International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Extracellular Vesicles in Skin: Biological Function and Therapeutic Potential

Siqi Yuan[1–3], Mengyu Jin[1–3], Yanyan Zhang[1–3], Mengting Zhang[4], Minjia Yuan[5], Xiaolei Ding[1–3], Juan Wang[1–3]

[1]Institute of Geriatrics, Affiliated Nantong Hospital of Shanghai University (The Sixth People's Hospital of Nantong), School of Medicine, Shanghai University, Nantong, Jiangsu, People's Republic of China; [2]Joint International Research Laboratory of Biomaterials and Biotechnology in Organ Repair (Ministry of Education), Shanghai University, Shanghai, People's Republic of China; [3]Shanghai Engineering Research Center of Organ Repair, School of Medicine, Shanghai University, Shanghai, People's Republic of China; [4]School of Pharmacy, Fudan University, Shanghai, People's Republic of China; [5]Shanghai Qiran Biotechnology Co., Ltd, Shanghai, People's Republic of China

Correspondence: Xiaolei Ding; Juan Wang, Email xlding@shu.edu.cn; Juanw@shu.edu.cn

Abstract: Extracellular vesicles (EVs) are nanoscale, lipid bilayer-enclosed particles containing bioactive molecules that play crucial roles in tissue homeostasis. These vesicles regulate cellular functions via delivery of protein, lipid, and nucleic acid cargos to target cells, thereby orchestrating essential biological processes, including cellular proliferation, activation, angiogenesis, and immune responses. The past decade has witnessed unprecedented growth in research examining EV functions in cutaneous physiology and pathogenesis. Here, we describe the biogenesis, composition and cellular uptake of EVs, critically highlighting the therapeutic effects and potential mechanisms of EVs from mammalian, plant and bacterial cells in skin diseases, including skin wound healing, hair growth, aging, inflammatory diseases and cancers. In addition, we discuss clinical translation challenges and outline future research directions for advancing EV-based therapeutics in clinical dermatology.

Keywords: extracellular vesicles, wound healing, hair growth, aging, inflammatory skin diseases, skin cancer

