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REVIEW

Wound Healing: Harnessing Extracellular Vesicles Derived from Adipose-Derived Stem Cells

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Abstract: Chronic wounds present a significant clinical challenge, placing a heavy burden on patients and highlighting the need for more effective treatments. Among emerging strategies, adipose-derived stem cells (ADSCs) and their extracellular vesicles (ADSC-EVs) show great promise due to their potent wound-healing capabilities. Clinical evidence indicates that ADSC transplantation effectively promotes healing across diverse chronic wound types, improving healing quality while reducing pathological scarring. As key paracrine mediators of ADSCs, ADSC-EVs have garnered considerable interest for their advantages in therapeutic development and reparative functions. ADSC-EVs precisely modulate critical cells within the wound microenvironment, including keratinocytes, macrophages, endothelial cells, and fibroblasts. This modulation promotes re-epithelialization, resolves inflammation, stimulates angiogenesis, and modulates extracellular matrix remodeling. These regulatory effects are attributed to the rich cargo of bioactive molecules carried by ADSC-EVs, including proteins and non-coding RNAs. Notably, preconditioning strategies and functional delivery materials can further enhance the modulatory effects of ADSC-EVs by enriching them with specific therapeutic molecules and enabling controlled release. Furthermore, ADSC-EVs serve as efficient drug delivery vehicles for exogenous therapeutics, enabling synergistic effects. In summary, both ADSCs and ADSC-EVs demonstrate considerable clinical potential for chronic wound management.

Keywords: diabetic wound, scar formation, ECM remodeling, angiogenesis

Introduction

Chronic wounds are injuries that fail to heal within the expected timeframe and exhibit impaired healing processes.[1] This impairment is primarily characterized by prolonged inflammation, reduced regenerative capacity, and compromised tissue remodeling.[2] Common underlying etiologies includes venous insufficiency, diabetic neuropathy, pressure ulcers, and arterial insufficiency. As a significant global health burden, chronic wounds affect approximately 1%–2% of the population during their lifetime.[1] Furthermore, they impact up to 5% of adults and account for as much as 10% of healthcare expenditures. Recent studies indicate that over a 5-year period, the number of patients with chronic wounds increased by 71%, while corresponding care costs rose by 48%.[3]

Clinical management strategies for chronic wounds vary depending on the type of chronic wound.[4] Debridement serves as the foundational approach, removing necrotic tissue, infected material, and foreign bodies to reduce the inflammatory and expose healthy tissue. Subsequent steps include infection control, maintaining a moist wound healing environment, ensuring adequate nutrition, and managing underlying diseases. Additionally, management involves pressure offloading, negative pressure wound therapy, improving tissue perfusion and oxygenation, and utilizing biological agents as adjunctive therapies. However, current treatment options remain substantially limited. Most approaches focus on symptomatic management rather than rectifying the dysfunctional wound microenvironment, which impedes the restoration of normal healing mechanisms.[5] Extended treatment durations and high healthcare costs further exacerbate the burden on patients and medical systems.[1] Thus, development innovative therapies that can fundamentally facilitate physiological wound healing represents a pressing challenge in modern clinical practice.

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In recent years, mesenchymal stem cells (MSCs) and their extracellular vesicles (EVs) are emerging as pivotal biotherapeutic agents in the realm of wound repair.[6,7] MSCs promote wound healing through their capacity to differentiate into skin cell lineages, such as fibroblasts and keratinocytes, as well as through paracrine signaling.[8,9] Notably, studies indicate that only a small proportion of transplanted MSCs actually differentiate at wound sites, underscoring the critical role of paracrine mechanisms in driving their therapeutic efficacy.[8,10,11] As key paracrine mediators, MSC-secreted EVs (MSC-EVs) exert their pro-repair functions through a diverse array of mechanisms, including immune modulation, angiogenesis activation, epithelial regeneration acceleration, and fibrosis suppression, thereby elevating healing quality.[9]

Among various sources of MSCs and MSC-EVs, adipose-derived stem cells (ADSCs) and their EVs (ADSC-EVs) have garnered significant attention in recent years, thanks to their accessibility, high abundance, and well-documented efficacy in promoting wound healing.[12–14] This review provides a comprehensive overview of the application of ADSCs in wound repair, with a particular focus on ADSC-EVs as an innovative acellular strategy to accelerate the healing process. The core therapeutic mechanisms of ADSC-EVs encompass modulation of the immune microenvironment, enhancement of tissue regeneration, and inhibition of pathological scar formation. By synthesizing the existing evidence, this review aims to establish a theoretical foundation for advancing the clinical translation of ADSC-EV-based therapies.

Mechanisms and Actions of ADSCs in Wound Healing

Extensive experimental evidence has established the therapeutic potential of ADSCs in accelerating wound repair.[15)] ADSCs can directly differentiate into skin cells to support tissue regeneration. They exhibit remarkable plasticity, differentiating into fibroblasts,[16,17] keratinocytes,[18] epithelial cells,[16] and endothelial cells[18,19] under specific microenvironmental cues. For instance, Altman et al demonstrated that ADSCs, co-transplanted with acellular dermal matrices into full-thickness skin defects, differentiated into vascular endothelial cells (expressing von Willebrand factor and smooth muscle actin (SMA)) and fibroblasts (positive for heat shock protein 47 (HSP47)), thereby significantly enhancing neotissue formation.[17] This differentiation capacity positions ADSCs as a self-renewing cellular reservoir for structural and functional wound restoration. In addition to their differentiation potential, ADSCs facilitate wound healing via their modulatory effects. Cui et al reported that ADSC transplantation promotes M2 macrophage polarization, thus attenuating chronic inflammation and reducing fibrosis.[20] The modulatory effects of ADSCs are largely attributed to their paracrine mechanisms. For example, Cerqueira et al found that ADSCs upregulated keratinocyte growth factor (KGF) expression, stimulating keratinocyte proliferation and modulating epidermal structure and morphology.[21] Additionally, Nie et al reported that ADSCs secrete angiogenic cytokines, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and fibroblast growth factor 2 (FGF2), which promote wound healing.[22]

The promising preclinical outcomes have propelled clinical translation of ADSCs in wound management, with multiple registered trials evaluating their therapeutic efficacy. As summarized in Table 1, a systematic search of the PubMed database identified 16 published clinical trials that evaluated the use of ADSCs in cutaneous wound healing. The included studies encompassed four distinct disease models: chronic ulcers (n = 4),[23–26] diabetic wounds (n = 5),[27–31] postoperative scar prevention (n = 3),[32–34] and scar revision (n = 4, 3 acne scars and 1 mature pediatric burn scar).[35–38] Regarding cell sources, investigations employed either processed adipose tissue (eg, via centrifugation or microfragment), stromal vascular fraction (SVF), or ADSCs. Except for two trials utilizing allogeneic materials, all interventions were autologous. Local injection was the predominant route of administration (14/16 studies), whereas the two trials utilized allogenic ADSCs incorporated into hydrogel or gel-based carriers for topical application.[29,30] The majority of trials were exploratory pilot studies; only two were Phase II clinical trials, and no Phase III studies have been reported. Sample sizes were generally modest: aside from two studies enrolling 100 and 114 participants, respectively, all remaining trials included fewer than 100 subjects, consistent with preliminary safety and efficacy assessments. Follow-up durations ranged from 3 to 12 months, adhering to standard wound-healing research protocols. Although most studies reported high follow-up compliance, two trials exhibited dropout rates exceeding 20%.[29,34] Twelve trials adopted randomized controlled designs; however, double-blinding was infrequently implemented (3/16) due to technical constraints. Risk-of-bias assessment using the Cochrane RoB 2.0 tool revealed a high risk of bias in 14 of 16 studies. No serious adverse events related to the treatments were reported. Fourteen trials concluded that ADSC-based therapy

