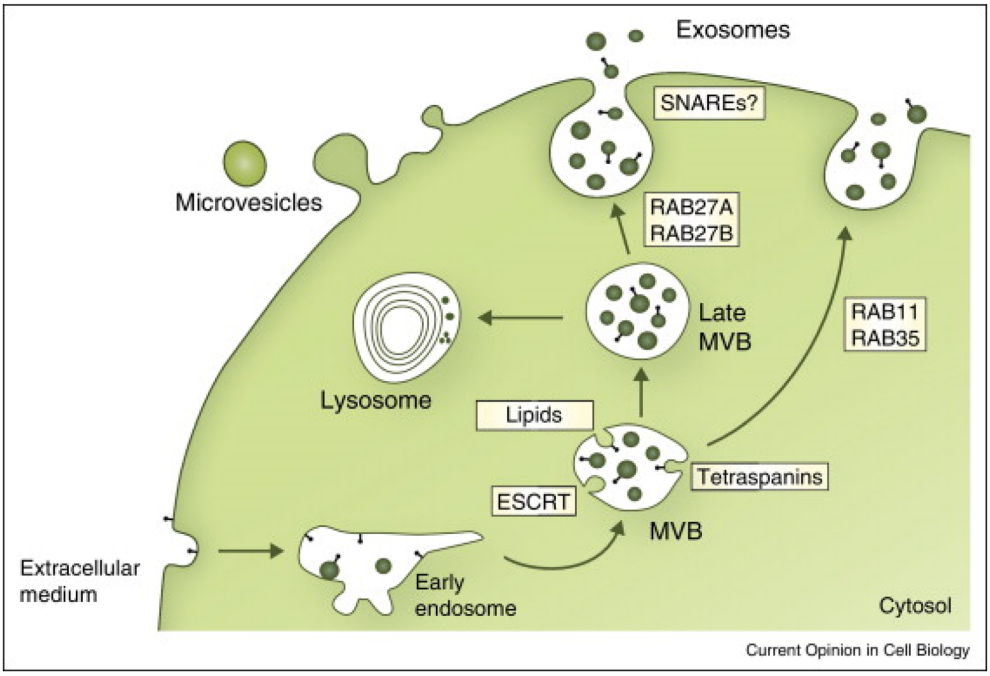

Fig. 2 Biogenesis and heterogeneity of extracellular vesicles, with emphasis on exosome formation. Cells release multiple types of membrane-enclosed vesicles into the extracellular environment, enabling the exchange of complex biological information. Among these, exosomes represent a distinct subpopulation that originates within the endosomal system of eukaryotic cells. Exosomes are formed through the inward budding of the limiting membrane of multivesicular bodies (MVBs), which generates ILVs that are subsequently secreted upon fusion of MVBs with the plasma membrane. Different classes of secreted vesicles coexist, reflecting diverse intracellular origins, mechanisms of biogenesis, molecular compositions, and biological functions. Multiple molecular pathways regulate exosome formation and release, suggesting the presence of heterogeneous exosome subtypes with specialized roles in intercellular communication. Reproduced from ref. 43 with permission from Elsevier, copyright 2014.

traction and closure.[50,20] Through dynamic crosstalk with macrophages, keratinocytes, and endothelial cells, fibroblasts further orchestrate key regenerative processes such as inflammation resolution, angiogenesis, and ECM remodeling within the wound environment.[20]

4.3. Functional properties and therapeutic potential of FB-EXOs

FB-EXOs are nanosized EVs enriched with proteins, lipids, and diverse nucleic acids, including miRNAs, mRNAs, and long non-coding RNAs (lncRNAs), that serve as critical mediators of cell-to-cell communication.[20,51–53] These vesicles play essential roles in processes such as wound repair, tissue regeneration, and skin remodeling by transferring bioactive cargo to recipient cells. Their molecular content includes key growth factors, such as transforming growth factor (TGF)-β1, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF)-1, and regulatory miRNAs (*e.g.*, miR-21 and miR-29), which collectively stimulate cellular proliferation, migration, angiogenesis, and immunomodulation.[20,25,51,53–55] In regenerative contexts, they promote fibroblast activation, keratinocyte movement, and neovascularization, thereby accelerating tissue repair and enhancing dermal reconstruction. Additionally, FB-EXOs have demonstrated protective effects against ultraviolet (UV)-induced cellular aging, which contributes to reduced collagen degradation and improved skin integrity.[25,53–56] However, their function is context dependent; exosomes from CAFs may instead facilitate tumor progression, immune evasion, and therapeutic resistance. Owing to their intrinsic stability, biocompatibility, and low immunogenicity, FB-EXOs are increasingly being explored as natural nanocarriers for targeted drug delivery and regenerative medicine applications.[20,25,51–57]

4.4. Targeting specificity of FB-EXOs

Surface molecules on FB-EXOs may contribute to preferential cellular interactions, uptake, and tissue tropism.[58,59,20] Recent studies further demonstrated that exosomes derived from three-dimensional cultured human dermal fibroblast spheroids (3D HDF-XOs) exhibit enhanced regenerative and anti-aging properties compared to conventional monolayer-derived exosomes. These exosomes are enriched with tissue inhibitor of metalloproteinases (TIMP)-1 and distinct regulatory miRNAs, enabling improved collagen synthesis, reduced matrix metalloproteinase (MMP)-1 expression, and enhanced dermal matrix integrity. Treatment with MSC-XOs and 3D HDF-XOs significantly reduced MMP-1 expression to near-normal levels, indicating effective suppression of collagen degradation induced by UV irradiation. Notably, 3D HDF-XOs exhibited a greater inhibitory effect on MMP-1 than the other treatment groups, suggesting enhanced preservation of extracellular matrix integrity and improved protection against