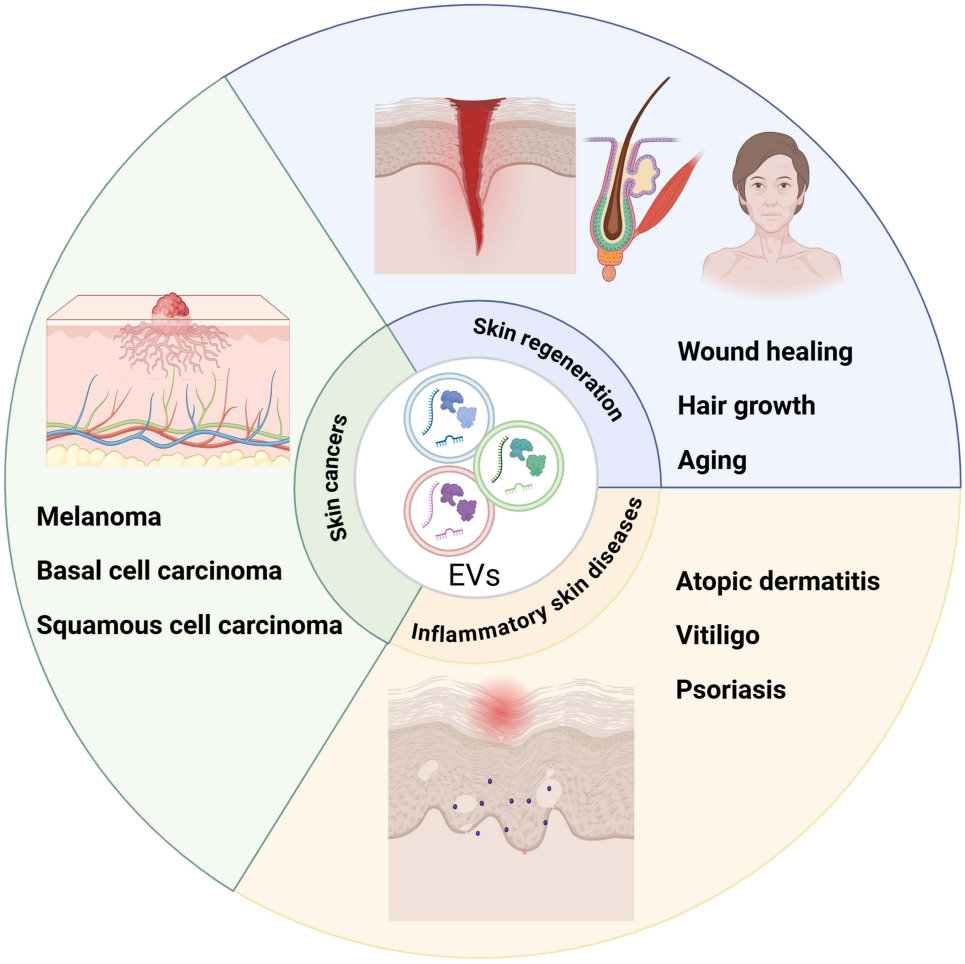
Introduction

The skin serves as a multifunctional barrier organ, performing critical protective roles including prevention of transepidermal water loss, defense against mechanical and environmental insults, thermoregulation, and immune surveillance.[1] This complex organ comprises three distinct anatomical layers: the epidermis, dermis, and hypodermis, each containing specialized cellular populations. The epidermis contains proliferative and differentiated keratinocytes that form the outermost barrier, protecting against external insults and preventing water loss. The dermis primarily houses fibroblasts that provide structural support and confer skin elasticity. The deepest hypodermis predominantly consists of adipocyte-rich tissue. These structures collectively engage in sophisticated intercellular communication networks to preserve tissue homeostasis, the ability to maintain its stable structure and function by resisting stress and remodeling over various scales.[2,3] Perturbations in these regulated homeostatic networks frequently lead to pathological conditions, ranging from impaired wound healing, aging, to inflammatory skin diseases, and even tumors, collectively posing substantial socioeconomic burdens.[4–6] Currently available therapies mainly contain skincare, medicines, surgeries, and cell therapies. However, these strategies often yield only modest, transient benefits and carry side effects,[4] necessitating deeper mechanistic insights and innovative therapeutic approaches.

Extracellular vesicles (EVs) are lipid bilayer-enclosed nanoparticles generated by diverse cell types, including mammalian, plant, and bacteria.[7,8] EVs contain diverse bioactive molecules,[9–11] and may transport these cargos to local tissue microenvironments or distant organs, where they are absorbed by recipient cells to modulate physiological and pathological processes, such as cell proliferation, migration, angiogenesis, and inflammatory responses.[12–15] This highlights their dual roles as both pathogenic mediators and potential therapeutic agents. Due to their nanoscale size and intrinsic targeting capabilities enabled by specific surface markers, EVs have additionally been investigated as carriers for delivery of therapeutic compounds.[16] Given their ubiquitous presence in biofluids, such as blood and urine, EVs also serve as diagnostic and prognostic markers.[17–20]

Received: 23 June 2025
Accepted: 4 September 2025
Published: 13 September 2025

Graphical Abstract



Accumulating evidence has established EVs as pivotal mediators of intercellular communication and promising therapeutic agents in maintaining skin homeostasis and treating cutaneous disorders.[21–23] For instance, we recently demonstrated that EVs derived from *Lactobacillus rhamnosus* GG promoted angiogenesis and re-epithelialization, leading to accelerated skin wound healing.[24] Compared to conventional dermatological therapy, EVs show multiple superior advantages, such as low immunogenicity, multifunctionality, biosafety, and targeted delivery,[25] that confer them as a promising platform for skin therapy.

In this review, we summarize current knowledge on biogenesis, secretion, and uptake of EVs, as well as their crucial roles in skin physiology. We present the latest progress in EV-based therapeutic strategies for skin repair, aging, and disease treatment.