Table 1 Clinical Trials of ADSC Therapy in Wound Management

Disease/ Indication	Intervention	Delivery Method	Phase	Enrollment	Inclusion Criteria	Exclusion Criteria	Follow-Up	Loss of Follow-Up	Randomization & Blinding	Risks of Bias	Key Outcome	Ref
Chronic leg ulcer	Autologous Centrifuged adipose tissue	Intralesional injection	II	n = 16 (8/8)*	Age 18–90 years; chronic venous and or mixed leg ulcers refractory to standard treatment for ≥ 9 months; area > 8 cm[2]; chronic pain refractory to home-based therapy	Clinical infection; PAD (ABI <0.8); anemia (Hb <10.0 g/dL); malnutrition (BMI <17.5); immobility; multi-organ failure; malignancy; immunosuppressive/ cytotoxic therapy	24 weeks	0	Randomized; non-blinding	High	Accelerated healing time (17.5 ± 7.0 vs 24.5 ± 4.9 weeks (P < 0.036)); early pain reduction (NRS: 2.7 ± 2.0 vs 6.6 ± 3.0 (P < 0.01)); comparable final healing rate	[23]
Chronic leg ulcer	Autologous SVF	Intralesional injection	\	n = 16	Multimorbid patients with chronic VLU/ AVLU (2–400 cm [2]) refusing skin grafting and vascular surgery; ≥6 months non-healing despite compression and negative pressure therapy; AVLU with chronic limb ischemia not exceeding stages Rutherford 4, Fontaine III; infected ulcers (EWMA stage 2–3); on anticoagulants/ anti-platelets; MRSA/ESBL resistant Gram negative species colonization	Age < 18 years; INR > 3.0; uncontrolled diabetes; diabetic foot ulcers; ankle systolic pressure < 40 mmHg; ABI < 0.5, toe pressure < 30 mmHg; malignancy; autoimmune disease; chemo- and immunosuppressive therapy; poor compliance; factor XIII deficiency; EWMA infection stage 1/4	9-44 months	0	Non-comparative pilot study	High	Complete re-epithelialization (VLU:7/7; AVLU: 4/9); early pain relief; limited efficacy in large ulcers	[24]

(*Continued*)

Table 1 (Continued).

Disease/ Indication	Intervention	Delivery Method	Phase	Enrollment	Inclusion Criteria	Exclusion Criteria	Follow-Up	Loss of Follow-Up	Randomization & Blinding	Risks of Bias	Key Outcome	Ref
Chronic ulcer	Autologous ADSCs and PRP	Intralesional injection	\	n = 40 (24/16)	Chronic venous, diabetic or ischemic ulcers.	Chemotherapy; Hb < 10.5 g/dL; platelets t < 100 x 10[3]/μL; serum albumin < 2.5 g/dL; malignant wounds; active infection	18 months	0	Randomized; non-blinded	High	Increased closure rate (0.2287 vs 0.0890 cm[2]/day (P = 0.0257)); comparable final healing	[25]
Chronic ulcer	Autologous ADSCs	Intralesional injection	\	100 (50/50)	Chronic non-healing diabetic, venous, trophic, or ischemic ulcers		6 months	5	Randomized; non-blinded	High	Reduced infection; improved healing; shorter healing duration (7.87 ± 2.50 vs 13.87 ± 2.84 weeks, P = 0.000)	[26]
Diabetic foot ulcer	Autologous SVF	Intralesional injection	\	n = 63	Type 2 diabetes; non-healing ischemic ulcer ≥3 cm[2] lasting> 3 months; approaching amputation	Age < 30 years; unstable cardiovascular diseases; smoking/CPD; active infection/sepsis; uncontrolled diabetes	6-12 months	9	Non-comparative study	High	Enhanced angiogenesis	[27]

Diabetic foot ulcer	Autologous fat grafting with or without PRP	Intradermal injection	\	n = 18 (6/6/6)	Age 18 to 90 at time of consent; diabetic foot ulcer measuring more than 0.5×0.5 cm and less than 10×10 cm; wound clean with a healthy granulating bed and minimal adherent slough; patient is able to provide their own consent and is willing to attend weekly follow-up visits	Active infection; severe ischemia (ABI < 0.3); uncontrolled diabetes; significant comorbidity; renal/liver failure; autoimmune disease; immunosuppression; unfit for surgery	17 months	0	Randomized; non-blinded (assessor-blinded)	High	Comparable clinical outcomes across groups	[28]
Diabetic foot ulcer	Allogenic ADSCs sheet	Topical administration	II	n = 54 (24/30)	Age 18–80 years; type 1/2 diabetes; ulcer history > 4 weeks; size 1–25 cm[2]; Wagner 1–2; detectable perfusion (ABI 0.7–1.3 or $TcPO_2$ > 30 mmHg)	> 30% wound size change in 1 week; infection; HIV; HbA1c > 15%; glucose > 450 mg/dL	12 weeks	15	Randomized; single-blinded	High	Improved closure rate (73% vs 47% at week 8; 82% vs 53% at week 12); Reduced healing time (28.5 vs 63.0 days for the Kaplan-Meier median times)	[29]

(*Continued*)

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Table 1 (Continued).

Disease/ Indication	Intervention	Delivery Method	Phase	Enrollment	Inclusion Criteria	Exclusion Criteria	Follow-Up	Loss of Follow-Up	Randomization & Blinding	Risks of Bias	Key Outcome	Ref
Diabetic foot ulcer	Allogenic ADSCs in fibrin gel	Topical administration	\	47 (23/24)	Age >18; ulcer 1–25 cm[2]; HbA1c <11%; $TcPO_2$ ≥ 30 mmHg or tibial pressure ≥ 50 mmHg	Non-diabetic etiology; size >25 cm [2]; HbA1c ≥ 11%; severe ischemia ($TcPO_2$ <30 mmHg or arterial pressure on the distal tibial arteries <50 mmHg); infection; allergy to thrombin; active venous thrombosis; contralateral ulcer; acute systemic disease; recent cancer treatment	\	1	Non-randomized; non-blinded	High	Faster time to 50% healing; more complete healing (7 vs 1 patient)	[30]
Minor diabetic limb amputation	Autologous micro-fragmented adipose tissue	Intralesional injection	\	n = 114 (57/57)	Type 1/2 diabetes; age > 18 years; irreversible digital/forefoot ulcer/gangrene; adequate perfusion (TcPO2 ≥30 mmHg, ABI ≥0.7, pressure index finger/arm toe/brachial index ≥ 0.6); triphasic/biphasic Doppler waveforms	Active malignancy (past 5 years); corticosteroid therapy; active vascular issues; inadequate lower extremity perfusion	6 months	7	Randomized; non-blinded	High	Improved healing rate (80% vs 46% (P = 0.0064)); improved skin tropism; no pain reduction	[31]