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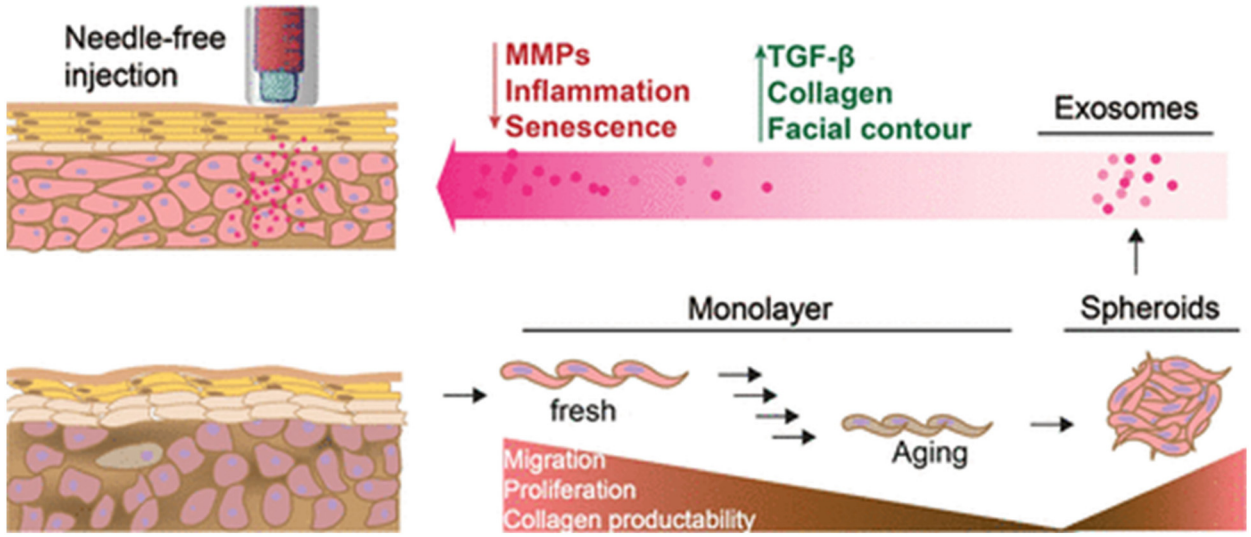

Fig. 3 Enhanced anti-aging efficacy of exosomes derived from three-dimensional (3D) human dermal fibroblast spheroids (HDF-XOs). Exosomes derived from three-dimensional (3D)-cultured human dermal fibroblast spheroids (3D HDF-XOs) were compared with those derived from conventional two-dimensional (2D) monolayer cultures. 3D HDF-XOs exhibited elevated expression of tissue inhibitor of metalloproteinases 1 (TIMP-1) and distinct miRNA cargo profiles, indicating altered functional signaling. *In vitro* and *in vivo* photoaging models demonstrated that 3D HDF-XOs significantly enhanced procollagen type I synthesis while reducing matrix metalloproteinase 1 (MMP-1) expression, primarily through downregulation of tumor necrosis factor α (TNF-α) and upregulation of transforming growth factor β (TGF-β) pathways. Needle-free injector delivery further confirmed their therapeutic potential, resulting in greater dermal collagen deposition compared to that of bone marrow mesenchymal stem cell-derived exosomes. These findings highlight the superior regenerative and anti-skin aging effects of exosomes derived from 3D-cultured HDF-XOs. Reproduced from ref. 59 with permission from American Chemical Society, copyright 2019.

photoaging. Mechanistically, 3D HDF-XOs suppressed tumor necrosis factor (TNF)-α-mediated inflammation while activating the TGF-β signaling pathway, thereby promoting procollagen type I expression and dermal collagen deposition. Furthermore, needle-free transdermal delivery of 3D HDF-XOs effectively ameliorated ultraviolet B (UVB)-induced oxidative stress, inflammation, and cellular senescence while enhancing fibroblast proliferation, migration, and ECM remodeling. These findings further support the potential of FB-EXOs as targeted regenerative nanoplatforms for wound healing and skin rejuvenation (Fig. 3).[59]

Targeted delivery within the wound microenvironment is essential for effective skin regeneration due to the complex anatomical and physiological barriers of the skin, including dense ECM organization, inflammatory gradients, oxidative stress, impaired vascularization, and limited therapeutic retention at the wound interface. These conditions are particularly prominent in chronic and diabetic wounds, where impaired cellular communication and tissue remodeling significantly delay healing. In this context, FB-EXOs have emerged as promising natural nanocarriers capable of mediating targeted intercellular signaling during tissue repair. FB-EXOs interact with keratinocytes, endothelial cells, immune cells, and resident fibroblasts to promote collagen synthesis, ECM remodeling, angiogenesis, inflammation resolution, and tissue regeneration. Several studies have highlighted molecular pathways that are critical for wound repair and are also relevant to the regenerative mechanisms of fibroblast-derived exosomes (FB-EXOs). For instance, Miscianinov *et al.* demonstrated that modulation of the TGF-β signaling pathway through miR-148b enhanced endothelial cell migration, proliferation, endothelial-to-mesenchymal transition (EMT), and angiogenesis during wound healing.[60] Similarly, Riedel *et al.* reported that inhibition of TGF-β signaling using antisense oligonucleotides increased vascular endothelial growth factor (VEGF) secretion, endothelial migration, and tube formation in chronic dermal wounds.[61] Furthermore, Jin *et al.* showed that melatonin-mediated activation of the adenosine monophosphate-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) signaling pathway protected endothelial progenitor cells from apoptosis under diabetic wound conditions,[62] while Song *et al.* demonstrated that melatonin reduced oxidative stress and inflammatory cytokine production, thereby enhancing keratinocyte proliferation and migration. Although these therapeutic strategies are not FB-EXO-based, they underscore the importance of key regenerative pathways, including TGF-β signaling, angiogenesis, oxidative stress regulation, and endothelial function, which are also modulated by FB-EXOs during wound healing.[63,64]

