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Review

Exosome therapeutics: A paradigm shift in skin repair through multidimensional immunomodulation and biomaterial-driven delivery

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ABSTRACT

Exosomes, nanoscale extracellular vesicles (30–150 nm) carrying bioactive molecules such as proteins, miRNAs, and lipids, are pivotal mediators of skin repair, modulating immune responses, angiogenesis, oxidative stress, and fibroblast function. This review synthesizes the mechanisms and clinical applications of exosomes in treating conditions such as diabetic ulcers, hypertrophic scars, photoaging, psoriasis, and alopecia. Exosomes from mesenchymal stem cells (MSCs), keratinocytes, and engineered sources regulate inflammatory pathways (e.g., NF-κB, IL-17/IL-23), promote angiogenesis through miRNA-mediated VEGF activation (e.g., miR-21–3p, miR-126), activate the NRF2 pathway to mitigate reactive oxygen species (ROS) accumulation, and modulate TGF-β/Smad signaling to reduce pathological scarring. Advanced delivery systems, including gelatin methacryloyl (GelMA) hydrogels, microneedles, and biomaterial scaffolds, enhance exosome stability and tissue penetration. Preclinical and early-phase clinical studies demonstrate accelerated wound healing, reduced scar formation, and enhanced skin regeneration. However, challenges such as standardized production, functional heterogeneity, long-term safety, and regulatory hurdles persist. Emerging technologies, such as single-exosome sequencing and artificial intelligence, offer solutions to optimize exosome therapy. As a promising cell-free therapeutic approach, exosomes require interdisciplinary collaboration to ensure efficacy and safety for clinical translation.

1. Introduction

Exosomes, nanoscale extracellular vesicles (30–150 nm) released upon fusion of multivesicular bodies with the plasma membrane, carry diverse bioactive molecules, including proteins, miRNAs, lipids, and metabolites, serving as key mediators of intercellular communication [1]. Their formation depends on the endosomal sorting complex required for transport (ESCRT) mechanism, with secretion regulated by the Rab GTPase family [2]. Exosomal cargo exhibits significant heterogeneity; for instance, mesenchymal stem cell (MSC)-derived exosomes are enriched with immunomodulatory proteins (e.g., TSG-6, HGF) and pro-regenerative miRNAs (e.g., miR-21–3p, miR-126), while keratinocyte-derived exosomes contain barrier repair-related lipids (e.g., ceramides, cholesterol). This cargo specificity enables exosomes to precisely modulate gene expression in target cells, such as by delivering miRNAs to silence pathogenic genes or activate repair pathways, positioning them as promising carriers for cell-free therapy [3,4].

As the body's largest organ, the skin maintains barrier function through a dynamic balance of the stratum corneum lipid matrix, tight junction proteins (e.g., Claudin-1), and natural moisturizing factors [5–8]. Barrier disruption triggers aberrant inflammatory cytokine activation (e.g., IL-4, IL-13), oxidative stress (e.g., reactive oxygen species [ROS] accumulation), and fibroblast dysfunction, contributing to conditions like diabetic ulcers (impaired angiogenesis) [9], hypertrophic scars (TGF-β/Smad pathway overactivation) [10], photoaging (accelerated collagen degradation) [11], and psoriasis (keratinocyte hyperproliferation) [12]. Conventional treatments, such as glucocorticoids and immunosuppressants, mitigate symptoms but are limited by side effects and high recurrence rates. Exosomes offer a promising alternative due to their low immunogenicity, multi-target regulation, and enhanced tissue penetration. For example, adipose-derived mesenchymal stem cell (ADSC) exosomes accelerate diabetic wound healing by delivering

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miR-146a to suppress NF-κB signaling [13], while engineered exosomes loaded with miR-138–5p target SIRT1 to reduce scar collagen deposition [14]. The skin's structural tissues and exosome composition are illustrated in Fig. 1.

Exosomes hold significant research value in skin repair, spanning mechanistic insights and clinical translation. Mechanistically, they elucidate interactions among immune cells, fibroblasts, and keratinocytes in the skin microenvironment. For instance, single-cell RNA sequencing demonstrates that umbilical cord mesenchymal stem cell (UCMSC) exosomes promote wound healing in mice by modulating neutrophil and macrophage activity [15]. Clinically, combining exosomes with biomaterials, such as gelatin methacryloyl (GelMA) microneedle patches loaded with human umbilical vein endothelial cell (HUVEC) exosomes, enhances transdermal delivery efficiency [16].

This review distinguishes itself through a comprehensive, translational perspective, integrating mechanistic insights with practical applications. Its novelty lies in several key areas: First, it moves beyond isolated discussions of engineered exosomes or delivery systems by synthesizing their synergy with advanced biomaterials (e.g., smart hydrogels, microspheres, microneedles, 3D-printed scaffolds, electrospun fibers), which enhance exosome stability, controlled release, and targeted therapeutic effects. Second, it emphasizes the functional specificity and heterogeneity of exosomes from diverse sources (e.g., MSCs, macrophages, tumor cells, plants), detailing their unique cargo (e.g., miRNAs, proteins) and therapeutic roles (e.g., immune regulation, angiogenesis, antioxidation) to guide source selection for specific skin conditions. Third, it critically addresses clinical translation challenges, including standardized production, separation purity, functional heterogeneity, and long-term safety, while evaluating emerging solutions like microfluidics, advanced chromatography, and cell-derived nanovesicles. Finally, it systematically explores exosome mechanisms in skin disease pathophysiology, elucidating their modulation of key signaling pathways (e.g., TGF-β/Smad in scarring, NRF2 in aging, IL-17/IL-23 in psoriasis) and cellular processes (e.g., macrophage polarization, fibroblast function), providing a robust scientific foundation for therapeutic development. By integrating exosome sources, modification techniques, delivery innovations, and mechanism-based actions, this review aims to guide future research and accelerate clinical translation of exosome therapies in dermatology. However, challenges such as standardized production, functional heterogeneity, and long-term safety validation persist. Future studies should leverage single-exosome sequencing, organoid models, and artificial intelligence to advance exosome therapies from bench to bedside.

2. Core mechanisms of exosomes in skin repair

2.1. Immunomodulation and anti-inflammatory effects

Exosomes play a key role in skin repair by precisely regulating immune cell activity and inflammatory cytokine networks. Their anti-inflammatory mechanisms are mainly manifested in the following two aspects.

2.1.1. Inhibition of pro-inflammatory cytokine release

Exosomes suppress pro-inflammatory signaling pathways by delivering functional miRNAs or proteins. For instance, adipose-derived mesenchymal stem cell (ADSC) exosomes reduce the expression of Th1-type cytokines, such as IL-6, TNF-α, and IFN-γ [3], while umbilical cord mesenchymal stem cell (UCMSC) exosomes mitigate keratinocyte hyperproliferation in psoriasis models by inhibiting the IL-17/IL-23 axis [12]. Additionally, neutrophil-derived exosomes deliver miR-31–5p to target the STAT3 pathway, decreasing TNF-α and IL-1β release and attenuating the inflammatory cascade in psoriasis [17].

2.1.2. Multidimensional immunomodulation: fine-tuning the immune landscape for skin repair

Exosomes exert sophisticated immunomodulatory effects by regulating the function and phenotype of immune cell subtypes, orchestrating the transition from inflammation to proliferation and remodeling in conditions like chronic wounds, fibrotic diseases, and inflammation-driven skin aging.

Exosomes promote macrophage polarization toward the pro-repair M2 phenotype. For example, M2 macrophage-derived exosomes enhance endothelial cell angiogenesis by delivering HIF-1α/VEGFA

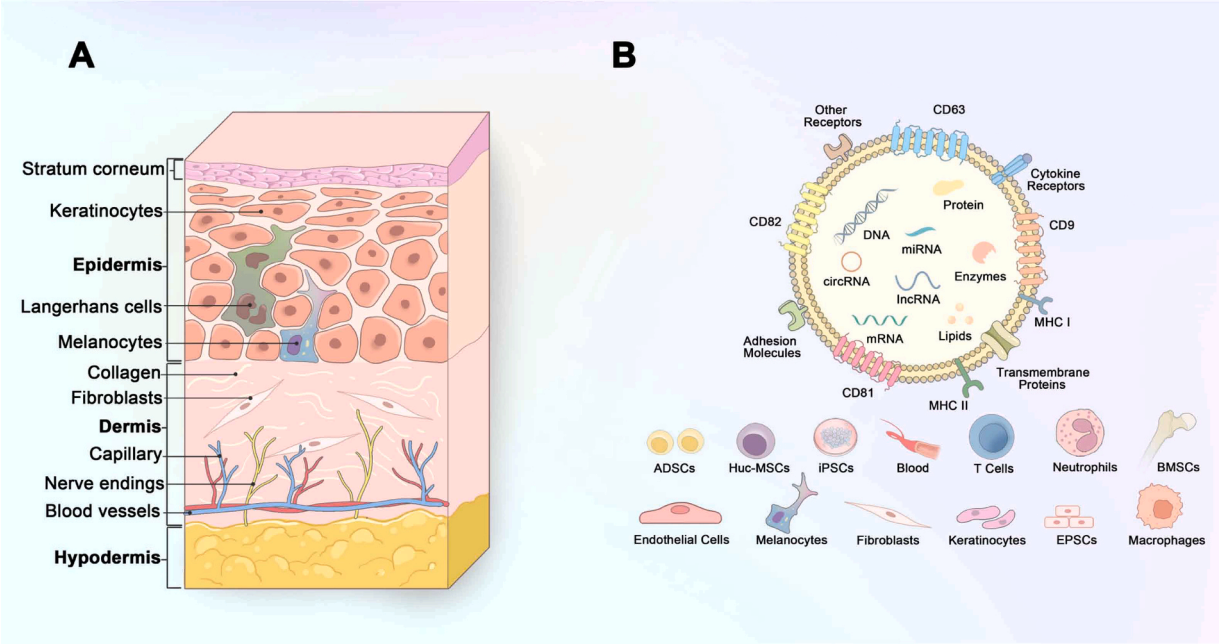

Fig. 1. Skin Structure and Exosome Composition. (A) The skin comprises the epidermis (keratinocytes, melanocytes, Langerhans cells), dermis (fibroblasts, blood vessels, nerve endings), and subcutaneous tissue (adipocytes, mesenchymal stem cells, blood vessels). (B) Exosomes regulating skin function originate from skin cells (keratinocytes, fibroblasts, melanocytes, endothelial cells), immune cells (T cells, neutrophils, macrophages), stem cells (ADSCs, BMSCs, UCMSCs, iPSCs, EPSCs), and blood, carrying characteristic biomarkers and diverse bioactive molecules.

signals [18]. Similarly, bone marrow mesenchymal stem cell (BMSC) exosomes deliver miR-153–3p to macrophages, targeting KPNA5 to drive M2 polarization, which suppresses chronic inflammation and supports tissue regeneration [19]. This polarization fosters a reparative immune microenvironment, accelerating wound healing.