Post-surgery scar	Autologous SVF-gel	Intradermal injection	\	n = 16 (self-controlled)	Females 18–60 years with mild/moderate breast hypertrophy requiring reduction.	Keloid history; allergy; diseases affecting wound healing; moderate and severe breast hyperplasia/cancer; hormone/chemotherapy; non-compliance	6 months	1	Double-Blind; randomized	Low	Reduced scar formation (VSS: 3.80 ± 1.37 vs 5.25 ± 1.18; VAS: 3.37 ±1.25 vs 4.94 ± 1.28); Improved aesthetic parameters (observed by Antera 3D camera).	[32]
Post-surgery scar	Autologous fat/nanofat grafting	Subcutaneous injection	\	45 (15/15/15)	Age 18–55 years; no additional diseases; no smoking history		6 months	0	Randomized; non-blinded (reviewer blinded)	High	Improved VSS score (except scar height); lower VAS score	[33]
Postsurgical scar	Autologous SVF	Intradermal injection	\	40 (self-controlled)	Females; age 18-60	Breast surgery with 1 year; oncologic history; psychiatric condition; systemic disease that will impair wound healing; smoking; pregnancy or active desire to become pregnant; carcinogen exposure; HRT	6 months & 1 year	9	Randomized; double-blinded	High	Improved scar appearance at 6 months (POSAS); no difference at 12 months; no photographic/histologic improvement	[34]
Acne scar	Autologous SVF	Intradermal injection	\	7 (self-controlled)	Age 18–70 years with clinical acne scars	Bleeding disorders; anticoagulants/steroids consumption; Hb< 10 g/dL; platelets < 150 x 10[3]/μL; active infection; malignancy or history of chemotherapy; breastfeeding or pregnancy; recent analgesics	3 months	0	Single-Blind; randomized	High	Improved dermal and skin thickness	[35]

(*Continued*)

Table 1 (Continued).

Disease/ Indication	Intervention	Delivery Method	Phase	Enrollment	Inclusion Criteria	Exclusion Criteria	Follow-Up	Loss of Follow-Up	Randomization & Blinding	Risks of Bias	Key Outcome	Ref
Acne scar	Autologous adipose ECM/ SVF-gel	Intradermal and subcutaneous injection	\	11 (self-controlled)	Age 16–40; Fitzpatrick III–IV; moderate to severe acne scars	Mental disorders; pregnancy; isotretinoin (3 months); recent laser/peeling (8 weeks)	24 weeks	1	Randomized; non-blinded (assessor-blinded)	High	Great improvement in in ECCA score (−60.25 vs − 43.25, $P < 0.001$) and scar volume (−33.17% vs −19.69%, $P = 0.004$) vs CO_2 laser	[36]
Post-acne scar	Autologous ADSCs	Intradermal injection	\	10 (self-controlled)	Bilateral facial acne scarring	Active acne; systemic retinoid (past 12 months); skin infection; dark skin types (V, VI); prior scar treatment; pregnancy; lactation in females; skin disease; laser complication; blood dyscrasias.	3 months	0	Non-randomized; non-blinded (reviewer blinded)	High	One ADSC injection comparable to three CO_2 laser sessions	[37]
Mature pediatric burn scar	Autologous fat grafting	Intralesioanl injection	\	n = 9 (self-controlled)	Pediatric patients with mature burn scars; age < 21 years; assent capability	Significant comorbidities; ASA > II	6-12 months	1	Randomized; double-blinded	Low	No significant scar improvement	[38]

Notes: *Numbers in parentheses represent patient allocation, with the value before the slash indicating the control group and the value after the slash representing the treatment group.

Abbreviations: PAD, peripheral arterial disease; ABI, ankle-brachial index; Hb, haemoglobin; BMI, body mass index; NRS, numeric pain rating scale; SVF, stromal vascular fraction; VLU, chronic leg ulcers of venous; AVLU, chronic leg ulcers of arterial-venous; INR, international normalized ratio; EWMA, European wound management association; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum-beta-lactamase; PRP, platelet-rich plasma; ADSCs, adipose tissue-derived stem cells; CPD, chronic pulmonary disease; $TcPO_2$, transcutaneous oxygen pressure; HIV, human immunodeficiency virus; HbA1c, haemoglobin A1c; VSS, Vancouver scar scale; VAS, visual analogue scale; HRT, hormone-replacement therapy; POSAS, patient and observer scar assessment scale; ECM, extracellular matrix; ECCA, Echelle d'Evaluation Clinique des Cicatrices d'acne; ASA, American society of anesthesiologist.

enhanced wound healing, attenuated scar formation, or improved existing scars, whereas two studies found no significant benefit relative to controls. Among the two low-bias trials, one demonstrated that autologous SVF gel significantly reduced post-mammoplasty scarring, whereas the other reported no significant improvement in mature pediatric burn scars following autologous fat transplantation.[32,38] Collectively, current clinical evidence supports the safety and therapeutic potential of ADSC-based interventions for chronic wound healing and scar modulation. Allogeneic ADSC transplantation has also demonstrated comparable safety and efficacy, thereby broadening clinical applicability. Nevertheless, given the predominant high risk of bias and limited sample sizes of low-bias studies (n = 16 and n = 9), large-scale, rigorously designed, double-blind randomized controlled trials are imperative to definitively establish the efficacy and safety of ADSC-based therapies in wound healing.

MSC-EVs as Cell-Free Therapeutics

EVs are lipid-bilayer vesicles ubiquitously released by virtually all cell types. Three principal EV subtypes, classified by biogenetic pathways, include exosomes, microvesicles, and apoptotic bodies (Figure 1).[39] The biogenesis of exosomes involves through three distinct stages.[40] Initially, the plasma membrane undergoes invagination to form early endosomes. These early endosomes then mature into multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs) through inward budding of the endosomal membrane. Finally, ILVs are released as exosomes via fusion of MVB with the plasma membrane. In contrast, microvesicles originate directly from the outward budding of the plasma membrane, while apoptotic bodies are generated during the fragmentation of apoptotic cells.[41] Among these three types of EVs, exosomes have been the most extensively studied. However, current isolation protocols often yield heterogeneous mixtures of exosomes and small microvesicles (size < 200 nm).[42] In this study, we use the term "EVs" to refer specifically to these mixed populations. "MVs" denotes larger microvesicles, which, according to the cited literature, are pelleted by centrifugation at 13,000 x g. "ApoBDs" refers to apoptotic bodies, which, based on the referenced studies, are generated by cells upon staurosporine-induced apoptosis.[43,44]

EVs are composed of lipids, proteins and nucleic acids (Figure 1). MSC-EVs express a variety of characteristic proteins, including ALG-2-interacting protein X (Alix), membrane transport proteins (annexin and Rab GTPase), tetraspanins (CD63, CD9 and CD81), major histocompatibility complex I/II (MHC I/II) and heat-shock proteins (HSP70).[45] Additionally, they carry a diverse array of bioactive molecules inherited from the donor cells, such as growth factors, enzymes, and RNAs. These bioactive molecules can be delivered to recipient cells within the wound bed via MSC-EV uptake, thereby improving re-epithelialization, promoting angiogenesis, and suppressing inflammation.[46,47]

Given that MSC-EVs exhibit regulatory functions comparable to those of MSCs, they are increasingly recognized as a promising cell-free alternative for MSC-based therapies.[48] Table 2 provides a detailed comparative analysis of the