4.5. Regulation of exosome secretion by fibroblasts

The secretion of FB-EXOs is highly influenced by the surrounding wound microenvironment during tissue repair. Various physiological and pathological conditions, including mechanical stress, inflammation, hypoxia, and oxidative stress, can alter both the quantity of exosomes released by fibroblasts and

the molecular composition of their cargo. Therefore, this section focuses on how these microenvironmental factors regulate FB-EXO production and modulate their regenerative functions during wound healing. Mechanical stress increased fibroblast-derived exosome secretion and altered exosomal miRNA profiles, with mechanically stimulated FB-EXOs promoting endothelial cell proliferation, migration, and angiogenic activity (Fig. 4).[65] Likewise, pro-inflammatory cytokines, such as TNF-α and interleukin-6 (IL-6), regulate both FB-EXO secretion and cargo composition by activating intracellular signaling pathways within fibroblasts. Inflammatory cytokines such as TNF-α and IL-6 can alter fibroblast activity and may consequently influence FB-EXO secretion and cargo composition.[66]

For clinical and translational applications, exosomes must be obtainable in sufficient quantities through practical and reproducible isolation methods. Although MSC-derived exosomes (MSC-EXOs) have shown therapeutic potential, MSC cultivation is labor-intensive and time-consuming and often requires invasive tissue harvesting. Additionally, the contamination of MSCs with red blood cells during isolation can compromise cell viability and reduce the regenerative efficacy, including the neovascularization capacity.[25,67] Consequently, there is a growing need for more accessible and efficient exosome sources. Fibroblasts have emerged as a favorable alternative because they can be readily isolated from skin using minimally invasive procedures and exhibit faster proliferation rates compared to MSCs. Importantly, fibroblasts are functionally specialized for maintaining skin integrity and coordinating wound repair, making their exosomes particularly relevant for regenerative applications.[25,67,68] Overall, FB-EXOs represent a practical and biologically relevant substitute for MSC-EXOs, with demonstrated effectiveness in promoting wound healing and tissue repair.[25,68,69]