The Biology of EVs

Classification of EVs

EVs are heterogeneous particles, typically cup-shaped or spherical, with diameters ranging from 40 to 1000 nm.[8] According to their dimensions and origins, EVs can be grouped into three types: exosomes, ectosomes, and apoptotic vesicles.[10] Ectosomes, ranging from 100 to 1000 nm in diameter, are formed via plasma membrane outward budding driven by cytoskeletal contraction.[26] Apoptotic vesicles, with diameters ranging from 100 to 2000 nm, are shed by cells during late apoptosis and

encompass cytoplasmic components. Their release is often triggered by cellular stress and activation signals.[27] The exosomes are the smallest EV subtypes, with diameters ranging from 30 to 150 nm, which are mainly derived from endosomal compartments. Unlike mammalian and plant extracellular vesicles (PEVs), bacterial EVs (BEVs) originate through distinct biogenesis pathways. Gram-negative bacteria primarily generate outer membrane vesicles (OMVs) via membrane blebbing or explosive cell lysis, whereas Gram-positive bacteria produce cytoplasmic membrane-derived vesicles (CMVs) primarily via blebbing.[28] Notably, most studies on EVs do not strictly distinguish these subtypes.[7,29] Hence, this review employs the unified term "EVs" to refer to all types of vesicles unless specific subtype identification is warranted.

The Composition and Functional Significance of EVs

EVs house a variety of bioactive compounds such as proteins, lipids, and nucleic acids, which participate in multiple cellular processes.[30] For example, growth factors, such as VEGF, TGF-β and EGF in EVs, directly promote cell proliferation and migration.[31] Meanwhile, tetraspanins-including CD9, CD63, CD81, and TSG101 not only mediate cell adhesion but also function as well-established EV biomarkers.[32–34] The lipid composition of EVs primarily includes ceramide, sphingomyelin, phosphatidylserine, and cholesterol. A distinguishing feature of EVs is their elevated membrane lipid contents compared to their cells of origin, which likely contribute to their structural stability and membrane integrity.[34,35] The nucleic acid components of EVs encompass various molecular species, including DNA, RNA, microRNA (miRNA), circular RNA (circRNA), and long non-coding RNA (lncRNA), which also mediate critical biological functions.[34,36,37] For instance, pluripotent stem cell-derived epidermal organoids were enriched with miRNAs associated with cellular proliferation, migration, and angiogenesis, such as miR-31-5p, miR-146a-5p and miR-191-5p.[38]

The molecular composition of EVs varies significantly based on their cellular origin and the surrounding extracellular environment. This compositional variability is exemplified by serum EVs derived from psoriasis patients, which have elevated miR-199a-3p compared to those from healthy individuals. Notably, miR-199a-3p expression was positively correlated with psoriasis area and severity index score,[39] underscoring the diagnostic value of circulating EVs. Cells or tissues under different culture conditions also generate EVs with distinct cargo profiles. EVs from three-dimensional dermal papilla (DP) spheroids contained elevated levels of pro-hair growth miRNAs compared to those from 2D monolayer cultures, thereby mediating superior hair growth-promoting activity.[40] Collectively, EVs are promising diagnostic biomarkers due to their potential to mirror the physiological or disease conditions of their parent cells.

The Biogenesis of EVs

The generation of EVs primarily involves the formation of intracellular multivesicular bodies (MVBs) and EV secretion[29] (Figure 1). Initially, the plasma membrane undergoes endocytosis to generate cup-shaped early-sorting endosomes (ESEs), which encapsulate cell surface proteins, extracellular constituents, such as lipids and proteins. Following this, the ESEs can merge with existing ESEs or exchange materials with the trans-Golgi network and endoplasmic reticulum, thereby expanding into the late endosomes, where a double invagination occurs and eventually generate MVBs containing intraluminal vesicles (ILVs), which are precursors to EVs.[41] The MVBs are either broken down by lysosomes for recycling or merge with the plasma membrane, secreting ILVs as EVs.[42] This process is controlled by various proteins, notably the endosomal sorting complex required for transport (ESCRT) machinery.[43] The apoptotic cells protrude outward to form apoptotic bodies.