Exosomes also regulate T cell subsets to achieve immune balance. ADSC exosomes inhibit excessive T cell activation induced by phorbol 12-myristate 13-acetate (PMA), reducing CD25 expression, suppressing IL-2 and IL-17A production, and reversing PMA-induced inhibition of the PI3K/Akt pathway and apoptosis. In early wound healing, these exosomes decrease epidermal γδ T cell aggregation and IL-17A levels, preventing excessive inflammation [20]. In psoriasis, regulatory T cell-derived exosomes loaded with drugs target lesion sites, inhibiting pro-inflammatory Th17 cells while promoting regulatory T cell (Treg) and tolerogenic dendritic cell differentiation, thus balancing local and systemic immunity [21]. This bidirectional regulation - both suppressing the excessive activation of effector T cells and promoting the function of regulatory immune cells - highlights the therapeutic potential of exosomes in restoring immune balance and inducing tolerance.

In the complex immune network of skin wound healing, dendritic cells (DCs) bridge innate and adaptive immunity, and precise regulation of their functional state is critical. Adipose-derived mesenchymal stem cell (ADSC) exosomes pretreated with TNF-α (T-exos) reprogram DC function by delivering enriched miR-146a-5p, which inhibits TXNIP protein expression and blocks NLRP3 inflammasome activation. This shifts DCs from a pro-inflammatory to a tolerant state, directly reducing excessive innate immune responses. More importantly, by modulating DC maturation and antigen presentation, T-exos indirectly influence T-cell activation and differentiation, promoting an appropriate adaptive immune response. This DC regulation coordinates inflammation suppression with tissue repair promotion [22].

Neutrophils, the first innate immune cells to reach the wound site, provide essential bactericidal defense in early healing. Under normal conditions, their inflammatory activity subsides promptly to facilitate the repair phase. n pathological states like type 2 diabetes mellitus (T2DM), persistent neutrophil infiltration and excessive release of pro-inflammatory cytokines and proteases exacerbate tissue damage. This abnormal activity mutually reinforces continuous DC activation, creating a vicious cycle. An effective immunomodulatory strategy, such as T-exos therapy, likely promotes neutrophil transition from a destructive to a reparative phenotype by improving the inflammatory microenvironment. This cooperates with regulated DCs to orchestrate a balanced immune response—from efficient antibacterial defense and inflammation resolution to orderly tissue reconstruction.

2.2. Promotion of angiogenesis

Angiogenesis, the formation of a functional vascular network, is essential for skin repair, ensuring adequate oxygen and nutrient delivery. Exosomes provide an efficient regulatory tool for this process by delivering pro-angiogenic active molecules. Exosomes regulate this process by delivering pro-angiogenic molecules, particularly through miRNA-mediated activation of the vascular endothelial growth factor (VEGF) signaling pathway. For instance, umbilical cord blood mesenchymal stem cell (UCMSC) exosomes enriched with miR-21–3p target the PTEN gene, relieving its suppression of the PI3K/Akt pathway and activating downstream VEGF signaling [4]. This mechanism promotes endothelial cell migration and neovascularization, increasing microvessel density and accelerating wound closure in diabetic mouse models compared to controls.

This mechanism promotes endothelial cell migration and neovascularization, increasing microvessel density and accelerating wound closure in diabetic mouse models compared to controls. Adipose-derived mesenchymal stem cell (ADSC) exosomes carrying miR-126 enhance VEGFR2 mRNA stability, stimulating endothelial cell proliferation [23]. When combined with extracellular matrix hydrogels, these exosomes further enhance vascular regeneration in diabetic ulcer models, promoting denser dermal microvessels and a mature three-dimensional vascular network.

To address the challenge of enzymatic degradation in wounds, advanced delivery systems enhance exosome stability and efficacy. For example, gelatin methacryloyl (GelMA) microneedle patches loaded with human umbilical vein endothelial cell (HUVEC) exosomes enable sustained miR-21–3p release, activating VEGF signaling and increasing vascular density in diabetic rat models [16]. In a diabetic rat model, this strategy significantly increased wound vascular density, and the mechanical penetration of the microneedles promoted exosome penetration into deeper tissues. Additionally, engineered exosomes overexpressing miR-132 (miR-132-exo) from adipose stem cells promote HUVEC proliferation and migration in vitro. In streptozotocin-induced diabetic mouse models, miR-132-exo enhance full-thickness wound and skin flap healing by reducing inflammation, promoting angiogenesis, and inducing NF-κB-mediated M2 macrophage polarization [24]. These findings elucidate the molecular mechanisms of exosome-driven angiogenesis and highlight innovative delivery strategies for treating complex wounds.

2.3. Upregulation of the NRF2 pathway and inhibition of ROS accumulation

Excessive reactive oxygen species (ROS) accumulation due to oxidative stress contributes to skin cell damage, collagen degradation, and impaired regeneration. Mesenchymal stem cell (MSC)-derived exosomes mitigate these effects by activating the NRF2 antioxidant defense system. For instance, MSC exosomes deliver quinone oxidoreductase 1 (NQO1) and heme oxygenase-1 (HO-1) to keratinocytes, reducing ROS toxicity via the KEAP1/NRF2 pathway [25]. In a UV-induced photoaging model, these exosomes enhance superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity while reducing the DNA oxidative damage marker 8-OHdG.

Exosomal circHIPK3 from umbilical cord mesenchymal stem cells (UCMSCs) is significantly upregulated in high-glucose (HG)-treated human umbilical vein endothelial cells (HUVECs). It competitively sponges miR-20b-5p, relieving suppression of downstream targets Nrf2 and VEGFA, thereby activating the miR-20b-5p/Nrf2/VEGFA axis. This promotes endothelial proliferation, migration, and angiogenesis (tube formation) while inhibiting apoptosis. Overexpression of miR-20b-5p reverses circHIPK3's pro-repair effects, confirming its dependence on this axis. Thus, UCMSC-derived exosomal circHIPK3 represents a promising therapeutic strategy for diabetic foot ulcers (DFU) via axis regulation [26].

At the clinical translation stage, innovative exosome delivery systems enhance their antioxidant potential. Researchers isolated coriander-derived exosome-like nanovesicles (CDENs) with antioxidant and anti-inflammatory properties and developed a biocompatible hydrogel for sustained CDEN release. CDENs are internalized by HaCaT cells and mouse skin, upregulating antioxidant enzymes, clearing reactive oxygen species (ROS), and reducing inflammation via Nrf2 pathway activation. In vivo, the CDENs-hydrogel modulates wound healing stage-specifically: promoting M2 macrophage polarization in the inflammatory phase, enhancing angiogenesis in the proliferative phase, and accelerating collagen deposition in the remodeling phase. These synergistic antioxidant, anti-inflammatory, and regenerative effects significantly accelerate wound closure, establishing CDENs-hydrogel as a safe, effective alternative for clinical wound management [27]. Recent studies also highlight regulation of the PI3K/mTOR/Beclin1 autophagy pathway, which may cooperate with Nrf2 to bolster cellular oxidative stress resistance—a promising future direction [28].

These studies confirm the pivotal role of exosomes in mitigating oxidative stress via the Nrf2 pathway and highlight their multidimensional regulatory advantages as "intelligent antioxidant carriers." By endogenously activating host defense mechanisms and synergizing with

exogenous antioxidants, exosomes offer innovative therapeutic strategies for oxidative damage-related conditions, including photoaging and ulcers.

2.4. Regulation of fibroblast function

As key mediators of intercellular communication, exosomes regulate fibroblast function and skin repair through diverse cargos, including proteins, microRNAs, and signaling molecules. Exosomes from various sources precisely modulate fibroblast proliferation, migration, differentiation, and extracellular matrix (ECM) metabolism by targeting pathways such as TGF-β/Smad, JNK/ERK, and Wnt/β-catenin, and delivering functional RNAs. For instance, adipose-derived mesenchymal stem cell (ADSC) exosomes reduce collagen deposition in hypertrophic scars by delivering miR-192–5p to inhibit the IL-17RA/Smad axis [29], Umbilical cord blood mesenchymal stem cell (UCMSC) exosomes promote scarless healing by suppressing TGF-β receptor signaling and fibroblast-to-myofibroblast transition [30]. Epidermal stem cell exosomes accelerate re-epithelialization and inhibit scarring by downregulating TGF-β1 [31], while human amniotic epithelial cell exosomes enhance scarless healing in rat models by activating matrix metalloproteinase-1 (MMP-1) to reduce ECM deposition and promote fibroblast proliferation and migration [32].