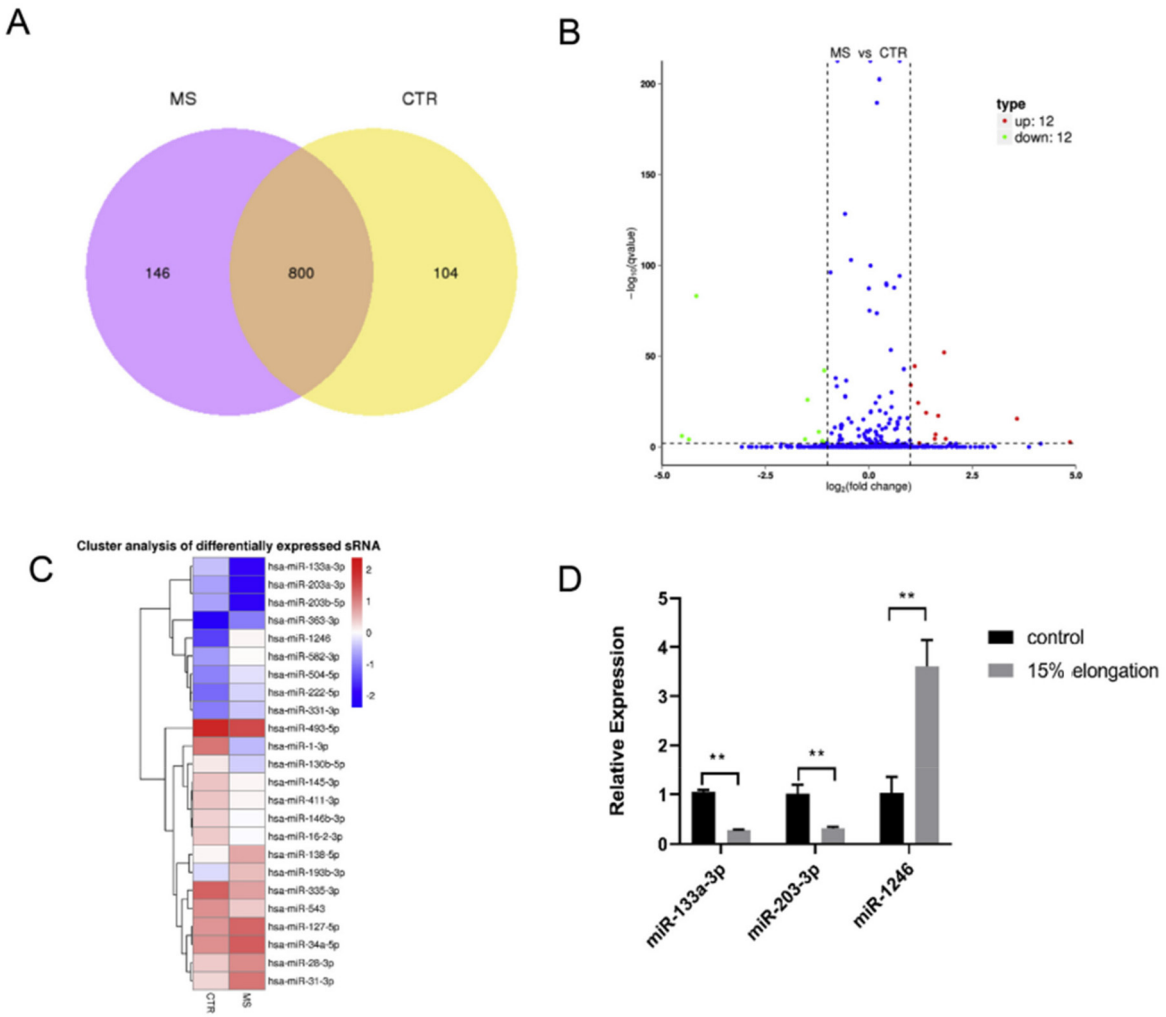

Fig. 4 Mechanical stress modulates the miRNA cargo of fibroblast-derived exosomes. (A) Venn diagram illustrating the distribution of differentially expressed miRNAs between control and mechanically stimulated fibroblasts. (B) Volcano plot showing significantly upregulated (red) and downregulated (green) miRNAs following mechanical stimulation. (C) Hierarchical clustering analysis of the 24 miRNAs exhibiting significant expression changes. (D) Validation by RT-qPCR, confirming the downregulation of miR-133a-3p and miR-203-3p and the upregulation of miR-1246 in mechanically stimulated fibroblasts compared with controls. Reproduced from ref. 65 with permission from Elsevier, copyright 2020.

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5. Role of fibroblasts in skin homeostasis and repair

Fibroblasts are central regulators of skin homeostasis and wound repair. Following injury, they become activated, proliferate, and migrate to the wound site, where they coordinate extracellular matrix (ECM) remodeling, wound contraction, and tissue regeneration.[25,59,70,71] In response to injury-associated signals, a subset differentiates into highly contractile myofibroblasts that promote matrix deposition and wound closure. Beyond ECM remodeling, fibroblasts regulate key signaling pathways involved in tissue repair, including Wnt signaling and growth factor-mediated pathways through the secretion of transforming growth factor-β1 (TGF-β1), fibroblast growth factors (FGFs), and other bioactive mediators.[25,71–73]

5.1. Regenerative potential of FB-EXOs in cutaneous repair

A growing body of research has demonstrated the regenerative potential of FB-EXOs in accelerating cutaneous wound healing. In an *in vivo* study using 48 male Wistar rats with standardized dorsal skin wounds, animals treated with either high-dose exosomes (HDEs) or low-dose exosomes (LDEs) exhibited significantly improved healing compared with a commercial ointment control. Notably, the HDE group demonstrated enhanced epithelialization and more advanced tissue remodeling.[25,73] Additional *in vivo* studies further confirmed the therapeutic efficacy of FB-EXOs. Compared with phosphate-buffered saline (PBS)-treated controls, FB-EXOs increased epidermal thickness, enhanced macrophage activation, and significantly reduced wound width, although epidermal stem cell-derived exosomes (ESC-EXOs) also contributed to tissue repair.[25,74] Similarly, exosomes isolated from the L929 mouse fibroblast cell line promoted dose-dependent fibroblast migration and proliferation while accelerating wound closure. These exosomes also upregulated genes associated with regenerative healing, including MMP1, MMP3, and COL3A1, demonstrating their ability to facilitate tissue repair.[25,67] Collectively, these findings demonstrate the therapeutic potential of FB-EXOs as a cell-free strategy for promoting cutaneous repair and tissue regeneration.

Beyond their regenerative effects, angiogenesis is indispensable for successful wound healing because newly formed blood vessels provide oxygen and nutrients required for tissue regeneration. FB-EXOs promote angiogenesis by delivering pro-angiogenic factors including VEGF, FGF, and miR-126. Experimental studies demonstrated that FB-EXOs enhance endothelial cell migration, tube formation, and vascular remodeling while increasing VEGF expression and CD31 levels, indicating active neovascularization.[25,67,75,76] Through the transfer of diverse bioactive cargos, FB-EXOs coordinate multiple regenerative processes, including cellular proliferation, inflammatory modulation, angiogenesis, oxidative stress regulation, and extracellular matrix (ECM) remodeling.[20]

5.2. Stimulation of cellular proliferation and migration

During the regenerative phase, FB-EXOs enhance the proliferation and motility of neighboring cells, particularly keratinocytes and endothelial cells.[65,77,20] This effect is largely mediated by their molecular payload, including regulatory miRNAs (*e.g.*, miR-21 and miR-29) and growth factors such as TGF-β. miR-21 has been implicated in regulating fibroblast activation and myofibroblast differentiation, thereby influencing tissue remodeling during wound healing.[78] Concurrently, exosome-associated TGF-β activates the TGF-β/SMAD signaling cascade, driving fibroblast differentiation into contractile myofibroblasts, enhancing matrix deposition, and improving wound contraction and structural repair.[79,20] Ahmadpour *et al.*[73] reported that topical administration of FB-EXOs significantly accelerated wound closure, enhanced re-epithelialization, promoted collagen deposition, and improved granulation tissue formation in a full-thickness Wistar rat wound model. Similarly, Xia *et al.*[80] demonstrated that exosomes isolated from young fibroblasts promoted fibroblast migration and differentiation into myofibroblasts in aged mice through exosomal miR-125b-mediated suppression of Sirt7, thereby enhancing ECM deposition and tissue remodeling.