The Uptake of EVs

The mechanisms underlying EV uptake remain incompletely understood.[44] Up to now, three primary pathways have been identified, including direct interaction, membrane fusion, and internalization.[45,46] EVs can directly interact with recipient cells via ligand-receptor binding, triggering downstream signaling cascades and regulating recipient cells. In membrane fusion, the lipid bilayers of EVs and the target cell merge, facilitating direct luminal component release into the cytoplasm. This process initiates with a hemi-fusion stalk formation via the hydrophobic EVs-plasma membrane interactions, which then expands to create a consistent structure. In the case of internalization, EVs are engulfed by the recipient cells, merging with intracellular spaces or endosomal routes to discharge their contents. This intricate process leverages standard endocytic methods, including clathrin-dependent endocytosis, lipid raft-driven endocytosis,

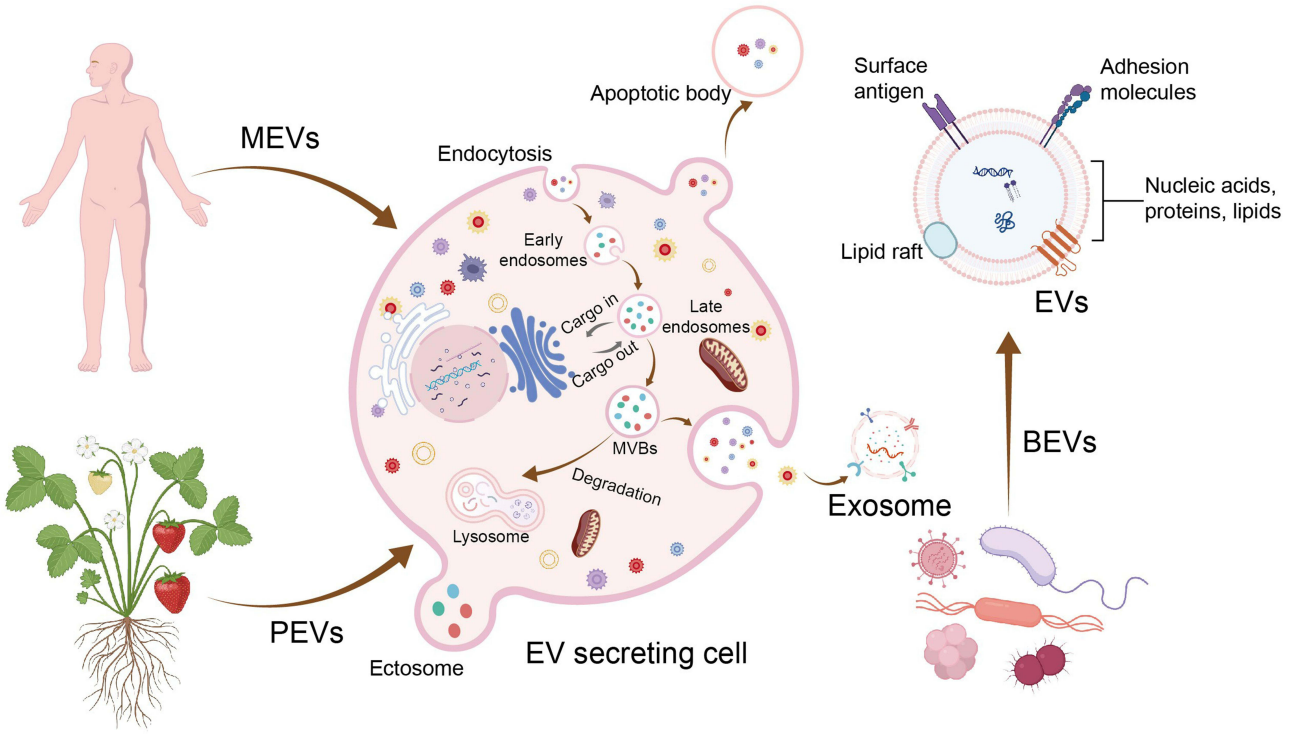


Figure 1 Biogenesis pathways of main EVs. Exosomes initially form through plasma membrane invagination to generate early endosomes, which subsequently mature into late endosomes and ultimately form MVBs. MVBs either fuse with lysosomes to degrade their contents or merge with the plasma membrane to secrete exosomes into the extracellular space. Apoptotic bodies and ectosomes are generated through outward buds.
Abbreviations: BEVs, bacterial extracellular vesicles; MEVs, mammalian extracellular vesicles; MVBs, multivesicular bodies; PEVs, plant extracellular vesicles.

caveolin-aided endocytosis, phagocytosis, and macropinocytosis. Notably, these pathways are not mutually exclusive and may coexist with the same set of EVs, which potentially utilize multiple routes for uptake.