In pathological scar regulation, exosomes target the miRNA–TGF-β/Smad network. For example, adipose-derived mesenchymal stem cell (ADSC) exosomes deliver miR-194 to suppress TGF-β1 expression, block Smad2/3 phosphorylation, and attenuate the fibrotic phenotype of keloid fibroblasts [33]. Mesenchymal stem cell (MSC) exosomes inhibit excessive fibroblast proliferation via the miR-138–5p/SIRT1 axis [14]. Conversely, scar-derived exosomes (e.g., from hypertrophic scar fibroblasts) exacerbate pathology by delivering profibrotic factors such as hsa_circ_0020792 to activate the TGF-β1/Smad pathway [34]. Notably, engineered exosomes (e.g., modified with miR-29a or miR-141–3p) enhance anti-fibrotic efficacy through improved targeting [35,36].

In skin regeneration, exosomes promote repair through synergistic mechanisms: ① modulating the inflammatory microenvironment (e.g., M2 macrophage exosomes promote angiogenesis via the HIF1AN/HIF-1α/VEGFA axis) [18]; ② mitigating oxidative stress (e.g., MSC exosomes activate the Nrf2 pathway) [25]; and ③ delivering pro-regenerative factors. Integration with delivery systems such as hydrogels and microneedles (e.g., GelMA loaded with exosomes) prolongs local retention and enhances tissue penetration [16,37,38]. Preclinical studies demonstrate that exosome therapy significantly improves complex wounds, including diabetic ulcers, atopic dermatitis [39], and photoaging [40]. Combining exosomes with biomaterials (e.g., collagen scaffolds, silk fibroin) synergistically boosts extracellular matrix (ECM) reconstruction [41].

Exosomes act as ideal regulators of fibroblast function and skin regeneration through a trifecta of mechanisms—signaling pathway intervention, RNA regulation, and microenvironment remodeling (e.g., Cu et al. on melanocyte regulation [42]; Shen et al. on scar-promoting mechanisms [43]. Future efforts should optimize exosome source selection, engineering modifications, and delivery strategies (e.g., Kee et al.'s regulation of skin matrix synthesis [44]) to address individual

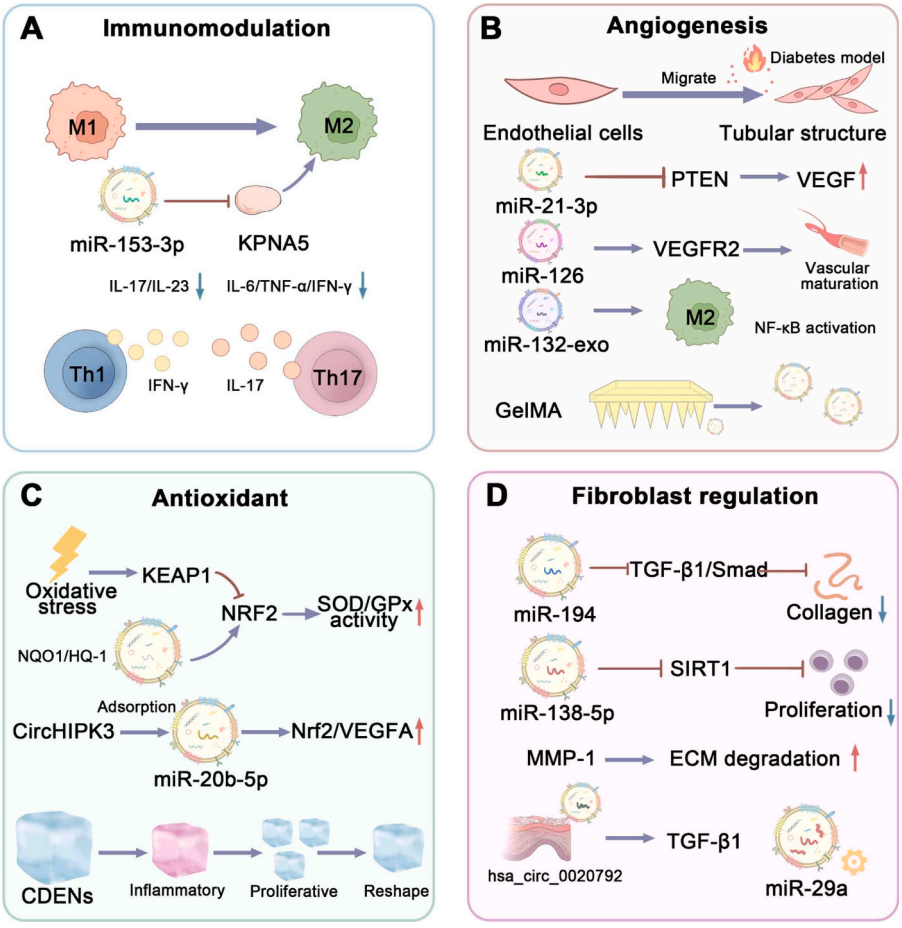

Fig. 2. Exosomes: Multi-dimensional Regulatory engines in Skin Repair. (A) Regulating the balance of immune inflammation: Inhibiting inflammatory factors and reshaping macrophage polarization. (B) Driving vascular network reconstruction: miRNA regulates the VEGF pathway and its delivery strategy. (C) Activate the antioxidant defense system: ROS clearance mediated by the NRF2 pathway. (D) Precise regulation of fibroblast function: Signaling pathway intervention and ECM metabolic balance.

heterogeneity and advance precise clinical therapies. Details of these mechanisms are illustrated in Fig. 2.

3. Sources and functional specificity of exosomes

3.1. Mesenchymal stem cell-derived exosomes

Mesenchymal stem cell (MSC)-derived exosomes are pivotal in skin regeneration and disease treatment due to their wide availability, low immunogenicity, and versatile differentiation potential. Adipose-derived mesenchymal stem cell (ADSC) exosomes restore UV-induced skin barrier damage by enhancing ceramide synthase (CERS3) expression in epidermal keratinocytes [23]. In diabetic wound models, ADSC exosomes deliver miR-21–3p to activate the PI3K/Akt pathway, upregulating vascular endothelial growth factor (VEGF) and angiopoietin-1 (ANGPT1), thereby promoting neovascularization and accelerating wound closure [45]. Umbilical cord mesenchymal stem cell (UCMSC) exosomes enhance chronic wound healing through multiple mechanisms. They suppress excessive neutrophil infiltration and promote anti-inflammatory M2 macrophage polarization [15]. Additionally, UCMSC exosomes counteract UV- and H2O2-induced damage in keratinocytes (HaCaT cells) by delivering 14–3–3 protein to activate the SIRT1 pathway, mitigating oxidative stress and enhancing autophagy in a time- and dose-dependent manner [46]. Bone marrow mesenchymal stem cell (BMSC) exosomes alleviate skin fibrosis in systemic sclerosis (SSc) by delivering miR-214 to inhibit the IL-33/ST2 signaling axis [47]. In SSc patients, reduced miR-214 expression correlates with elevated pro-fibrotic IL-33 and ST2 levels.Mechanistically, miR-214 targets IL-33, preventing its interaction with the ST2 receptor. In a bleomycin-induced skin fibrosis mouse model, BMSC exosomes reduce TGF-β1-induced fibroblast proliferation, migration, and fibrotic gene expression (e.g., α-SMA), decreasing collagen deposition and improving fibrosis by downregulating the IL-33/ST2 axis. These findings highlight MSC-derived exosomes as versatile therapeutic carriers for skin regeneration and fibrotic disease management.

3.2. Exosomes from other cell sources

Exosomes from non-mesenchymal stem cell sources play distinct roles in skin pathology and repair. Keratinocyte-derived exosomes modulate melanin metabolism through miR-675 [48] but may exacerbate psoriasis inflammation by activating the TLR4/NF-κB pathway [49]. Platelet-derived exosomes (PLT-Exos) mitigate skin photoaging by reducing senescence markers p16 and p21 [50]. Fibroblast-derived exosomes suppress scar formation by delivering TGF-β1 antagonists, such as miR-181a [51]. Conversely, melanoma cell-derived exosomes promote tumor metastasis via RAB27A signaling [52], highlighting the need for targeted modulation of exosomes from pathological sources to prevent adverse effects.

3.3. Bioengineering exosomes and biomaterial scaffolds for an immune-tuned microenvironment

Exosomes, as natural nanocarriers, exhibit low immunogenicity and excellent biocompatibility. However, their native functionality often falls short in complex pathological skin microenvironments. Engineering strategies—such as gene editing and drug loading—enable precise modification of exosomal cargo (e.g., miRNAs, siRNAs, small-molecule drugs), enhancing targeting specificity, stability, and therapeutic efficacy. This shift from passive delivery to active targeting opens new avenues for precision medicine in skin repair, enabling interventions against specific immune cells or signaling pathways.