5.3. Modulation of the inflammatory response

The initial inflammatory stage of wound healing must be tightly controlled to remove pathogens and damaged tissue while creating conditions favorable for regeneration. FB-EXOs significantly contribute to this regulation by influencing macrophage behavior and broader immune cell activity, thereby balancing the magnitude and duration of inflammation.[20] In addition, exosome-associated factors, like TGF-β and other anti-inflammatory mediators, encourage macrophage polarization from the proinflammatory M1 phenotype to the reparative M2 phenotype.[81] M2 macrophages exhibit immunoregulatory and pro-regenerative properties, contributing to reduced inflammation, enhanced tissue remodeling, and accelerated wound healing.[20]

5.4. Enhancement of angiogenesis

Angiogenesis is essential for restoring vascular supply to injured tissue. FB-EXOs promote neovascularization through the delivery of VEGF, FGF, and miR-126.[20] VEGF, a key component within these vesicles, interacts with VEGF receptors (VEGFRs) on endothelial cells and triggers downstream signaling pathways, particularly phosphoinositide 3-kinase (PI3K)/Akt, thereby stimulating endothelial cell proliferation, migration, and capillary-like tube formation.[82,83,20] FB-EXOs maintain ECM homeostasis by regulating matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), thereby balancing matrix degradation with collagen deposition (Fig. 5).[84,20] In the early phase of repair, exosome-mediated stimulation of MMP release facilitates the removal of necrotic debris and breakdown of damaged ECM. As healing progresses, MMP activity is reduced, favoring stable matrix accumulation and preventing excessive degradation.[85] These exosomes also play a key role in collagen production. Growth factors such as TGF-β carried within exosomes activate SMAD signaling, enhancing the synthesis of type I and type III collagen by fibroblasts, which improves the strength and elasticity

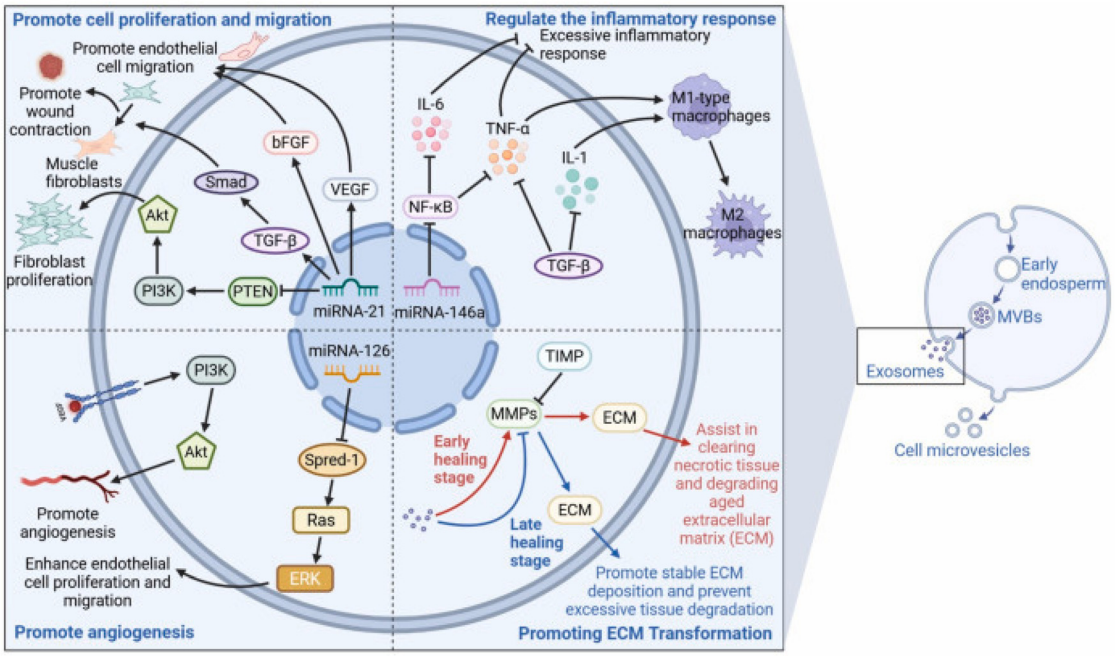

Fig. 5 Role of fibroblast-derived exosomes in wound healing. FB-EXOs deliver bioactive proteins, growth factors, and regulatory miRNAs to recipient cells, promoting cell proliferation, angiogenesis, inflammatory modulation, oxidative stress regulation, and ECM remodeling through pathways including TGF-β/SMAD, PI3K/Akt, NF-κB, and Nrf2/ARE. These coordinated effects accelerate tissue regeneration and wound repair. Despite their therapeutic promise, challenges related to large-scale production, standardization, and clinical translation remain. Reproduced from ref. 20 with permission from Elsevier, copyright 2025.