Following uptake, EVs deliver biological information to local or distant target cells via body fluids, influencing gene expression and cellular functions, consequently modulating diverse physiological and pathophysiological processes, including tissue repair, metabolic functions, aging and immune responses.

Biological Functions and Therapeutic Activities of EVs in Skin

EVs are enriched with a variety of bioactive molecules that modulate the functions of recipient cells. This intercellular communication contributes critically to skin homeostasis maintenance. For example, EVs-derived from erythrocytes, a cell type in circulation, can be converted to hair components and promote lipid formation of the skin surface, thereby maintaining cutaneous structural integrity.[47] Consequently, their potential applications in dermatology have attracted considerable attention.[21,48,49] Here, we summarize the latest advances in the role of EVs for skin-related conditions, highlighting their regenerative, hair growth-promoting, anti-aging, anti-inflammatory, and anticancer properties (Table 1).

EVs and Wound Healing

Cutaneous damage and wounds represent major clinical challenges, imposing substantial social and medical burdens.[96] Chronic conditions such as diabetes, ageing or infection, frequently lead to impaired wound healing.[97,98] The wound healing process involves three precisely coordinated stages, mainly inflammation, proliferation, and remodeling.[99] After injury, the vessels contract and initiate blood coagulation program. The immune cells, like neutrophils and macrophages, are quickly drawn to the wound sites to kill pathogens and release cytokines after injury. During the proliferative stage, keratinocytes, endothelial cells, and fibroblasts activate to restore the wound epithelial layer, form new blood vessels (neovascularization), and secrete extracellular matrix (ECM) to seal the wound. Subsequently, the ECM is degraded and remodeled. Dysregulation of cellular activity within the wound microenvironment is the primary factor contributing to delayed healing processes.

Table 1 The Effects of EVs on Skin Physiology and Pathology

Application	Source	Targets or Pathways	Bioactive Cargos	Processes and Effects	References
Wound healing	HUMSCs	ITCH/JUNB/IRE1α	miR-27b	Activate keratinocytes and fibroblasts in vitro, accelerate wound healing in vivo	[50]
		RETNLG, SLC2A3, BCL2A1B	ND	Promote M2 macrophage polarization	[51]
		TLR4-NF-κB	miR-181c	Reduce inflammatory cytokine production	[52]
		Wnt4/β-catenin	ND	Promote angiogenesis	[53]
		PI3K/Akt; ERK1/2	miR-21-3p	Promote angiogenesis and fibroblast function	[54]
	BMSCs	ND	miR-223	Promote M2 polarization of macrophages	[55]
	ADMSCs	ND	ND	Promote M2 polarization of macrophages, activate endothelial cells and fibroblasts, facilitate wound healing in vivo	[56]
		miR-146a/Src	ND	Mitigate endothelial cell senescence, promote angiogenesis, promote wound healing in natural aging and type-2 diabetes mouse wound-healing models	[57]
	White adipose tissues	ND	ND	Promote diabetic wound healing	[58]
	Endothelial cells	YAP, PI3K/Akt/mTOR	ND	Promote fibroblast proliferation, increase microvascular density, collagen deposition, macrophage infiltration	[59]
	Epidermal stem cells	PI3K/ protein kinase B, TGFβ, MAPK	ND	Reduce inflammation, promote M2 polarization of macrophages, activate wound cell proliferation	[60]
	Young fibroblasts	Sirt7	miR-125b	Promote fibroblast transdifferentiation into myofibroblasts	[61]
	Lactobacillus rhamnosus GG	PI3K/AKT	miR-21-5p	Activate keratinocytes and endothelial cells in vitro, accelerate wound healing in excisional wound healing mice model	[24]
	Lactobacillus druckerii	ND	ND	Promote the proliferation of skin cells, new blood vessel formation and wound healing in excisional wound healing mice model	[62]
	Dandelion	*S.aureus* exotoxins	ND	Neutralize *S. aureus* exotoxins, accelerate *S. aureus*-associated wound healing	[63]
Hair growth	DP cells (human and mouse)	Wnt/β/Shh/ TGF-β	miR-140-5p	Accelerate the onset of hair follicle anagen and delay catagen, enhance the proliferation and migration of ORS cells, promote HFSC proliferation and differentiation	[64–66]
	3D-cultured mouse DP cells	Wnt/β-catenin	miR-218-5p	Promote the development of hair follicles	[40]
	Human fibroblasts	Wnt/β-catenin; Axin2, Lef1	ND	Promote the migration, proliferation, and differentiation of ORS cells and elongation of the hair shaft	[67]
	Murine macrophages (RAW264.7)	Wnt/β-catenin, P-AKT	Wnt3a and Wnt7b	Promote the proliferation, migration, and levels of hair-inductive markers of DP cells, increase the hair shaft size in vivo	[68]
	Human ADMSCs	Wnt/β-catenin	Wnt3a	Promote the proliferation of DP and ORS cells, increase hair shaft elongation	[69]
	Skin or hair follicle MSCs-originated apo-EVs	Wnt/β-catenin	ND	Improve skin and hair follicle MSC functions, promote hair growth	[70]