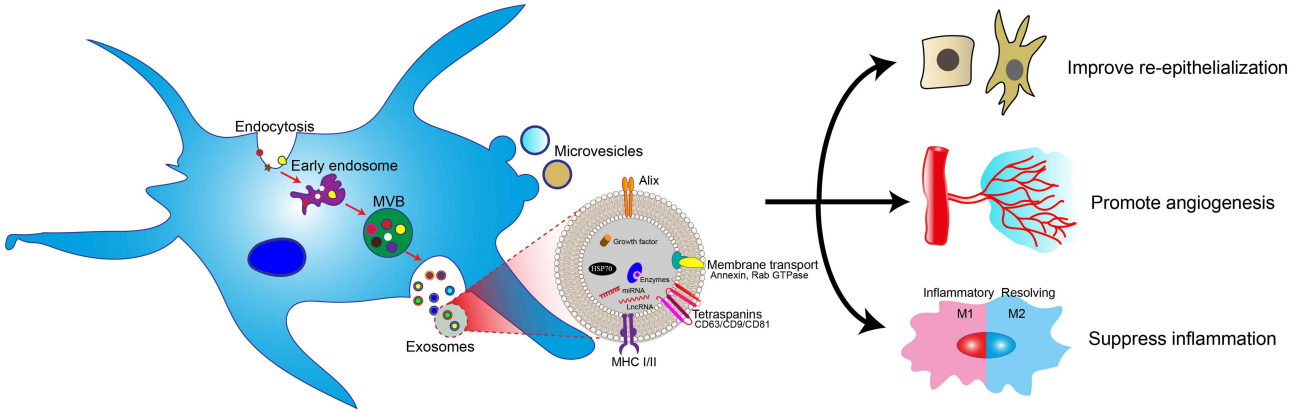

Figure 1 Schematic illustration of the biogenesis, composition, and regenerative function of MSC-EVs. Micovesicles are generated through direct outward budding of the plasma membrane, while exosomes are released via fusion of MVBs with the plasma membrane. MVBs are formed from early endosomes, which originate through invagination of the plasma membrane during endocytosis. MSC-EVs are composed of a lipid bilayer membrane and express a variety of proteins, including Alix, Annexin, Rab GTPase, tetraspanins (CD63, CD9, CD81) and MHC I/II. They also carry bioactive cargo, such as HSP70, growth factors, enzymes, and nucleic acids. MSC-EVs promote tissue regeneration by improving re-epithelialization, promoting angiogenesis, and suppressing inflammation.

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Table 2 The Advantages of MSC-EVs Over MSCs in the Context of Therapeutic Development

	MSCs	MSC-EVs
Contents	Difficult to characterize	Easier to characterize than MSCs (with established databases available to provide detailed information on their composition)[49]
Stability	Potency fluctuates with cell viability; sensitive to production/administration variables[50]	Consistent potency when properly processed/stored[51]
Storage & shipping	Requires stringent conditions; environmental fluctuations affect potency; cryopreservation may alter functionality[52]	Tolerates cryopreservation; lyophilization enables ambient-temperature shipping[53]
Cost	High cost for production, cryostorage, shipping, and administration[54]	Cost reduction possible via preconditioning (eg Low-intensity pulsed ultrasound enhances both yield and potency)[55]
Administration	Limited delivery routes[50]	Support non-invasive routs (nebulization, intranasal)[56,57]
Biodistribution	Active homing to the focal	Penetrate biological barriers; amenable to targeted engineering approaches[58]
Risks	Risk of immune rejection[59]	No immunogenic; minimal risk of malign transformation[59]

advantages of MSC-EVs over MSCs in the context of therapeutic development. The superior characteristics of MSC-EVs, including ease of identification,[49] high stability,[50,51] convenient storage and transport,[52,53] cost-effectiveness,[54,55] flexibility in clinical administration routes,[50,56,57] the ability to cross biological barriers and be engineered for targeted delivery,[58] and minimal risk of side effects,[59] make them more readily translatable to clinical applications than MSCs.

The Role of ADSC-EVs in Wound Healing

Wound healing is a dynamically orchestrated physiological process initiated by tissue injury and progresses through four interdependent phases: hemostasis, inflammation, proliferation, and remodeling.[60] Chronic or diabetic wounds often stall in the inflammatory stage, leading to impaired healing. ADSC-EVs have emerged as master regulators of this complex process, actively modulating cellular behaviors across the wound environment (Figure 2).[61] By delivering bioactive cargo to keratinocytes, fibroblasts, endothelial cells, and macrophages, ADSC-EVs accelerate re-epithelialization, induce angiogenesis, resolve pathological inflammation, and mitigate aberrant fibrosis. This multifaceted intervention strategy positions ADSC-EVs as a highly promising therapeutic platform for the treatment of recalcitrant wounds.

ADSC-EVs Modulate Immune Microenvironment

Inflammation exerts a dual role in wound healing, intricately regulated in a dynamic manner.[62,63] In the early stages of wound formation, a well-balanced inflammatory response is essential for effectively eliminating pathogens and necrotic tissue, thereby establishing a sterile environment conducive to tissue repair. However, as the healing process progresses, the timely resolution of inflammation becomes a critical juncture for initiating tissue regeneration and remodeling. In pathological conditions such as diabetes, the inflammatory response becomes abnormally prolonged, giving rise to a persistent pro-inflammatory state that ultimately impedes the repair process. Within this context, the dysfunction of core immune effector cells, particularly neutrophils and macrophages, emerges as a central cellular mechanism underlying the impaired healing of chronic wounds. Recent research has indicated that ADSC-EVs possess the capacity to remodel the wound inflammatory microenvironment by modulating these immune cells, thereby overcoming the state of healing stagnation.

Macrophages function as the central orchestrators of wound repair, with their dynamic phenotypic transition (M1→M2) precisely coordinating the progression of healing.[62] In the early phase, M1 macrophages secrete pro-inflammatory cytokines, vigorously eliminating pathogens and cellular debris.[64] In the later phase, M2 macrophages

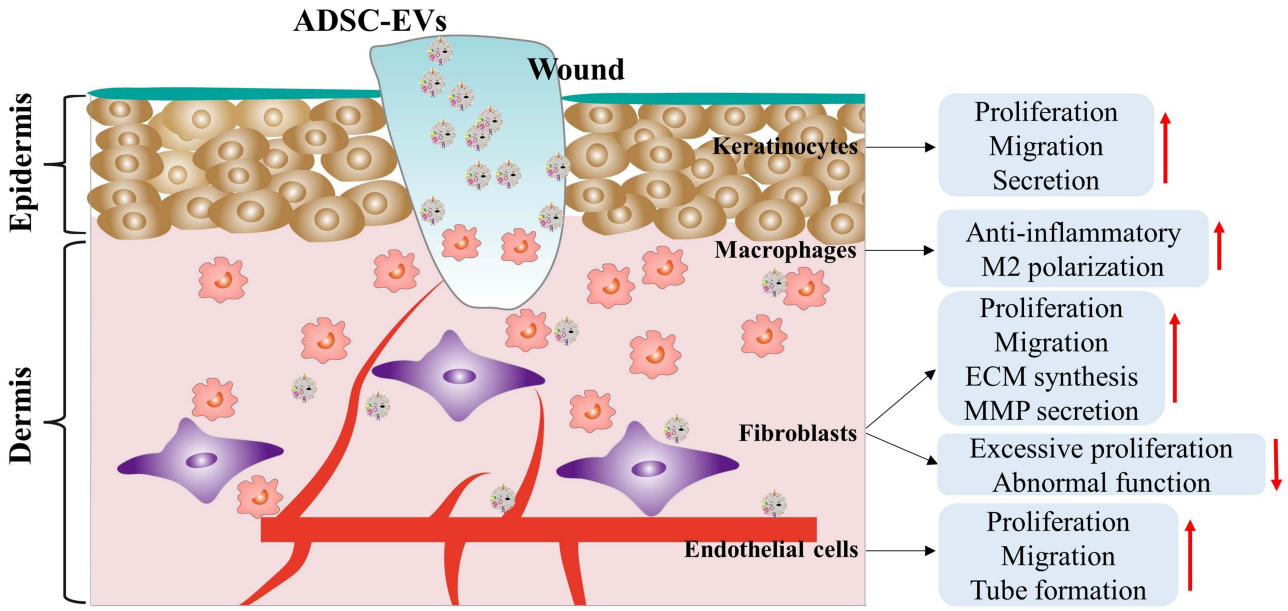

Figure 2 ADSC-EVs function as multi-target regulators to orchestrate wound healing. They accelerate tissue regeneration through: stimulating keratinocytes to drive proliferation, migration, differentiation, and paracrine secretion; activating fibroblasts to promote proliferation, migration, ECM synthesis, and matrix metalloproteinase (MMP) secretion; enhancing endothelial function via enhancing proliferation, migration, and tube formation; inducing macrophage M2 polarization and promoting anti-inflammatory cytokine release; and suppressing pathological fibroblast activity by inhibiting over proliferation and abnormal function (upward red arrow indicating promotion, downward red arrow indicating inhibition). Collectively, these actions restore tissue integrity by accelerating re-epithelialization and angiogenesis while resolving inflammation and preventing scar formation.