of newly formed tissues.[20,79] Beyond their miRNA cargo, FB-EXOs also contain bioactive proteins such as FGF and MMPs, which regulate fibroblast proliferation, keratinocyte migration, angiogenesis, and controlled ECM turnover.[20,86–88]

5.5. Role of exosomes in modulating oxidative stress

Oxidative stress in wound healing acts as a "double-edged sword". Controlled levels of reactive oxygen species (ROS) are beneficial for initiating inflammation and stimulating cell proliferation, whereas excessive ROS can damage tissues and contribute to fibrosis or chronic, non-healing wounds.[89,90] FB-EXOs contain antioxidant-related components that help maintain the redox balance and create a supportive environment for tissue repair.[20] These exosomes regulate oxidative stress by delivering antioxidant enzymes and signaling molecules to target cells. SOD converts superoxide to H_2O_2; catalase decomposes H_2O_2 into water and oxygen, whereas glutathione peroxidase reduces H_2O_2 and lipid peroxides using glutathione.[91,20] This protective effect is particularly important in later phases of healing, where it preserves newly regenerated tissue and supports remodeling.[20] In addition, FB-EXOs can activate intracellular antioxidant pathways in recipient cells. Certain exosomal miRNAs and proteins stimulate the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling axis, enhancing endogenous antioxidant enzyme expression and strengthening cellular resistance to oxidative stress.[20,26]

5.6. FB-EXOs mediate keratinocyte dysregulation in hypertrophic scar formation

Cui *et al.* investigated how FB-EXOs isolated from hypertrophic scar tissue influence epidermal cell behavior during scar formation. Exosomes obtained from hypertrophic scar fibroblasts were applied to normal human keratinocytes and compared to exosomes derived from healthy dermal fibroblasts. The hypertrophic scar FB-EXOs significantly altered keratinocyte activity by promoting proliferation, modifying differentiation patterns, and regulating apoptosis- and cell cycle-associated pathways. Furthermore, these exosomes influenced EMT-related markers, suggesting their involvement in tissue remodeling and pathological epidermal alterations during hypertrophic scar development. Collectively, these findings demonstrated that FB-EXOs act as important mediators of fibroblast–keratinocyte communication and contribute to abnormal wound healing and fibrosis, highlighting their potential as therapeutic targets for scar management.[10,92]

5.7. Fibroblast secretome as a source of regenerative exosomes

The fibroblast secretome comprises soluble bioactive factors and EVs, including exosomal populations of endosomal origin.[93] Dermal fibroblasts secrete a wide range of these bioactive molecules to communicate with surrounding cells and to maintain or repair the ECM architecture.[94,95] Many products marketed as "growth factor-based" therapies are, in fact, secretome-derived formulations that contain exosomes.[10,35]

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Recent advances highlighted that EVs play a central role in intercellular signaling cascades.[32] Exosomal populations are small EVs of endosomal origin that transport proteins, lipids, and nucleic acids to recipient cells.[96] Fibroblast-derived growth factors and secretome products account for a large proportion of published clinical studies investigating topical regenerative therapies.[10,97]

6. Clinical translation and therapeutic potential of FB-EXOs

FB-EXOs demonstrate substantial clinical promise due to their ability to coordinate multiple aspects of wound repair, including cell proliferation and migration, angiogenesis, ECM remodeling, and immune regulation. These vesicles are particularly attractive for treating chronic wounds such as diabetic foot ulcers, venous ulcers, and pressure injuries, where persistent inflammation, poor vascularization, and impaired tissue remodeling limit the effectiveness of conventional therapies. Their cargo of growth factors, regulatory RNAs, and anti-inflammatory mediators improved the wound microenvironment, accelerated closure, and reduced scar formation in preclinical models. Beyond standalone therapy, FB-EXOs can be integrated with biomaterials such as hydrogels, scaffolds, and nanocomposites to enable sustained delivery of regenerative signals and enhance tissue engineering outcomes, including bioengineered skin substitutes. Owing to their intrinsic biocompatibility, low immunogenicity, and nanoscale structure, they also serve as promising drug-delivery platforms capable of transporting anti-inflammatory or antimicrobial agents directly to pathological sites. Importantly, their compositions can be tuned by altering fibroblast culture conditions, opening opportunities for personalized regenerative therapies tailored to specific wound environments. While comparisons with exosomes from other cell sources reveal functional differences, FB-EXOs are promising candidates for matrix-related tissue repair, although direct comparative evidence demonstrating superiority over other EV sources remains limited.[85,98–102] Table 1 provides an overview of recent studies highlighting the regenerative and wound-healing potential of fibroblast-derived exosomes.