(*Continued*)

https://doi.org/10.2147/IJN.S548986

Table 1 (Continued).

Application	Source	Targets or Pathways	Bioactive Cargos	Processes and Effects	References
Anti-aging	ADMSCs	Src kinase signaling	miR-146a	Alleviate oxidative stress-induced endothelial cell senescence, restore endothelial cell functions, improve photoaging rat phenotypes	[57, 71]
	BMSCs	MMP1	miR-29b-3p	Reverse UVB-induced inhibition on HDF migration and oxidative stress	[72]
	Human dermal fibroblasts	TNF-α/P-AKT/NF-κB, TGF-β	miR-223, miR-133a, miR-196a, TIMP-1	Promote the proliferation and migration of fibroblasts, improve UVB-induced aging phenotype	[73]
Atopic dermatitis	ADMSCs	ND	ND	Reduce pathological symptoms, inhibit the infiltration of inflammatory cells, restore epidermal barrier functions in AD mouse model	[74, 75]
	IFN-γ-primed MSCs	JAK1, STAT6, IL-4/13	ND	Attenuate skin inflammation, alleviate pruritus, and improve barrier function	[76, 77]
	Lactobacillus plantarum	ND	ND	Inhibit the secretion of IL-6, restore the cell viability of keratinocytes, reduce epidermal thickening and the IL-4 level in *S. aureus*-induced mouse AD models	[78]
	Grapefruit	JAK-STAT3/MAPK/PI3K-AKT	Hexosylceramides and ceramides, cis-miR159a-3p	Display anti-inflammatory and antioxidant effects in keratinocytes and macrophages, mitigate DNCB-induced atopic dermatitis	[79]
Vitiligo	Keratinocytes	SOX1, β-catenin	miR-200c	Enhance melanogenesis	[80]
Psoriasis	HUMSCs or IFN-γ-primed HUMSCs	ND	ND	Inhibit the proliferation and activation of keratinocytes, peripheral blood mononuclear cells and T cells in vitro, reduce psoriasis symptoms including thickness, erythema, and scales of skin lesions, exhaust Th17 cells, increase Th2 cells, reduce the enrichment of inflammatory cytokines	[81, 82]
	ESCs	IL-17, C5b-9 complex formation	ND	Inhibit the infiltration of neutrophils and cytokine production in vivo	[83]
	Human gingiva-derived MSCs	ND	ND	Ameliorate murine psoriasis-like skin inflammation, reduce the levels of Th1- and Th17-related cytokines	[84]
	Cutibacterium acnes	ND	ND	Inhibit the proliferation and migration of keratinocytes, inhibit inflammatory factors in vitro, restore microbiota diversity, and alleviate psoriasis symptoms in vivo	[85]
	Staphylococcus Epidermidis ATCC12228 strain	IL-36R	ND	Reduce the characteristic psoriatic skin features, including acanthosis, cellular infiltrate, and IL-6, IL-23, IL-17F and IL-36R expression	[86]
	Parabacteroides goldsteinii	ND	ND	Reduce epidermal hyperplasia, suppress skin inflammation and ameliorate symptoms of psoriasis	[87]
	MSCs-EVs with high PD-L1 expression	PD-L1	ND	Inhibit the activation of various immune cells, reshape the inflammatory ecosystem of psoriasis mouse models	[88]