release anti-inflammatory cytokines, driving angiogenesis and collagen remodeling. The core defect in chronic wounds lies in the retention of macrophages in the M1 phenotype, which prevents the resolution of inflammation and blocks the transmission of repair signals. ADSC-EVs can reverse this imbalance through macrophage modulation. For instance, Yin et al discovered that ADSC-EVs promote M2 macrophage polarization via their cargo circRps5, which regulates miR-124-5p.[65] Similarly, Li et al demonstrated that the long non-coding RNA (lncRNA) H19 carried by ADSC-EVs facilitates M2 polarization by modulating miR-130b-3p.[66] Beyond altering polarization, ADSC-EVs also regulate macrophages to release pro-repair factors. Wang et al discovered that ADSC-EVs promote the release of Interleukin-33 (IL-33) from macrophages, thereby modulating M2 polarization and enhancing wound repair.[67] Hsu et al reported that ADSC-EVs induce monocytes/macrophages to secrete transforming growth factor-β1 (TGF-β1), activating the TGF-β/Smad3 signaling pathway to promote healing.[68] Hypoxic preconditioning is a common strategy to enhance MSC-EV yield and efficacy.[69] Hypoxia-induced ADSC-EVs deliver circ-Snhg11 to regulate the miR-144-3p/hypoxia-induced factor-1α (HIF-1α) signaling axis, promoting M2 polarization.[70] Additionally, ADSC-EVs serve as delivery vehicles for active factors, modulating macrophages via carried proteins or nucleic acids to facilitate repair. For example, Su et al generated miR-21-5p-enriched ADSC-EVs through miR-21-5p overexpression in ADSCs; these EVs effectively promoted wound healing, reduced inflammatory cytokine expression, and enhanced M2 polarization.[71] Yu et al significantly enhanced M2 polarization and accelerated wound healing by using ADSCs overexpressing thymosin β4 (Tβ4) to generate Tβ4-loaded ADSC-EVs, thereby suppressing inflammation.[72]

Neutrophils, as the first responders to wounds, control infection by releasing antimicrobial peptides and forming neutrophil extracellular traps (NETs).[73] In physiological healing, neutrophils should undergo timely apoptosis and be cleared by macrophages after fulfilling their tasks. However, in diabetic wounds, delayed neutrophil apoptosis and excessive NET release lead to impaired clearance. ADSC-EV therapy can reduce neutrophil numbers at wound sites, thereby promoting diabetic wound healing.[74] Beyond macrophages and neutrophils, other immune cells also contribute to the healing network. For instance, increased mast cell degranulation correlates with impaired diabetic wound healing.[75] Administration of ADSC-EVs may reduce the proportion of degranulated type 3 mast cells at diabetic wound sites, thereby accelerating the healing process.[74]

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ADSC-EVs Promote Tissue Regeneration

The proliferation phase is a critical stage in wound healing, encompassing pivotal physiological processes including granulation tissue formation, re-epithelialization, neovascularization, collagen deposition, and wound contraction.[76] The phase requires coordinated action of multiple cell types, such as fibroblasts, keratinocytes and endothelial cells.[63] In chronic wounds, however, persistent inflammation or hypoxia severely impair cellular functionality, disrupting the proliferative phase.[77] ADSC-EVs promote the proliferation, migration and functional recovery of these cells under pathological conditions, thereby accelerating wound healing and facilitating the resolution of refractory wounds.

Fibroblasts, as essential players in wound healing, are recruited to the wound site during the inflammation-resolution transition.[78] They secrete matrix metalloproteinase (MMPs) to degrade fibrin clots and produce extracellular matrix (ECM) components that replace provisional matrices.[79] The resulting ECM not only supports fibroblast migration and activity, but also provides a structural and signaling foundation for angiogenesis, granulation tissue formation, and epithelialization.[80] ADSC-EVs have emerged as potent regulators of fibroblast function, facilitating wound healing through multiple mechanisms. In 2016, Hu et al first reported that ADSC-EVs could optimize fibroblast characteristics by promoting their proliferation and migration, and by upregulating the expression of several genes, including collagen type I and type III, neuro-cadherin, proliferating cell nuclear antigen (PCNA) and cyclin D1, thereby accelerating wound healing.[81] In 2021, Wang et al demonstrated that ADSC-EVs could enhance the proliferation and migration of human fibroblasts and promote collagen deposition via the phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B (Akt) signaling pathway.[82] Given the presence of the inflammatory stimulation and hypoxia in chronic wounds, the regulatory effects of ADSC-EVs on fibroblasts under these conditions have also been explored. Heo et al reported that ADSC-EVs were able to suppress the inflammatory response of fibroblasts stimulated by interferon gamma (IFNγ) and tumor necrosis factor α (TNFα).[83] Patel et al further demonstrated that ADSC-EVs counteract the adverse effects of hydrogen peroxide and lipopolysaccharide on fibroblasts by transporting lncRNA GAS5 and regulating Toll-like receptor 7 (TLR7).[84]

Keratinocytes are the predominant cells in the epidermis, playing a crucial role in wound healing. Upon injury, they reestablish an epithelial barrier through coordinated cell migration, proliferation and differentiation.[85] Moreover, keratinocytes secrete various factors that promote re-epithelialization, stimulate angiogenesis and enhance the production of connective tissue matrix. Accumulated evidence indicates that ADSC-EVs can promote the proliferation and migration of keratinocytes.[86] For instance, Zhang et al demonstrated that ADSC-EVs enhance HaCaT cell migration by activating the AKT/HIF-1α signaling pathway.[75] Similarly, Lv et al found that ADSC-EVs facilitate HaCaT cell proliferation and migration via the Wnt/β-catenin signaling pathway.[87] Notably, the overexpression of miR-21-5p in ADSC-EVs further intensifies this regulatory effect. In addition to these findings, ADSC-EVs have been shown to augment the regulatory capacity of keratinocytes. Ren et al reported that ADSC-derived MVs upregulate the expression of VEGF-A, vascular endothelial growth factor receptor 2 (VEGFR2), α-SMA and fibronectin in HaCaT cells, thereby accelerating wound healing through enhanced angiogenesis and re-epithelialization.[42] Similar to fibroblasts, keratinocytes in chronic wounds are often subjected to inflammation and hypoxia, which can impair their function. The impact of ADSC-EVs on keratinocytes under these conditions has also been investigated. Ma et al observed that hydrogen peroxide suppresses HaCaT cell proliferation and migration while promoting apoptosis.[88] However, treatment with ADSC-EVs effectively reversed this detrimental effect. He et al further demonstrated that ADSC-EVs counteract the inhibitory effects of hydrogen peroxide on HaCaT cell proliferation and migration by transporting MALAT1 to target miR-124 and activate the Wnt/β-catenin signaling pathway.[89]