Genetic engineering modifies parent cells, such as adipose-derived stem cells (ADSCs), to produce exosomes with specific functional molecules. For example, miR-146a-modified ADSC exosomes reduce inflammation in diabetic ulcers by inhibiting the IRAK1 pathway [53]. Similarly, miR-218–5p-loaded exosomes promote hair follicle regeneration via β-catenin pathway activation [54], circ-Astn1-modified exosomes regulate wound healing through the miR-138–5p/SIRT1/FOXO1 axis [55], and siRNA-NF-κB-engineered exosomes suppress skin inflammatory lesions [56]. Drug co-delivery systems further advance this strategy; for instance, exosomes loaded with triptolide (TPL) and modified with the tumor-targeting ligand TRAIL bind DR5 receptors on cancer cells, simultaneously activating TRAIL- and mitochondrial-mediated apoptosis. This dual action markedly enhances melanoma cell (A375) killing while inhibiting proliferation, migration, and invasion, with in vivo studies confirming precise tumor targeting and reduced toxicity [57]. These engineered exosomes improve cellular affinity and optimize repair by modulating key pathways. Differences between natural and engineered/pretreatment-modified exosomes are illustrated in Fig. 3.

Engineered exosomes achieve enhanced therapeutic efficacy when integrated with biomaterial scaffolds, which provide three-dimensional structures for controlled release and protect vesicles from rapid degradation. Hydrogels based on hyaluronic acid (HA) or chitosan serve as effective delivery platforms; loaded with exosomes and applied topically, they enable gradual cargo release to modulate local immune responses. For example, hydrogels incorporating M2-polarizing exosomes shift the wound microenvironment from pro-inflammatory to pro-regenerative, markedly improving repair in chronic wounds. Similarly, microneedle (MN) patches enable minimally invasive, direct dermal delivery of engineered exosomes, ensuring precise targeting of skin-resident immune cells.

Advanced bioengineering and smart material design create an immune-tuned microenvironment that synergistically optimizes skin repair. With continued standardization and clinical validation, engineered exosomes are poised to become a cornerstone of precision therapy for skin disorders. Future research should prioritize loading efficiency, single-cell technologies for personalized design, and expanded clinical trials to confirm safety and efficacy.

3.4. Special pretreatment to enhance exosome function

Pretreatment of mesenchymal stem cells (MSCs) enhances exosome cargo and biological activity for skin repair. Hypoxia-pretreated adipose-derived mesenchymal stem cell (ADSC) exosomes (HExo) promote diabetic foot ulcer (DFU) healing in mice by overexpressing circular RNA circ-0001747. This circRNA binds miR-199a-5p, relieving its suppression of HIF1α, thereby activating angiogenesis, reducing oxidative stress, and inhibiting apoptosis to improve the wound microenvironment. HExo targeting the miR-199a-5p/HIF1α axis offers a promising exosome-based strategy for DFU treatment [58]. Similarly, pioglitazone-pretreated MSC exosomes enhance angiogenesis by upregulating vascular endothelial growth factor (VEGF) expression [59]. Quercetin-pretreated MSC exosomes (MSCs-exoQr) improve diabetic skin wound (DSW) healing in rats by enhancing fibroblast proliferation and migration, correcting gut microbiota dysbiosis (e.g., increasing Faecalibacterium abundance), and modulating metabolic pathways (e.g., arachidonic acid pathway), thereby accelerating repair [60]. These pretreatment strategies optimize exosome functionality, supporting their therapeutic potential in complex wound healing.

3.5. Application potential of cross-species exosomes

Plant- and animal-derived exosomes offer unique therapeutic benefits. Lemon exosomes promote wound healing by shifting macrophage polarization toward a pro-repair phenotype and enhancing proliferation and migration of vascular endothelial cells and fibroblasts. To overcome delivery limitations, they are encapsulated in a gelatin methacryloyl (GelMA)–dialdehyde starch (DAS) hydrogel that adheres to skin, absorbs moisture, and permits breathability, enabling sustained exosome release and significantly improving diabetic wound repair [61]. Deer antler

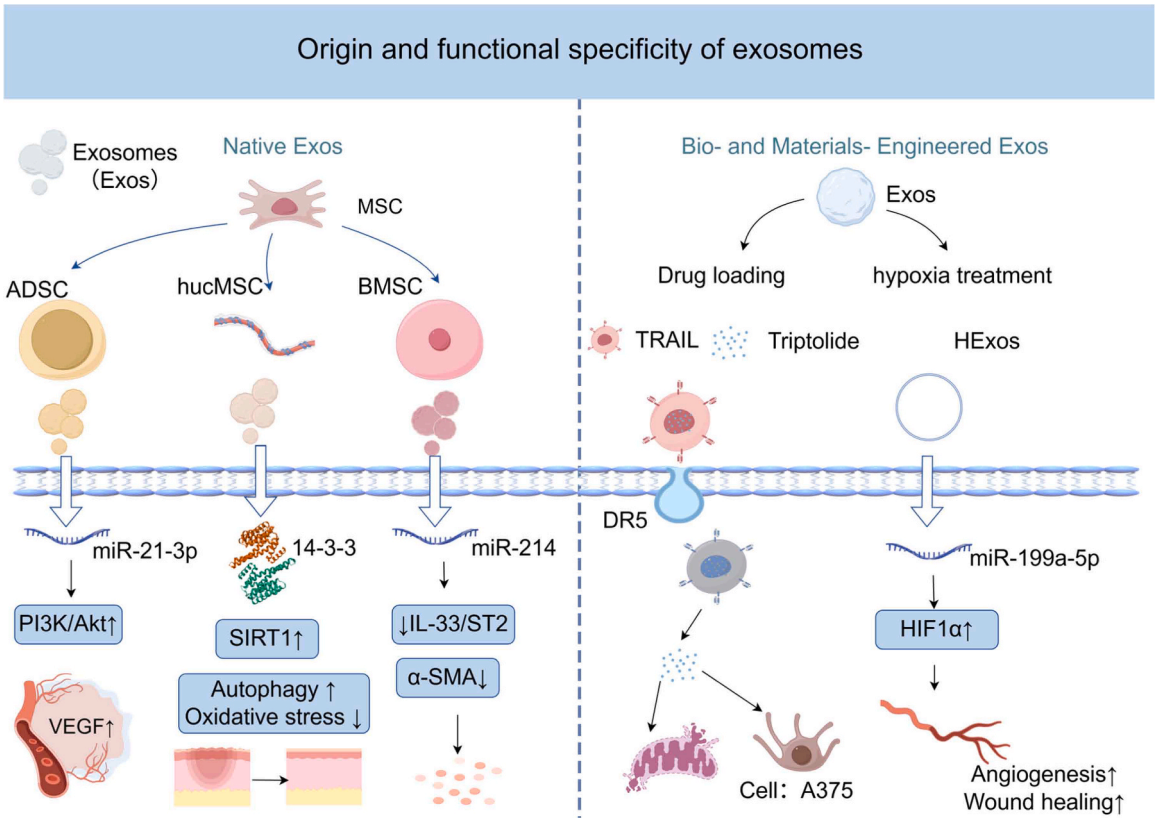

Fig. 3. The differences between natural exosomes and engineered/pre-treated exosomes.

MSC exosomes accelerate regeneration by activating the STAT3 pathway via miR-21–5p. Fusing plant and MSC exosomes synergistically modulates autoimmune skin diseases [62]. The low immunogenicity and high biocompatibility of cross-species exosomes position them as promising biologics, though their mechanisms and safety require further validation.

4. Innovative strategies for exosome delivery systems

4.1. Biomaterial carriers

Hydrogels, such as gelatin methacryloyl (GelMA) and collagen sponges, serve as effective exosome delivery carriers, enabling sustained release and mimicking the extracellular matrix (ECM) through their three-dimensional structure. GelMA's photocrosslinkable properties allow precise control of exosome release kinetics. For instance, GelMA hydrogels loaded with human umbilical vein endothelial cell (HUVEC) exosomes enhance skin wound healing and regeneration [38]. Collagen sponges, with their porous structure, promote cell infiltration. Pre-treated bone marrow mesenchymal stem cell (BMSC) exosomes combined with collagen scaffolds accelerate wound healing by promoting M2 macrophage polarization [63]. These biomaterials extend exosome half-life, provide mechanical support, and facilitate nutrient delivery, making them ideal for chronic ulcers and full-thickness skin defects. Recent advancements include acid-sensitive acetal bonds, enabling pH-triggered release for enhanced carrier responsiveness [64].

4.2. Microneedles and transdermal technologies

Microneedle technology enhances exosome delivery by penetrating the stratum corneum, enabling efficient transdermal administration. Cryomicroneedles loaded with lyophilized exosomes dissolve in the skin, rapidly releasing their cargo into the dermis to promote repair in aging skin [65]. A hyaluronic acid microneedle patch (rExo@DMFMNs) delivers regulatory T cell (Treg) exosomes and dimethyl fumarate (DMF) to treat psoriasis comprehensively. This patch targets the thickened stratum corneum, releasing DMF to inhibit keratinocyte proliferation via NF-κB suppression and activate the Nrf2 antioxidant pathway, while Treg exosomes induce tolerogenic immune cell differentiation and suppress Th17-mediated inflammation (see Fig. 4). In mouse models, this approach reduces epidermal hyperplasia and inflammation, balancing local and systemic immunity with high biocompatibility and minimal side effects, offering a precise, multi-target therapeutic strategy for psoriasis [66]. Microneedles are particularly effective for superficial wounds, such as photoaging and acne scars, combining non-invasiveness with high bioavailability.