Melanoma	Human melanoma cells (A375)	CREB and STAT signaling	PD-L1	Promote lipid metabolism and facilitate senescence in T cells	[89]
	Mouse melanoma cells (B16)	VCAM-1, MHC-I	Integrins (α4, α9 and β1), tumor antigens	Induce transcriptional changes and proliferation of lymphatic endothelial cells, promote the apoptosis of CD8+ T cells	[90]
	Ginseng	TLR-4, MyD88	Ceramide lipids and proteins	Promote the M1 polarization of macrophages, increase the apoptosis of melanoma cells, suppress melanoma growth in vivo	[91]
	iPSCs	ND	ND	Enhance dendritic cells-mediated antitumor immunity	
	Natural Killer Cells	PARP	Perforin and FasL	Exert cytotoxic effects on melanoma cells in vitro and in vivo	[92]
	Engineered EVs from HUMSCs loading triptolide	Caspase cascade	ND	Inhibit proliferation, invasion, and apoptosis of melanoma cells in vitro, inhibit tumor growth and extended the survival time in vivo	[93]
Basal cell carcinoma	The blood of metastasis BCC	ND	ND	Promote fibroblast proliferation, migration, and invasion.	[94]
Cutaneous squamous cell carcinoma	M2 macrophage	STEAP3	Circ_0088494	Inhibit Ferroptosis	[95]
	ALA-PDT-treated SCC	ND	ND	Promote dendritic cell maturation	[95]

Abbreviations: ADMSCs, adipose derived mesenchymal stem cells; apo-EVs, apoptotic EVs; BMSCs, bone marrow derived mesenchymal stem cells; DP, dermal papilla; ESCs, embryonic stem cells; HDF, human dermal fibroblast; HFSC, hair follicle stem cell; HUMSCs, human umbilical cord derived mesenchymal stem cells; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stem cells; ND, not determined; ORS, outer root sheath.

Emerging research underscores the promising role of EVs in wound healing through the regulation of cellular behaviors to promote re-epithelialization, angiogenesis, and the restoration of inflammatory responses (Figure 2). Among the most extensively studied EVs in regenerative medicine are those derived from mesenchymal stem cells (MSCs).[100] EVs from