The microvasculature at the wound site supplies essential nutrients and oxygen, supporting cell proliferation and differentiation, thereby facilitating wound healing. However, in non-healing wounds, such as those associated with diabetes and certain chronic conditions, angiogenesis is severely impaired.[90] Endothelial cells are pivotal in driving angiogenesis.[91] Accumulative evidence indicates that ADSC-EVs can modify endothelial cells, enhancing their proliferation, migration and tube formation capabilities during wound healing.[92,93] For instance, Sun et al reported that ADSC-EVs significantly promote the proliferation, migration and tube formation of human umbilical vein endothelial cells (HUVECs).[94] Further mechanism studies revealed that elevated expression of EGR-1 in ADSC-EVs activates the keratin pseudouridine synthase 1 (DKC1)/VEGF-A axis by upregulating lncRNA-SENCR in HUVECs, thereby enhancing

angiogenesis and facilitating wound healing. Heo et al demonstrated that ADSC-EVs can facilitate the proliferation and tube formation of HUVECs and upregulate multiple pro-angiogenic genes by transporting miR-132 and miR-146a.[95] In diabetic wounds, endothelial cells are compromised by high glucose levels and oxidative stress. High glucose condition could impair HUVEC migration and tube formation and downregulate angiogenic genes.[96] Treatment with ADSC-EVs can reverse these impairment by reducing reactive oxygen species (ROS) production and protecting mitochondrial function through the sirtuin 3 (SIRT3)/superoxide dismutase 2 (SOD2) pathway.[96] Oxidative stress induced by hydrogen peroxide can trigger HUVEC apoptosis and abolish their migratory capacity.[97] ADSC-EVs released from MMP-degradable polyethylene glycol (PEG) hydrogels can significantly alleviate the hydrogen peroxide-induced oxidative stress in HUVECs, thereby promoting diabetic wound healing.[97]

ADSC-EVs Prevent Scar formation

During wound healing, excessive fibroblast proliferation and dysfunction, combined with disordered collagen deposition, frequently result in hypertrophic and keloid scars.[98] These pathological scars cause adverse effects, including pain, pruritus, and aesthetic concerns, that significantly impair patients' psychological well-being and quality of life.[99]

ADSC-EVs mitigate scar formation by regulating fibroblasts.[100] Hu et al demonstrated that ADSC-EVs optimize fibroblast function, enhancing collagen I/III synthesis during early healing while suppressing late-stage collagen expression to minimize scarring.[81] Subsequently, the same group reported that ADSC-EVs promote ECM remodeling by increasing the collagen type III:I ratio, further reducing scar formation.[101] Chen et al showed that ADSC-EVs downregulate miR-181a to activate SIRT1 in hypertonic scar fibroblasts, reducing collagen and α-SMA expression.[102] In vivo studies confirmed that ADSC-EVs decrease collagen deposition in murine wounds and exhibit superior anti-scarring effects compared to EV-free ADSC secretome, including attenuated collagen accumulation and myofibroblast aggregation.[103]

MicroRNAs are pivotal mediators of ADSC-EVs effects. Li et al identified miR-192-5p in ADSC-EVs as an inhibitor of IL-17RA in fibroblasts, suppressing collagen deposition, myofibroblast differentiation, and hypertonic scarring.[104] Liang et al revealed that ADSC-EV-derived miR-128-1-5p targets the TGF-β1/Smad axis, inhibiting TGF-β1, Smad2/3 phosphorylation, and fibrosis markers (α-SMA and collagen I).[105] This mechanism attenuates myofibroblast differentiation and collagen deposition, ultimately mitigating scar fibrosis in diabetic wounds.

Anti-scarring efficacy can be enhanced through delivery optimization. Wang et al embedded ADSC-EVs in multifunctional pH-responsive hydrogel, improving diabetic wound healing with accelerated re-epithelialization, angiogenesis, collagen organization, and reducing scarring.[92] Zhou et al reported that intravenous ADSC-EV administration augments topical therapy, yielding well-organized collagen fibers and narrower scar width.[106]

ADSC-EVs also serve as miRNA delivery vehicles. In murine scald models, miR-29a-loaded ADSC-EVs inhibited scarring by suppressing the TGF-β2/Smad3 pathway.[107] Meng et al delivered miR-141-3p-enriched ADSC-EVs via dissolvable microneedle arrays, reducing hypertonic skin thickness in rabbit ears and downregulating α-SMA, COL-1, fibronectin, TGF-β2, and p-Smad2/3.[108]

ADSC-derived ApoBDs (ADSC-ApoBDs) similarly regulate scarring. Yan et al reported that ApoBDs derived from young and aged ADSCs both reduce scar formation in a rat skin defects, with young ADSC-ApoBDs showing superior wound closure and scar minimization.[43]

ADSC-EVs Promote Diabetic Wound Healing

Diabetic wounds, the most prevalent chronic wounds, present a significant clinical challenge due to their increasing global prevalence and refractory nature.[109] These wounds are characterized by sustained inflammation, oxidative stress, and neuropathy, rendering conventional therapies largely ineffective.[110] Hence, developing novel treatments targeting multiple pathological pathways is essential.

Recent studies demonstrate that ADSC-EVs effectively promote the diabetic wound regeneration by restoring skin cell functionality and modulating the immune microenvironment. Li et al were the first to demonstrate that ADSC-EVs enhance the proliferation and angiogenesis of endothelial progenitor cells (EPCs) under high-glucose conditions, highlighting their therapeutic potential for diabetic wound healing.[111] Song et al further revealed that ADSC-EVs can

stimulate the proliferation and migration of HaCaT cells, as well as the proliferation and tube formation of HUVEC cells, collectively accelerating the healing process of diabetic wounds.[112] In addition, ADSC-EVs have been shown to regulate fibroblast function to prevent scar formation in diabetic wounds. This is achieved through the delivery of miR-128-1-5p, which modulates the TGF-β1/Smad signaling pathway.[105] Moreover, Yin et al discovered that circRps5 carried by ADSC-EVs promotes the M2 polarization of macrophages by regulating miR-124-5p, thereby resolving inflammation.[65] These findings collectively illustrate the multifaceted therapeutic mechanism of ADSC-EVs in diabetic wound management.

Preconditioning strategies are extensively utilized to enhance both the yield and therapeutic efficacy of MSC-EVs.[113] In the context of diabetic wound healing, methods such as hypoxia and low-intensity ultrasound stimulation have been employed to enhance the performance of ADSC-EVs. Hu et al demonstrated that hypoxia-conditioned ADSC-EVs embedded in gelatin methacryloyl (GelMA) hydrogel could accelerate diabetic wound healing by delivering circ-Snhg11.[114] This exosomal circ-Snhg11 targets the miR-144-3p/NFE2L2/HIF1α pathway, thereby promoting the migration, proliferation and tube formation of vascular endothelial cells. In 2024, two additional research groups reported that hypoxia-pretreated ADSC-EVs had superior potential for diabetic wound healing compared to normoxia-pretreated ADSC-EVs by delivering circRNAs, including circ-IGF1R and circ-Erbb2ip.[115,116] Detailed mechanistic investigations revealed that circ-IGF1R facilitates angiogenesis by modulating the miR-503-5p/HK2/VEGFA axis, while circ-Erbb2ip enhances angiogenesis and mitigates ROS and inflammatory responses by regulating the miR-670-5p/Nrf1 pathway. Beyond hypoxia, low-intensity ultrasound stimulation has been shown to stimulate the secretion of ADSC-EVs and enhance their biological functions.[117] According to nanoparticle tracking analysis (NTA), ultrasound stimulation of ADSCs at a parameter of 1.5 W/cm^2 for 30s resulted in a 45-fold increase in EV secretion. Furthermore, these stimulated ADSC-EVs were found to be enriched in wound healing-related miRNAs and accelerated diabetic wound healing in vivo through the promotion of cell proliferation, keratinocyte differentiation and migration, re-epithelialization, collagen deposition, and angiogenesis.