4.3. Combination therapies

Combining exosomes with photothermal therapy, antimicrobial peptides, or small-molecule drugs enhances therapeutic outcomes by overcoming the limitations of single therapies. A multifunctional hydrogel integrating gold nanorods (AuNRs) and M2 macrophage exosomes (M2-Exos) enables synergistic treatment of diabetic wounds [9]. This dual-crosslinked (covalent and ionic) hydrogel exhibits anti-swelling properties and near-infrared (NIR) photothermal effects. Under NIR irradiation, AuNRs eliminate reactive oxygen species (ROS) and exert bactericidal effects, while M2-Exos promote angiogenesis and reduce inflammation. In animal models, this system accelerates healing of diabetic oral mucosal ulcers and skin defects by enhancing re-epithelialization and tissue regeneration while combating bacterial infection. This approach innovatively integrates exosome-mediated repair with nanomaterial-based photothermal therapy, offering a multi-target strategy for anti-inflammatory, antibacterial, and pro-angiogenic effects in chronic diabetic wounds. Similarly, co-delivery of the antimicrobial peptide LL-37 with exosomes disrupts biofilms and

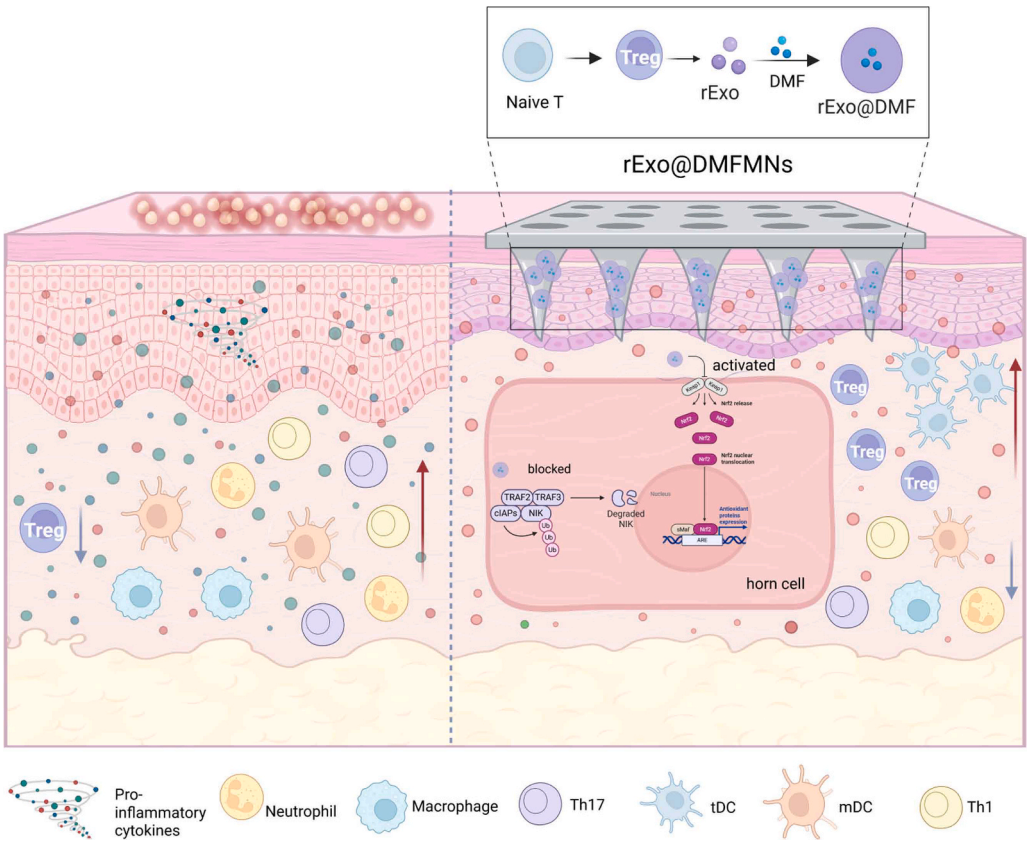

Fig. 4. rExo@DMFMNs Mechanism of microneedle patch treatment for psoriasis.

enhances immunomodulation, improving infected wound debridement [67]. Emerging strategies, such as ROS-responsive prodrug assemblies for targeted oxidative stress management [68] and GSH-responsive systems to inhibit metastasis via the EMT pathway [69], highlight the potential of responsive drug-exosome systems to further optimize combination therapies [69].

4.4. Biomimetic nanocarriers

Biomimetic nanocarriers, utilizing cell membrane coating technology, enhance exosome targeting and immune evasion capabilities. Advanced systems, such as folic acid-hyaluronic acid dual-targeted nanoparticles and aptamer-triptolide complexes, demonstrate receptor-specific delivery for precise therapeutic applications [70,71]. Research on malignant melanoma reveals that tumor-derived exosomes promote brain metastasis by disrupting the blood-brain barrier (BBB). Using a biomimetic BBB model (comprising brain microvascular endothelial cells, astrocytes, and microglia), studies show that these exosomes compromise BBB integrity and activate neuroglial cells by interfering with autophagy and immune-related pathways [72].Transcriptomic analysis confirms these mechanisms, validating the BBB chip as an effective in vitro tool for studying brain metastasis and supporting targeted exosome therapies to inhibit tumor progression.

5. Clinical applications of exosomes in skin diseases

Exosomes represent a revolutionary cell-free therapy with significant potential in dermatology. Derived from diverse sources—including mesenchymal stem cells, skin cells, and plant cells—they are applied across multiple skin disorders via mechanisms such as immune modulation, repair promotion, and anti-aging effects. A summary is provided in Table 1.

5.1. Chronic wounds and diabetic foot ulcers

Exosomes represent a core strategy for treating chronic wounds, particularly diabetic foot ulcers (DFUs), by promoting epithelialization and angiogenesis. Adipose-derived mesenchymal stem cell (ADSC) exosomes carrying miR-204–5p inhibit the TGF-β1/Smad pathway to accelerate diabetic wound healing [73]. In vitro, ADSC exosomes enhance rat skin fibroblast (RSF) proliferation and migration under high-glucose conditions while reducing collagen I (Col1) and α-smooth muscle actin (α-SMA) expression to suppress fibrosis. Mechanistically, miR-204–5p binds TGF-β1 mRNA, blocking Smad2/3 phosphorylation and mitigating scar formation. Animal experiments confirmed that ADSC-Exos treatment significantly accelerates diabetic wound repair, achieving scarless healing [73]. Another study demonstrates that ADSC exosomes accelerate wound healing by inducing M2 macrophage polarization and IL-33 release [74]. Mechanistically, they suppress pro-inflammatory cytokines (TNF-α, IL-6), enhance angiogenesis and collagen deposition, and activate the Wnt/β-catenin pathway via IL-33 to stimulate keratinocyte proliferation and epithelialization. In IL-33 knockout mice, wound healing is impaired, but ADSC exosomes restore function through an IL-33-dependent mechanism [74]. Biomaterial carriers, such as GelMA hydrogels loaded with human umbilical vein endothelial cell (HUVEC) exosomes, enable sustained release and boost efficacy, increasing diabetic wound closure rates by 40 % [38]. Engineered bone marrow mesenchymal stem cell (BMSC) exosomes loaded with miR-542–3p further promote repair [75]. In vitro, miR-542–3p exosomes are efficiently internalized by human skin fibroblasts (HSF) and human microvascular endothelial cells (HMEC), enhancing proliferation, migration, angiogenesis, and collagen I/III expression. In vivo, local injection accelerates wound closure, collagen deposition, and neovascularization by activating cellular repair pathways [75].

Table 1
Comprehensive summary of exosomal applications in skin health and recovery.