7. Future perspectives

Despite encouraging progress, several challenges must be addressed before FB-EXOs can be fully translated into clinical practice. Future research should prioritize the development of standardized isolation, purification, and characterization protocols to ensure reproducibility, scalability, and regulatory compliance. A deeper understanding of exosome heterogeneity and cargo selection mechanisms is also required to control their biological effects and avoid unwanted fibrosis or aberrant tissue responses. Advances in bioengineering are expected to enable the design of customized exosomes with defined therapeutic payloads, improved targeting capabilities, and controlled release profiles when integrated with smart biomaterials such as hydrogels or scaffolds. In addition, combining exosome-based therapies with emerging technologies, including gene editing, multi-omics profiling, and precision medicine approaches, may allow patient-specific modulation of wound environments and regenerative outcomes. In recent years, several advanced strategies have been proposed to enhance the therapeutic efficacy of exosome-based wound healing approaches, including the incorporation of exosomes into biomaterial platforms such as hydrogels and electrospun scaffolds for sustained and localized delivery. These engineered systems have demonstrated improved wound-closure rates, particularly in diabetic wound models. Emerging bioengineering strategies are being explored to modify exosomal cargo, enhance the specificity of therapeutic delivery, and develop more effective exosome-based approaches for different wound conditions.[103,104] As these technologies continue to progress toward clinical translation, important considerations regarding therapeutic safety, dosage optimization, and long-term efficacy remain active areas of investigation in current exosome-based clinical studies.[104] Rigorous *in vivo* studies and well-designed clinical trials are essential to validate their long-term safety, biodistribution, and efficacy. Ultimately, the convergence of exosome biology, biomaterials science, and translational medicine is anticipated to establish fibroblast-derived exosomes as a next-generation, cell-free therapeutic platform for regenerative medicine and chronic wound management.

The influences of donor variability, cellular source, age, disease condition, and microenvironmental factors on exosomal cargo compositions and regenerative efficacies also

Table 1 Representative recent studies highlighting the therapeutic applications of fibroblast-derived exosomes in wound healing and regenerative medicine

Study	Exosome source	Experimental model	Key findings	Therapeutic outcomes
Ahmadpour *et al.*[73]	Fibroblast-derived exosomes	Full-thickness wound model (Wistar rats)	Enhanced epithelialization, collagen deposition, and granulation tissue formation	Accelerated wound healing
Xia *et al.*[80]	Young fibroblast-derived exosomes	Aged mouse wound model	Exosomal miR-125b promoted fibroblast migration and ECM remodeling	Improved wound closure and tissue regeneration
Yan *et al.*[26]	Fibroblast-derived exosomes	Cutaneous wound model	Activated KEAP1/Nrf2 pathway through miR-29a-3p	Enhanced wound repair and skin quality
Hu *et al.*[59]	3D HDF-XOs	Photoaging and skin regeneration models	Increased collagen synthesis and reduced MMP-1 expression	Enhanced skin regeneration and anti-aging effects

require further investigation. In addition, standardized protocols for exosome isolation, characterization, dosage optimization, and delivery strategies are still lacking and must be established to improve reproducibility and translational consistency. More large-scale *in vivo* studies and clinical trials are needed to validate long-term therapeutic efficacy and safety across different wound types and patient populations. Furthermore, emerging areas such as engineered exosomes, biomaterial-assisted delivery systems, gene-edited exosomal cargo, multi-omics profiling, and personalized regenerative medicine remain relatively underexplored and represent promising future directions for enhancing the clinical applicability of FB-EXO-based therapies.

8. Exosome-based therapies in facelift procedures: clinical and at-home applications

Exosome-based therapies are increasingly being explored as adjunctive strategies to enhance outcomes following facelift procedures, particularly in improving wound healing and minimizing complications such as ischemia-induced tissue necrosis. In clinical settings, microneedling-assisted transdermal delivery of exosomes has shown promising results by creating controlled microchannels that facilitate deeper penetration of bioactive signals, thereby accelerating tissue repair and regeneration. Notably, in a reported clinical case, a 35 year-old woman who underwent a facelift developed concerns of partial flap necrosis due to compromised circulation near the anterior tragus incision site. Treatment with microneedling-assisted delivery of pharyngeal-derived exosomes (EXOP and Exodew), administered every 3 days over four sessions, successfully prevented progression to complete necrosis and significantly enhanced wound healing, highlighting the therapeutic potential of this approach in managing ischemic complications.[105]

Despite its efficacy, microneedling-assisted delivery typically requires professional supervision and may involve temporary downtime due to its invasive nature. As a result, non-invasive, at-home exosome delivery systems have emerged as complementary approaches for post-procedural care and maintenance. These systems, including microspicule-based platforms and dermarollers, enhance transdermal absorption , making them suitable for sensitive or recovering skin following aesthetic procedures such as facelifts. Although the regenerative effects of these systems are more gradual compared to those of clinical treatments, they provide sustained support for collagen synthesis, inflammation reduction, and overall skin recovery.[106]

Facial rejuvenation procedures can be broadly classified into surgical and non-surgical approaches. Surgical techniques include conventional facelift (rhytidectomy), full facelift, mini facelift, endoscopic facelift, and superficial musculoaponeurotic system (SMAS) facelift, which primarily reposition and tighten facial soft tissues. In contrast, non-surgical facelift procedures, such as thread lifts and other minimally invasive skin-tightening treatments, aim to improve facial aesthetics with reduced invasiveness, shorter recovery times, and lower procedural risk. Recent advancements in cosmeceutical formulations further demonstrate the translational potential of exosomes in post-facelift care. Clinically inspired, at-home exosome-based systems have been developed to deliver regenerative signals that enhance cellular communication, promote dermal remodeling, and improve skin firmness and elasticity without additional procedural burdens. Collectively, these approaches highlight the evolving role of exosome-based therapies in facelift recovery, offering both intensive clinical interventions and accessible at-home solutions to optimize healing and aesthetic outcomes. Commercial at-home exosome-based skincare systems have also been introduced for post-procedural care and skin maintenance. However, their clinical efficacy and the biological activity of their exosome-related components require further independent validation.[106,107] Skin ageing is a multifactorial process driven by intrinsic factors, including genetic and metabolic changes, as well as extrinsic environmental influences. These processes contribute to characteristic features such as wrinkles, reduced elasticity, and pigmentation abnormalities. Exosomes have emerged as promising regenerative mediators because they facilitate intercellular communication through the transfer of bioactive proteins, lipids, and nucleic acids. Exosomes derived from mesenchymal stem cells, adipose-derived stem cells, and other cell sources have been reported to promote skin cell proliferation, enhance collagen synthesis, reduce oxidative stress, and modulate inflammatory and matrix-remodelling pathways. Their therapeutic performance may be further improved through delivery approaches such as microneedling and hydrogel-based systems. However, challenges related to large-scale production, purification standardization, reproducibility, and long-term safety still need to be addressed before widespread clinical application.