ADSC-EVs also act as versatile delivery vehicles for functional proteins or RNAs, enhancing diabetic wound healing. Li et al overexpressed nuclear factor erythroid 2-related factor 2 (Nrf2) in ADSC-EVs to boost their therapeutic efficacy.[111] Using a murine diabetic wound model, they demonstrate that Nrf2-overexpressing ADSC-EVs significantly reduced ulcerated areas. This effect resulted from increased granulation tissue formation, angiogenesis, and growth factor secretion. Overexpressing Nrf2 could significantly reduce the ulcerated area by increasing granulation tissue formation, angiogenesis and growth factor secretion, combined with reduced inflammatory response and oxidative stress in the wound beds. In a separate study, Shi et al utilized ADSC-EVs to deliver mmu_circ_0000250 for treating diabetic wound.[118] Overexpression of mmu_circ_0000250 in ADSC-EVs restored endothelial progenitor cell function and enhanced angiogenesis in diabetic wounds in vivo by promoting autophagy activation.

In recent years, research focus has expanded beyond EVs from viable ADSCs, revealing that ApoBDs released by apoptotic ADSCs are emerging as promising candidates for diabetic wound repair.[119] Mao et al elucidated that ADSC-ApoBDs potently redirect macrophage polarization toward an anti-inflammatory phenotype, markedly attenuating wound inflammation and stimulating angiogenesis.[44] Critically, mechanistic studies identified miR-20a-5p, a highly enriched functional cargo within ADSC-ApoBDs, as a regulator of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway. By suppressing pathological overactivation of this pathway, miR-20a-5p reshapes the wound immune microenvironment, establishing conditions conducive to healing. This work not only deciphers a fundamental reparative mechanism but also paves the way for clinical translation of apoptotic body-based therapies for diabetic wounds.

Beyond standalone applications, ADSC-EVs can also be integrated with functional scaffolds to augment healing effect. The core advantage of the scaffold lies in its spatial anchoring ability, which can locally retain therapeutics and achieve controllably and sustained release, eliminating the need for repeated dosing and extending therapeutic activity.[120,121] Wu et al designed a chitosan hydrogel/ADSC-EV composite dressing, in which ADSC-EVs can be continuously released into the wound microenvironment as the hydrogel degrades gradually, thus prolonging the therapeutic effect.[122] The functional expansion of scaffolds can further enhance therapeutic efficacy. For example, co-loading silver ions and ADSC-EVs into the hydrogel can simultaneously achieve antibacterial effects, clearance of

oxidative stress damaged cells, and establishing a regenerative microenvironment to facilitate wound healing.[123] Targeting the core pathological feature of hypoxia in diabetic wounds, Shiekh et al developed an oxygen-ADSC-EV co-delivery system, OxOband™.[124] This porous cryogel can accelerate wound closure, reduce the risk of infection, enhance collagen deposition, promote rapid re-epithelialization, stimulate robust neovascularization, and alleviate oxidative stress. This strategy of integrating multifunctional materials with ADSC-EVs provides a new paradigm for development customized intelligent wound dressings on demand.

The studies mentioned above underscore the therapeutic promise of ADSC-EVs in diabetic wound repair. Nevertheless, autologous ADSCs isolated from diabetic donors yield EVs (dEVs) with markedly impaired bioactivity. Vuong et al demonstrated that healthy-donor ADSC-EVs (nEVs) robustly promote endothelial survival and neovascularization, whereas dEVs lose these pro-angiogenic properties.[125] Under high glucose conditions, nEVs effectively suppress endothelial–mesenchymal transition (EndMT), while dEVs promote EndMT by activating the TGF-β/Smad3 signaling pathway. This pathological shift drives vascular dysfunction and ultimately delays wound closure. The finding underscores the therapeutic promise of ADSC-EV therapy as a powerful means to compensate for the functional deficit of endogenous diabetic ADSCs.

Conclusion and Perspective

Wound healing remains a significant challenge in both laboratory research and clinical practice. ADSCs and ADSC-EVs have garnered considerable attention due to their accessibility, high abundance, and demonstrated efficacy in promoting wound healing.[12–14] This review summarizes recent advances in the application of ADSCs and ADSC-EVs for wound healing, covering the current status of ADSC-related clinical trials, as well as the molecular mechanisms and representative applications of ADSC-EVs.

Evidence indicates that ADSC-EVs primarily exert their regulatory effects via the delivery of bioactive cargo, including RNAs and proteins (Figure 3). By targeting multiple cell types, including keratinocytes, macrophages, fibroblasts, and endothelial cells, they effectively promote re-epithelialization, suppress excessive inflammation, optimize ECM remodeling, and stimulate neovascularization to accelerate healing. Moreover, strategies such as cellular preconditioning, therapeutic cargo loading, and integration with functional biomaterials may further enhance the therapeutic potential and clinical applicability of ADSC-EVs.

Despite the significant regenerative potential of ADSC-EVs, their clinical translation faces several challenges. First, regarding large-scale production and purification: while bioreactor-based cell expansion coupled with tangential flow filtration (TFF) for EV enrichment is technically feasible, TFF-derived products suffer from insufficient purity and high impurity content.[126–128] These impurities can mask inherent EV functions, alter in vivo pharmacokinetics, and introduce immunogenicity or batch variability, ultimately compromising therapeutic stability and predictability. While alternative methods such as asymmetric flow field-flow fractionation and size-exclusion chromatography can achieve higher purity, their scalability remains limited.[129,130] Second, mechanistic elucidation and heterogeneity present core difficulties: EVs exhibit intrinsic heterogeneity in size, composition, origin, and function across subpopulations.[131] This complexity precludes straightforward bioactivity assessment via single-target mechanisms like small-molecule drugs, fundamentally hindering precise mechanistic understanding, reliable potency standardization, and the development of uniform therapeutic products. Overcoming these hurdles demands advanced sorting technologies, deeper mechanistic studies, and functional potency assays aligned with clinical endpoints.

To date, three clinical trials have evaluated ADSC-EVs for wound management.[132–134] All reported no adverse events, supporting their safety profile. Alinda et al conducted a randomized controlled trial comparing ADSC-conditioned medium (rich in ADSC-EVs) with framycetin gauze dressing for chronic plantar ulcers in leprosy.[132] Treatment with ADSC-conditioned medium significantly reduced mean ulcer area from the second week and mean depth from the third week onward, confirming its therapeutic potential. Estupinan et al compared topical ADSC-EV administration with microneedling-based platelet-rich plasma (PRP) for photoaged facial skin repair.[133] Both interventions improved skin conditions, including wrinkling, dyschromia, erythema, texture, and overall appearance, with topical ADSC-EVs achieving outcomes comparable to PRP microneedling, suggesting a viable alternative. KWON et al incorporated ADSC-EVs into a gel and conducted a double-blind randomized self-controlled trial on acne scar