Category	Specific Item	Description and Examples	Key Findings & Outcomes
Source	Mesenchymal Stem Cells (MSCs)	Adipose-derived stem cells (ADSCs), umbilical cord blood/ Wharton's jelly MSCs (UCB-MSCs, WJ-MSCs), bone marrow MSCs (BMSCs). Prized for immunomodulatory, pro-angiogenic, and anti-fibrotic cargo.	Improved wound healing, reduced inflammation, enhanced angiogenesis, and ameliorated fibrosis in various models.
	Skin Cells	Human foreskin fibroblasts (e.g., BJ-5ta line), keratinocytes.	Targeted action on skin components. BJ-5ta Exo counteracted UVB-induced photoaging by scavenging ROS, promoting collagen synthesis, and facilitating DNA repair.
	Immune Cells	Macrophages, neutrophils.	M2 macrophage-derived exosomes promote repair, while neutrophil-derived exosomes can exacerbate inflammation in conditions like psoriasis.
	Plant-Derived	Apple-derived nanovesicles (ADNVs), Leontopodium alpinum (Edelweiss) exosomes (LEOEXO). Offer low immunogenicity, scalability, and inherent bioactive properties.	ADNVs improved collagen synthesis and reduced MMPs. LEOEXO delivered resveratrol effectively, enhancing its anti-inflammatory and anti-aging effects.
Engineering & Preparation	Genetic Engineering	Transfection of parent cells to load specific miRNAs (miR-146a, miR-218–5p) or proteins (LAMP-2B fusions).	Enhanced targeting and specific functionality (e.g., miR-146a-Exos inhibited IRAK1 for anti-inflammation).
	Chemical Modification	Click chemistry to conjugate targeting ligands (e.g., TRAIL) or therapeutic proteins to the exosomal surface.	Improved specific cell targeting (e.g., TRAIL for cancer cells).
	Drug Loading	Electroporation, incubation, or extrusion to load small molecules (Triptolide) or siRNA (siRNA-NF-κB).	Enabled combination therapy and enhanced therapeutic potency (e.g., TRAIL-Exo/TPL for melanoma).
Cell Pre-Treatment	Hypoxia	Pre-conditioning MSCs in low oxygen environments.	Upregulated pro-angiogenic circRNAs (e.g., circ-0001747), enhancing diabetic wound vascularization.
	Drug/Cytokine	Treating parent cells with molecules like Quercetin or IFN-γ.	Enhanced exosome efficacy; IFN-γ-iExo improved skin barrier in atopic dermatitis by inhibiting T-cell responses.
Application Parameters	Dose/Concentration	Ranges widely preclinically; ~5 × 10^10 particles in a clinical ADSC-Exo microneedling trial.	Effective dose-dependent responses observed in both animal and human studies.
	Route of Administration	Local Injection: Intralesional (scars, alopecia). Topical: Hydrogels, microneedle (MN) patches, sprays. Systemic: IV injection (e.g., for systemic sclerosis).	MN patches and hydrogels provided sustained release and improved bioavailability. Local injection ensured high concentration at the site.
	Frequency	Animal models: Single or multiple doses (e.g., weekly). Clinical: Multiple sessions (e.g., 3 treatments at 3-week intervals).	Multiple administrations often needed for chronic conditions to achieve optimal effect.
	Follow-up Duration	Animal models: Days to weeks (e.g., 7–21 days for wounds). Clinical: Up to 24 weeks (e.g., for alopecia trials).	Long-term follow-up in clinical studies confirmed sustained efficacy and safety.
Key Cargo	miRNA	miR-146a: Anti-inflammation (IRAK1). miR-218–5p, miR-21–3p: Angiogenesis, hair regeneration (β-catenin). miR-214: Anti-fibrosis (IL-33/ST2).	miRNAs are primary mediators, regulating key pathways to reduce inflammation, promote repair, and inhibit fibrosis.
	Proteins	14–3–3 ζ: Anti-photoaging (SIRT1). Cytokines (IL-10, TGF-β1): Immunomodulation, ECM synthesis.	Proteins directly modulate cellular processes like antioxidant defense and collagen production.
	Other RNA	circHIPK3: Acts as a miRNA sponge, activating Nrf2/VEGFA pathway for angiogenesis.	circRNAs provide a stable regulatory mechanism for sustained pathway activation.
Molecular Mechanisms	Immunomodulation	Polarize macrophages to M2 phenotype; inhibit Th17/Th1 responses; promote Treg differentiation.	Shifted wound microenvironment from pro-inflammatory to pro-regenerative, crucial for chronic wounds and dermatitis.
	Angiogenesis	Deliver pro-angiogenic miRNAs (miR-126, miR-21–3p) to activate PI3K/Akt and VEGF signaling.	Increased microvessel density in wounds, improving oxygenation and nutrient delivery.
	ECM Remodeling	Activate TGF-β1/Smad for collagen/elastin synthesis; inhibit MMP-1 to prevent degradation.	Restored skin elasticity and strength, reduced wrinkles in photoaging and improved scar quality.
	Anti-Oxidation/Anti-Senescence	Activate NRF2/HO-1 pathway; clear ROS; repair DNA damage (via Rad51); reduce senescent markers (p16/p21).	Protected cells from oxidative stress, delayed aging, and promoted survival of key skin cells.
Disease Models & Results	Chronic Wounds/ Diabetic Ulcers	ADSC-Exos (via miR-204–5p) inhibited TGF-β1/Smad, reducing fibrosis and promoting scarless healing. HUVEC-Exos in GelMA hydrogel accelerated healing by 40 %.	Accelerated wound closure, enhanced granulation tissue formation, increased angiogenesis, and reduced scarring.
	Psoriasis/Atopic Dermatitis	BMSC-Exos inhibited IL-17/IL-23/STAT3 axis. ASC-Exos promoted ceramide synthesis to restore skin barrier.	Reduced epidermal hyperplasia, decreased inflammatory cytokines (IL-6, TNF-α), and improved skin hydration.
	Skin Photoaging	BJ-5ta fibroblast Exos scavenged ROS, increased SOD/GPx activity, promoted collagen I via TGF-β1/Smad, repaired DNA.	Significantly alleviated wrinkle formation, water loss, and collagen/elastin degradation in UVB-exposed skin.
	Hypertrophic Scars/ Keloids	Targeted exosomal miR-21 which inhibits Smad7, activating TGF-β-Smad2/3 and promoting collagen overproduction.	Inhibition of exosomal miR-21 reversed pro-fibrotic effects, reducing collagen deposition.
	Systemic Sclerosis	AMSC-exos inhibited the TGF-β1/Smad3 pathway, reducing collagen synthesis and skin thickening.	Subcutaneous injection improved skin fibrosis in mouse models, offering a cell-free alternative to MSC therapy.
	Melanoma/Skin Cancer	TRAIL-Exo/TPL system targeted DR5 receptor, inducing dual apoptosis. Exo-HES enhanced hesperidin delivery and toxicity to B16F10 cells.	Significant inhibition of tumor growth, proliferation, and migration with reduced systemic toxicity.
	Androgenetic Alopecia	ASC-Exos activated Wnt/β-catenin pathway in dermal papilla cells, upregulating VCAN and other hair growth genes.	24-week treatment significantly increased hair density in patients with no serious side effects.

5.2. Inflammatory skin diseases

Exosomes exhibit bidirectional immunomodulatory effects in treating psoriasis and atopic dermatitis (AD). For psoriasis, bone marrow mesenchymal stem cell (BMSC) exosomes suppress Th17 cell activity by inhibiting the IL-17/IL-23 axis and reducing STAT3 phosphorylation [12]. In AD, adipose-derived mesenchymal stem cell (ADSC) exosomes restore skin barrier function by promoting ceramide synthesis. In an oxazolone-induced AD mouse model, subcutaneous injection of ADSC exosomes reduces transepidermal water loss (TEWL), enhances stratum corneum hydration, and dose-dependently lowers inflammatory cytokines (e.g., IL-4, IL-13, TNF-α). Mechanistically, ADSC exosomes activate the de novo ceramide synthesis pathway, increasing epidermal lamellar body formation. RNA sequencing confirms their role in repairing skin barrier-related gene expression, regulating lipid metabolism, and suppressing inflammation (see Fig. 5) [76].

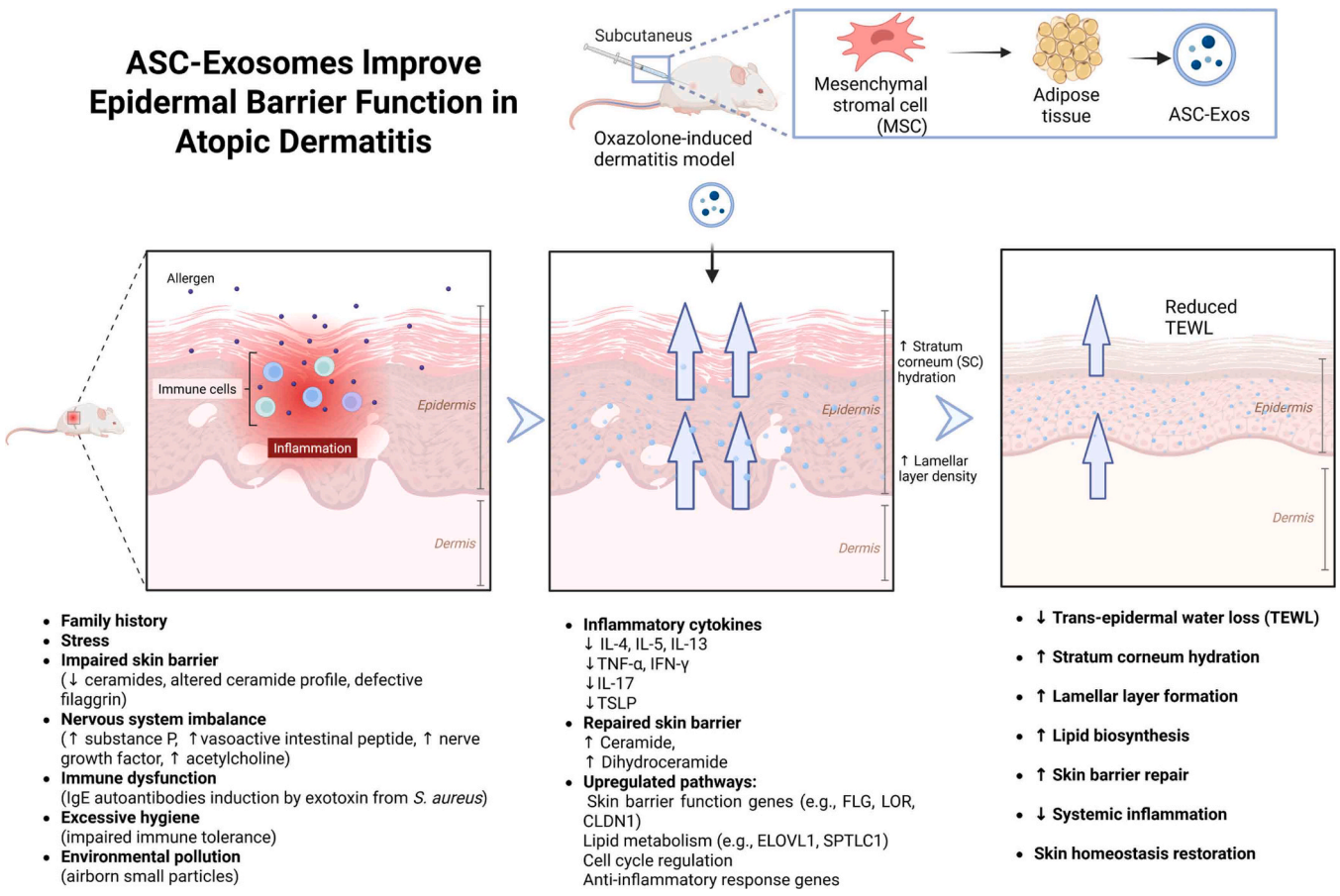

Fig. 5. Mechanism of ASC-Exos exosomes in the treatment of atopic dermatitis.