A comprehensive understanding[108] of facial anatomy and surgical sequencing is essential for the subunit approach to facelifting and facial rejuvenation. In contrast to conventional techniques that primarily focus on generalized skin tightening, the subunit approach interprets facial aging as a regionally heterogeneous and multilayered process involving the skin, superficial and deep fat compartments, the SMAS, mimetic musculature, retaining ligaments, and the underlying skeletal framework. Each facial subunit, including the forehead, periorbital region, midface, jawline, and neck, demonstrates its own characteristic pattern of ptosis, volume redistribution, and structural weakening. Therefore, surgical correction must be tailored according to the specific anatomical and functional demands of each region. In practice, this often includes careful dissection along defined tissue planes, release of key ligamentous attachments, repositioning of ptotic soft tissue units, reinforcement or resuspension of the SMAS layer, and final redraping of the skin with minimal tension. Such a strategy not only enhances surgical precision but also supports

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more natural contour restoration, improved facial balance, and more durable rejuvenation outcomes. In this context, the subunit approach represents an anatomy-driven and structurally oriented framework for modern facial rejuvenation.

9. Conclusions

Fibroblast-derived exosomes have emerged as pivotal regulators of wound healing and tissue regeneration through their ability to mediate intercellular communication and deliver bioactive molecules that influence proliferation, migration, angiogenesis, inflammation, and extracellular matrix remodeling. Compared to conventional cell-based therapies, these nanoscale vesicles offer distinct advantages, including low immunogenicity, intrinsic stability, and the capacity to function as cell-free therapeutic agents or targeted delivery systems. Their integration with advanced biomaterials and tissue-engineering strategies further enhances their regenerative potential by enabling sustained, localized, and biologically responsive treatment. In addition to wound repair, fibroblast-derived exosomes have suggested promising applications in skin rejuvenation, scar modulation, anti-aging therapy, and regenerative aesthetics.

Although these exosomes are promising, several challenges still need to be addressed before their broader clinical translation can be achieved. Variability in exosomal cargo compositions, differences in cellular sources, delivery efficiencies, therapeutic reproducibility, and limited large-scale clinical validation remain important concerns. Future research should focus on optimizing exosome engineering strategies, improving targeted delivery systems, integrating smart biomaterials and responsive hydrogel platforms, and developing scalable regenerative formulations suitable for personalized medicine applications. Furthermore, advances in bioengineering, artificial intelligence-assisted cargo profiling, and precision regenerative medicine may enable the development of customized exosome-based therapies with improved therapeutic specificity and clinical efficacy. Continued interdisciplinary collaboration among biomaterials science, molecular biology, bioengineering, and clinical medicine will be essential to accelerate translational progress. Overall, fibroblast-derived exosomes represent a versatile and innovative regenerative nanoplatform with substantial potential for advancing next-generation therapies for chronic wounds, tissue regeneration, and complex skin disorders.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Abbreviations

AMPK	Adenosine monophosphate-activated protein kinase
ARE	Antioxidant response element
CAF	Cancer-associated fibroblast
CAT	Catalase
CD31	Cluster of differentiation 31
ECM	Extracellular matrix
EMT	Endothelial-to-mesenchymal transition
ERK	Extracellular signal-regulated kinase
ESC-EXO	Epidermal stem cell-derived exosome
EV	Extracellular vesicle
FB-EXO	Fibroblast-derived exosome
FGF	Fibroblast growth factor
GAG	Glycosaminoglycan
GPx	Glutathione peroxidase
HDE	High-dose exosome
HDF	Human dermal fibroblast
HDF-XO	Human dermal fibroblast-derived exosome
IGF-1	Insulin-like growth factor-1
IL-6	Interleukin-6
ILV	Intraluminal vesicle
LDE	Low-dose exosome
lncRNA	Long non-coding RNA
MMP	Matrix metalloproteinase
MMP-1	Matrix metalloproteinase-1
MSC	Mesenchymal stem cell
MSC-EXO	Mesenchymal stem cell-derived exosome
mTOR	Mammalian target of rapamycin
MVB	Multivesicular body
NF-κB	Nuclear factor kappa-B
Nrf2	Nuclear factor erythroid 2-related factor 2
PBS	Phosphate-buffered saline
PI3K	Phosphoinositide 3-kinase
PRP	Platelet-rich plasma
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TGF-β	Transforming growth factor-beta
TIMP	Tissue inhibitor of metalloproteinases
TIMP-1	Tissue inhibitor of metalloproteinases-1
TNF-α	Tumor necrosis factor-alpha
UVB	Ultraviolet B
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Data availability

The corresponding author can provide the datasets upon request.

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