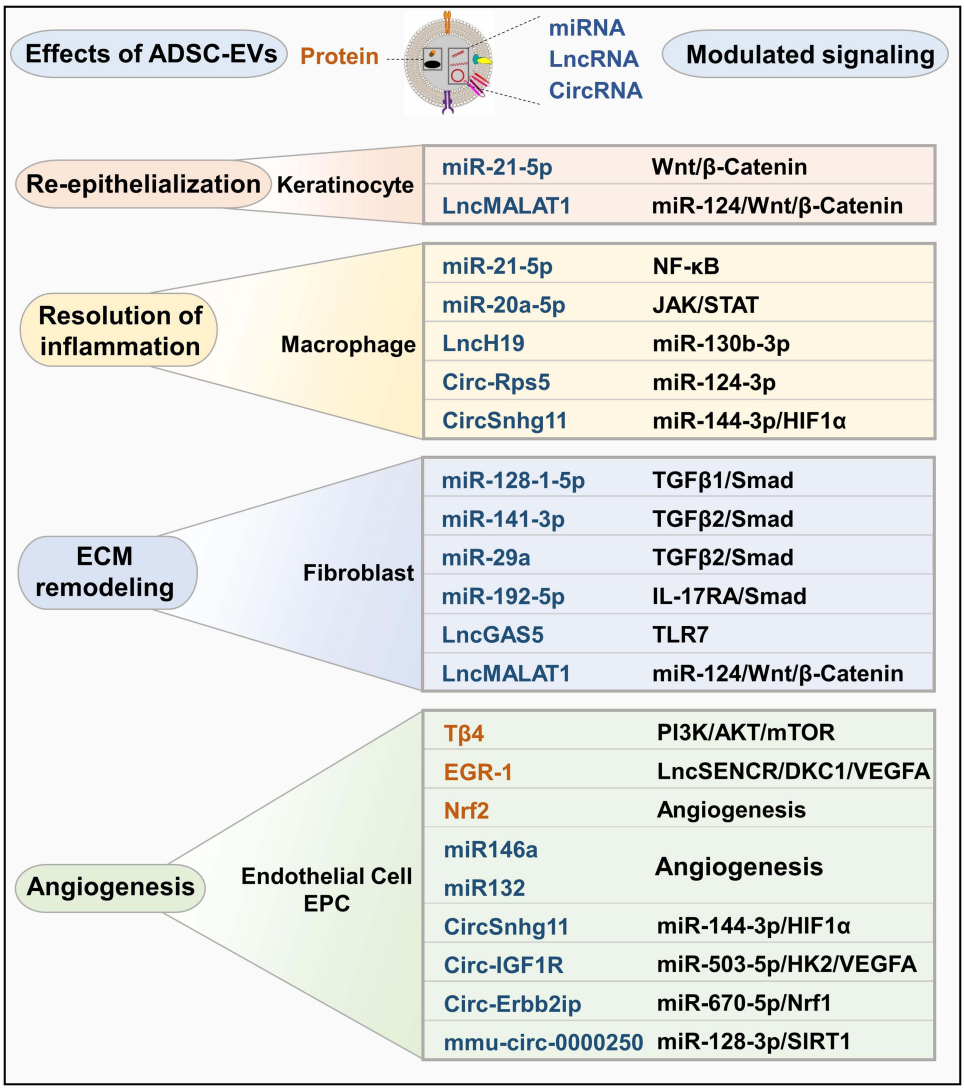

Figure 3 The roles and mechanisms of RNAs and proteins carried by ADSC-EVs in wound healing (RNAs in blue, proteins in Orange). These molecules specifically promote the functionality of keratinocytes, macrophages, fibroblasts, endothelial cells, and endothelial progenitor cells. By doing so, they accelerate re-epithelialization, resolve inflammation, optimize ECM remodeling, and stimulate angiogenesis.

repair.[134] The ADSC-EV gel significantly improved scar status relative to the blank gel, as measured by a reduction in Échelle d'évaluation clinique des cicatrices d'acné scores (32.5% vs 19.9%, $P < 0.01$). Additional trials using ADSC-EVs for chronic wound treatment have been registered on ClinicalTrials.gov. However, existing clinical studies exhibit notable limitations: investigated conditions are relatively specific (eg, leprosy-associated plantar ulcers, photoaged skin, and acne scars), most trials lack double-blind randomized designs (except for the acne scar study), and sample sizes are small (fewer than 50 participants). Future research should prioritize larger, double-blind randomized controlled trials targeting a broader spectrum of chronic wounds, such as diabetic ulcers, to further validate the efficacy and safety of ADSC-EVs.

Abbreviations

ADSCs, adipose-derived stem cells; EVs, extracellular vesicles; MSCs, mesenchymal stem cells; MSC-EVs, mesenchymal stem cells-derived EVs; ADSC-EVs, ADSC-derived EVs; SMA, smooth muscle actin; HSP47, heat shock protein 47; KGF, keratinocyte growth factor; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor; FGF2, fibroblast growth factor 2; Abbreviation: PAD, peripheral arterial disease; ABI, ankle-brachial index; Hb, haemoglobin;

BMI, body mass index; NRS, numeric pain rating scale; SVF, stromal vascular fraction; VLU, chronic leg ulcers of venous; AVLU, chronic leg ulcers of arterial-venous; INR, international normalized ratio; EWMA, European wound management association; MRSA, methicillin-resistant Staphylococcus aureus; ESBL, extended-spectrum-beta-lactamase; PRP, platelet-rich plasma; ADSCs, adipose tissue-derived stem cells; CPD, chronic pulmonary disease; TcPO2, transcutaneous oxygen pressure; HIV, human immunodeficiency virus; HbA1c, haemoglobin A1c; VSS, Vancouver scar scale; VAS, visual analogue scale; HRT, hormone-replacement therapy; POSAS, patient and observer scar assessment scale; ECM, extracellular matrix; ECCA, Echelle d'Evaluation Clinique des Cicatrices d'acne; ASA, American society of anesthesiologist; MVs, microvesicles; MVB, multivesicular body; ILVs, intraluminal vesicles; ApoBDs, apoptotic bodies; Alix, ALG-2-interacting protein X; MHC I/II, major histocompatibility complex I/II; HSP70, heat shock protein 70; long non-coding RNA, lncRNA; Interleukin-33, IL-33; TGF-β1, transforming growth factor-β1; Tβ4, thymosin β4; MMPs, ma rix metalloproteinases; PCNA, proliferating cell nuclear antigen; PI3K, phosphatidylinositol 3-kinase; Akt, Protein Kinase B; IFNγ, interferon gamma; TNF α, tumor necrosis factor α; HIF-1α, hypoxia-induced factor-1α; TLR7, Toll-like receptor 7; VEGFR2, vascular endothelial growth factor receptor 2; α-SMA, α-smooth muscle actin; DKC1, keratin pseudouridine synthase 1; HUVECs, human umbilical vein endothelial cells; ROS, reactive oxygen species; PEG, polyethylene glycol; SIRT3, sirtuin 3; SOD2, superoxide dismutase 2; IL-1β, interleukin 1β; STAT3, signal transducer and activator of transcription 3; IL-10, interleukin 10; NETs, neutrophil extracellular traps; DSPE-PLLA, phosphoethanolamine phospholipid-grafted poly-L-lactic acid; ADSC-ApoBDs, ADSC-derived ApoBDs; EPCs, endothelial progenitor cells; RSFs, skin fibroblasts; NTA, nanoparticle tracking analysis; Nrf2, nuclear factor erythroid 2-related factor 2; JAK, Janus kinase; STAT, signal transducer and activator of transcription; GelMA, gelatin methacryloyl; dEVs, ADSC-EVs derived from diabetic patients; nEVs, ADSC-EVs derived from healthy patients; EndMT, endothelial–mesenchymal transition; TFF, tangential flow filtration.

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Disclosure

The authors declare that there are no competing interests.

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