5.3. *Anti-aging and skin regeneration*

Exosomes delay skin aging by modulating extracellular matrix (ECM) metabolism. Human foreskin fibroblast-derived exosomes (BJ-5ta Exo) effectively mitigate ultraviolet B (UVB)-induced photoaging through multiple mechanisms: scavenging reactive oxygen species (ROS), enhancing antioxidant enzyme activity (e.g., superoxide dismutase, glutathione peroxidase), activating the TGF-β1/Smad pathway to promote collagen synthesis, and reducing senescence markers (e.g., γH2AX, p53/p21) via Rad51-mediated DNA repair. In mouse models, BJ-5ta Exo alleviate UVB-induced wrinkles, water loss, and collagen/elastin degradation while suppressing matrix metalloproteinase-1 (MMP-1) expression. These findings position BJ-5ta Exo as promising cosmetic ingredients for preventing or repairing photoaging damage [77].

Umbilical cord blood mesenchymal stem cell exosomes (USC-CMExos) promote skin rejuvenation. Following uptake by human dermal fibroblasts (HDF), USC-CMExos significantly enhance migration and collagen synthesis. In a human skin model, exosomes penetrate the outer epidermis within 3 h, reach deeper layers by 18 h, and markedly increase collagen I and elastin expression after 3 days. These findings demonstrate that USC-CMExos effectively elevate skin collagen and elastin levels, providing a promising approach for anti-aging cosmetics or reparative therapies [78].

Clinical studies demonstrate that combining human adipose-derived stem cell exosomes (HACS) with microneedling safely and effectively improves facial skin aging. In a randomized, split-face controlled trial of 28 subjects (three treatments at 3-week intervals), the HACS side received exosome delivery via microneedling, while the control side received saline. Objective measures of wrinkles, elasticity, hydration, and pigmentation significantly improved on the HACS-treated side ($p = 0.005$). Histopathology revealed collagen and elastic fiber regeneration without serious adverse effects. This protocol harnesses the synergistic effects of exosome-mediated repair and microneedle-enabled transdermal delivery, establishing a novel cell-free anti-aging strategy [79].

Plant exosome research has advanced with the development of LEOEXO@RES, a delivery system comprising Leontopodium alpinum (edelweiss) exosomes (LEOEXO) loaded with resveratrol (RES) to overcome RES's poor transdermal absorption. LEOEXO@RES efficiently delivers RES, markedly enhancing anti-inflammatory, anti-senescence, and antioxidant effects (e.g., inhibiting ROS and p16 expression). The mechanism leverages LEOEXO's transdermal synergy and RES's anti-aging activity, using plant waste for eco-friendly production. In vitro and in vivo studies confirm reduced skin inflammation and delayed aging, establishing a novel cell-free, green delivery strategy for anti-aging skincare [80].

Evidence from studies on human fibroblast-derived, stem cell-derived, and plant-derived exosomes validates their efficacy in combating skin aging and highlights the need for deeper deeper mechanistic insights [81]. Improvements in wrinkles, hydration, and elasticity arise from precise modulation of specific skin cell populations [82]. This reinforces exosomes as multifaceted signaling hubs capable of coordinated, multicellular targeting within the skin niche.

The regenerative effects of exosomes are mediated through their coordinated action on various skin cell types:

Fibroblasts: As the primary ECM producers, fibroblasts are central targets. Exosomes (e.g., from USC-CMExos) enhance collagen I and elastin synthesis by activating the TGF-β1/Smad pathway while simultaneously inhibiting MMP-1 generation. They also combat fibroblast senescence by reducing markers like p16/p21 and facilitating DNA damage repair [78,83].

Keratinocytes: Exosomes are critical for maintaining the epidermal

barrier. They promote keratinocyte proliferation and migration, accelerating re-epithelialization. Furthermore, they enhance the synthesis of essential barrier lipids, such as ceramides, by upregulating enzymes like ceramide synthase (CERS3), thereby improving stratum corneum integrity and hydration [84].

Melanocytes: Exosomes help regulate pigmentation and prevent age-related spot formation. For example, milk exosome-derived miR-2478 suppresses melanogenesis by modulating the Akt-GSK3β pathway. This helps achieve a more uniform skin tone [85].

Endothelial Cells: In aged skin, microvascular rarefaction contributes to poor nutrient delivery and waste removal. Exosomes promote angiogenesis by delivering pro-angiogenic miRNAs (e.g., miR-21–3p, miR-126) that activate VEGF signaling in endothelial cells, thereby restoring dermal microcirculation and supporting overall skin vitality [84,86].

Plant-derived exosomes further expand anti-aging applications. For example, apple-derived nanovesicles (ADNVs) enhance type I collagen synthesis and suppress MMP production in dermal fibroblasts by attenuating TLR4/NF-κB signaling [85].

In conclusion, exosomes offer a powerful cell-free anti-aging strategy by simultaneously targeting multiple hallmarks—from oxidative stress and ECM degradation to mitochondrial dysfunction and chronic inflammation—via coordinated modulation of diverse skin cell populations.

5.4. Scars and fibrotic diseases

Exosomes mitigate pathological scar formation and fibrotic diseases by targeting the TGF-β/Smad pathway. In keloids, exosomes from fibroblasts deliver elevated levels of microRNA-21 (miR-21, $P < 0.001$) compared to normal fibroblasts, activating the TGF-β/Smad pathway by inhibiting Smad7 expression. This promotes Smad2/3 phosphorylation, enhancing cell proliferation, collagen I/III synthesis, and inhibiting apoptosis. Inhibiting exosomal miR-21 reverses these effects, suggesting that targeting miR-21 may suppress keloid progression by upregulating Smad7, offering a novel therapeutic strategy [87].

In a scleroderma model, adipose-derived mesenchymal stem cell (AMSC) exosomes mimic the anti-fibrotic effects of parent cells, alleviating skin fibrosis in systemic sclerosis (SSc) by inhibiting the TGF-β1/Smad3 pathway. In vitro, co-culture of AMSC exosomes with SSc patient fibroblasts (direct or indirect) significantly reduced collagen synthesis. In a bleomycin-induced mouse model, subcutaneous AMSC exosome injection decreased skin thickening and collagen deposition, yielding effects comparable to AMSC transplantation. Mechanistically, exosomes suppress Smad3 phosphorylation by blocking TGF-β1 signaling, thereby inhibiting fibroblast activation. As a cell-free therapy, AMSC exosomes avoid risks of stem cell transplantation, providing a novel strategy for SSc skin fibrosis [88].

5.5. Skin cancer and melanoma

Exosomes function as drug carriers and immunomodulators in skin cancer therapy, with engineered exosomes showing significant promise. Exosomes loaded with copper/tin nanocomposites (S1-Exo@CuS/SnS) effectively target cutaneous squamous cell carcinoma (A431 cells), inducing apoptosis (40.2 % early, 22.1 % late) and G0/G1 cell cycle arrest. In vitro, S1-Exo@CuS/SnS outperforms doxorubicin (1.1-fold higher anti-tumor effect) without toxicity to normal human skin fibroblasts (HSF). Mechanistically, the exosomal delivery system (~120 nm, stable) enhances nanomaterial stability, synergistically activating apoptotic pathways and inhibiting proliferation [89].

In melanoma, exosome-encapsulated hesperidin (Exo-HES) overcomes hesperidin's poor water solubility and low oral bioavailability (2.5-fold increase). Prepared via sonication, Exo-HES forms stable ~106 nm spherical particles. In vitro, Exo-HES exhibits higher toxicity against B16F10 melanoma cells than free hesperidin, enhancing cellular uptake, ROS generation, and mitochondrial damage while inhibiting migration and colony formation (confirmed by wound healing and Transwell assays). In vivo, oral Exo-HES increases bioavailability 2.5-fold, significantly suppressing melanoma growth in mice without hematological, biochemical, or tissue toxicity, offering a low-toxicity therapeutic strategy [90]. Exosomes also function as diagnostic biomarkers. Plasma exosomal miR-1180–3p levels are reduced in melanoma patients (AUC > 0.85), enabling non-invasive diagnosis [91]. Sequencing and PCR analyses show that miR-1180–3p suppresses melanoma cell proliferation, migration, and invasion (confirmed by scratch and Transwell assays) by targeting the overexpressed ST3GAL4 gene. ST3GAL4 knockdown reverses malignancy, identifying the miR-1180–3p/ST3GAL4 axis as a novel therapeutic target, particularly in Asian populations

5.6. Rare and refractory skin diseases

Exosomes offer innovative therapeutic and diagnostic approaches for rare and refractory skin diseases like systemic sclerosis (SSc) and bullous pemphigoid (BP). In SSc, extracellular vesicles (EVs) from adipose-derived mesenchymal stem cells (ADSC) alleviate skin and lung fibrosis by delivering miR-29a-3p. In a hypochlorous acid (HOCl)-induced SSc mouse model, both large-sized (IsEVs) and small-sized EVs (ssEVs) reduce fibrosis 21–42 days post-injection. Inhibiting miR-29a-3p in MSCs abolishes EV efficacy, confirming its critical role. Mechanistically, miR-29a-3p targets pro-fibrotic genes (e.g., Dnmt3a, Pdgfrb) and upregulates anti-apoptotic genes (e.g., Bcl2, Bcl-xl), reversing fibrosis through epigenetic and cell survival regulation. This study highlights miR-29a-3p as a key effector in EV-based, cell-free SSc therapy [92].

In BP, blister fluid exosomes (expressing CD63, CD81, CD9) exacerbate disease by transmitting inflammatory signals. Internalized by human keratinocytes, these exosomes activate ERK1/2 and STAT3 pathways, promoting IL-6 and IL-8 release and neutrophil migration via CXCL8 upregulation. Proteomic analysis identifies inflammation-related proteins (e.g., S100A8/A9) in exosomes, with keratinocytes and neutrophils as likely sources. These findings elucidate the role of blister fluid exosomes in BP's local inflammatory response, suggesting targeted exosome therapies as a novel treatment strategy [93].

5.7. Hair regeneration and alopecia treatment

Exosomes promote hair regeneration by activating hair follicle stem cells and human dermal papilla cells (hDPCs). Umbilical cord mesenchymal stem cell (UCMSC) exosomes, expressing CD9 and CD63 markers, enhance hDPC proliferation by activating the PI3K/Akt pathway. In vitro, UCMSC exosomes increase the proportion of hDPCs in S and G2/M phases, upregulating pro-proliferation proteins (e.g., β-catenin, cyclin D1) via Akt and GSK-3β phosphorylation. Inhibiting PI3K/Akt abolishes this effect, confirming the pathway's critical role [94].

Adipose-derived mesenchymal stem cell (ADSC) exosomes stimulate androgenetic alopecia (AGA) treatment by activating the Wnt/β-catenin pathway, upregulating β-catenin, LEF-1, and alkaline phosphatase (ALP) activity. In vitro, ADSC exosomes enhance hDPC proliferation, hair shaft growth (increased Ki-67 expression), and expression of hair growth-related genes (e.g., VCAN). A 24-week clinical trial with 30 AGA patients demonstrated significantly increased hair density and patient satisfaction with no serious side effects [95].

For alopecia areata (AA), mesenchymal stem cell exosomes loaded with baricitinib (EV-B) improve local drug delivery compared to oral baricitinib, which has systemic side effects and poor penetration. In a mouse AA model, EV-B enhances hair coverage more effectively than baricitinib alone or blank EVs. Mechanistically, EV-B inhibits the JAK-STAT inflammatory pathway and activates Wnt/β-catenin-mediated hair follicle regeneration, offering a targeted, safe, locally administered therapy [96].

6. Discussion

6.1. Standardized production and quality control

Standardized production and rigorous quality control are critical for the clinical translation of exosomes, yet they face significant challenges. Common isolation methods, such as ultracentrifugation and size exclusion chromatography, yield variable recovery rates (15 %–80 %) [97], leading to inconsistent product yields and active component concentrations. Long-term storage at –80°C risks exosomal membrane protein denaturation, aggregation, or loss of function, compromising stability and efficacy. A comprehensive quality control framework is essential, encompassing physical characteristics (e.g., particle size of 30–150 nm via Nanoparticle Tracking Analysis), biochemical markers (e.g., >90 % positivity for CD63 and TSG101 via flow cytometry or Western blot), and functional stability (e.g., retaining >80 % biological activity, such as cell migration or angiogenesis, after 6 months at –80°C). The International Organization for Standardization's ISO/TC276 committee is advancing automated Good Manufacturing Practice (GMP) production lines to reduce batch variability to < 15 % [98]. However, heterogeneity due to cell source variability (e.g., donor differences, cell passage senescence) remains a challenge, as exosome cargo (e.g., nucleic acids, proteins) and function differ across batches, even under identical conditions [99,100].

6.2. In-depth expansion of mechanism research

Advancements in exosome mechanism research rely on integrating multi-omics technologies to elucidate cell-specific and pathway-driven effects.Single-cell sequencing reveals that adipose-derived mesenchymal stem cell (ADSC) exosomes selectively stimulate VEGF secretion in Col1a1 + fibroblasts in diabetic wounds, with minimal impact on inflammatory macrophages, highlighting their cell-type-specific regulatory properties [15]. This selectivity depends on target cell receptor distribution (e.g., integrin subtypes), explaining variable exosome effects across tissue microenvironments. Multi-omics approaches, combining transcriptomics and proteomics, enable systematic analysis of exosome action networks. For example, β-chitin nanofiber hydrogels loaded with ADSC exosomes accelerate wound healing by upregulating complement factor D (CFD) and its downstream Aldoa/Actn2 axis, activating NF-κB signaling [101]. Similarly, proteomic and bioinformatics analyses show that platelet-rich plasma exosomes (PRP-Exos) enriched with sphingosine-1-phosphate (S1P) promote angiogenesis in diabetic wounds by activating the S1PR1 receptor and the Akt/FN1 signaling axis in endothelial cells. Knockdown of S1PR1 abolishes FN1-mediated pro-angiogenic effects, supported by proteomic evidence of FN1 and S1PR1 co-localization [102]. By integrating single-cell resolution, dynamic pathway analysis, and receptor-ligand interactions, multi-omics technologies provide a comprehensive understanding of exosome spatiotemporal specificity, advancing mechanistic insights from descriptive outcomes to detailed regulatory mechanisms.

6.3. Clinical translation bottlenecks

The clinical translation of exosomes is hindered by challenges in scaled production and safety. Low production efficiency and complex isolation/purification processes limit scalability. While 3D dynamic culture and engineering modifications (e.g., protein overexpression) improve exosome yield, they face issues with cost, scalability, and regulatory compliance, failing to ensure dose consistency for large-scale clinical trials [103,104]. Additionally, optimizing drug loading and targeting specificity remains critical. Techniques such as genetic engineering, chemical modification (e.g., click chemistry for ligand attachment), and physical modification enhance targeting but may compromise exosome membrane integrity and natural functions [105,106]. Long-term in vivo stability, immunogenicity, and off-target toxicity require rigorous preclinical and clinical validation. Moreover, exosome heterogeneity (e.g., variable cargo within a single cell line) and complex in vivo microenvironments (e.g., tumor microenvironments actively uptake and remodel exosomes) reduce delivery efficiency and therapeutic predictability [107,108].

6.4. Ethical and regulatory framework

The ethical and regulatory framework for exosome therapies faces challenges in classification, safety assessment, and clinical standardization. The International Society for Extracellular Vesicles (ISEV) emphasizes defining exosomes as either "active pharmaceutical ingredients" or "drug delivery vehicles," as this dictates production standards (e.g., Good Manufacturing Practice requirements) and approval pathways [109]. Exosome therapies must meet safety standards akin to traditional biologics, with added scrutiny on heterogeneity (e.g., batch-to-batch variability) and off-target risks [109,110]. Debate centers on flexible regulations for personalized therapies [111]versus unified quality control metrics (e.g., purity, drug loading efficiency, functional activity) to minimize risks [109,112]. Ethical concerns include donor consent for stem cell-derived exosomes and long-term monitoring of carcinogenicity and immunogenicity [109,111]. Future frameworks should balance innovation with risk control, potentially via adaptive approval for indications like cancer or rare diseases [109,112]. A key unresolved issue is distinguishing exosomes from synthetic nanoparticles to avoid standardization disputes [109,113].

Emerging trends favor a precision medicine framework for exosome regulation, exemplified by the ME-HaD consortium's multinational data-sharing model [109]. Key research gaps include: (1) insufficient large-scale safety data [112]; (2) unvalidated cross-species toxicity prediction models [109]; and (3) conflicts between intellectual property protection and patient rights (e.g., commercialization of donor-derived exosomes) [111]. Future efforts should prioritize standardized automated production and dynamic regulation based on Real-World Evidence (RWE) [101,110].

7. Conclusion

Exosomes, as natural drug delivery systems, offer unique advantages in skin repair and regeneration due to their multi-targeting capabilities and low immunogenicity. Through mechanisms such as immune response modulation, angiogenesis promotion, oxidative stress inhibition, and regulation of fibroblast function and extracellular matrix (ECM) metabolism, they provide innovative therapies for conditions including diabetic ulcers, scars, photoaging, psoriasis, alopecia, and skin cancers. Engineered modifications, optimized pretreatment, and cross-species exosome exploration enhance their therapeutic potential. Biomaterial carriers (e.g., hydrogels, microneedles), combination therapies, and biomimetic delivery systems improve exosome delivery efficiency and efficacy. However, challenges in standardized production, functional heterogeneity, long-term safety, and ethical/regulatory frameworks persist for clinical translation. Future research needs to deeply integrate multi-omics technologies, organoid models, and artificial intelligence, and address technical bottlenecks through interdisciplinary collaboration, ultimately promoting the transition of exosomes from basic research to safe and effective clinical treatments.

CRediT authorship contribution statement

Fengrui Cheng: Visualization, Investigation, Funding acquisition. **Jingping Wu:** Visualization, Formal analysis. **Jun Lu:** Supervision, Resources, Methodology. **Hongbin Cheng:** Resources, Project administration, Funding acquisition, Conceptualization. **Pingfang Ye:** Writing – review & editing, Validation. **Dan Zhang:** Writing – review & editing, Validation. **Yabo Yao:** Software, Data curation. **Tinghan Deng:** Writing – review & editing, Writing – original draft, Validation,

Conceptualization. **Yiyi Zhang:** Software, Data curation.

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Informed Consent Statement

Not applicable.

Institutional Review Board Statement

Not applicable.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hongbin Cheng reports financial support was provided by Administration of Traditional Chinese Medicine of Sichuan Province. Jingping Wu reports financial support was provided by Administration of Traditional Chinese Medicine of Sichuan Province. Fengrui Cheng reports financial support was provided by Sichuan Provincial Health Commission. Hongbin Cheng reports financial support was provided by Sichuan Provincial Department of Science and Technology. Hongbin Cheng reports financial support was provided by Joint Innovation Fund of Health Commission of Chengdu and Chengdu University of Traditional Chinese Medicine. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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