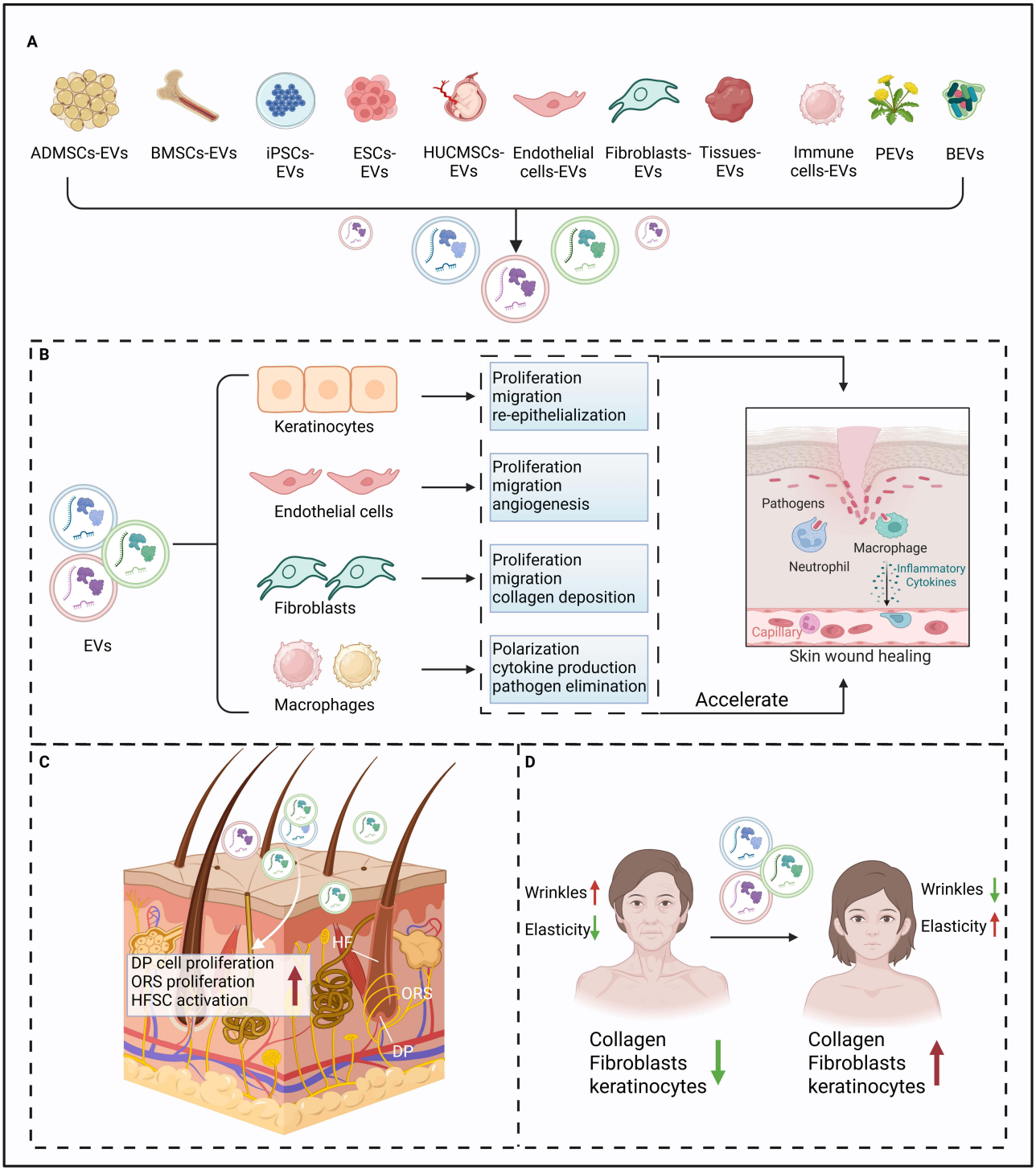


Figure 2 The therapeutic application of EVs in cutaneous medicine and aesthetics. EVs from diverse sources, including MSCs, endothelial cells, fibroblasts, immune cells, tissue extracts, plants, and bacterial cultures (**A**), modulate key regenerative processes in dermatological applications including wound healing (**B**), hair follicle growth (**C**), and skin aging (**D**). Upward red arrows represent promotion; downward green arrows represent repression. Created with Biorender.com.

Abbreviations: ADMSCs, adipose mesenchymal stem cells; BMSCs, bone marrow mesenchymal stem cells; DAMPs, damage associated molecular patterns; DP, dermal papilla; ESCs, epidermal stem cells; HUMSCs, human umbilical cord mesenchymal stem cells; MSCs, mesenchymal stem cells; ORS, outer root sheath. TLR, Toll-like receptor.

human MSCs of the umbilical cord (HUMSCs) activated human keratinocytes and fibroblasts, thus enhanced re-epithelialization and collagen formation, and accelerated cutaneous wound healing in vivo.[50] Since excessive inflammation compromises wound healing processes, a well-regulated inflammatory response is required. EVs from HUMSCs,[52,101] bone marrow MSCs (BMSCs),[55] and adipose MSCs (ADMSCs)[56] have been shown to suppress excessive inflammation by reprogramming pro-inflammatory M1 macrophages into the anti-inflammatory M2 phenotype, thereby accelerating chronic wound healing. Pseudotime analysis of single-cell RNA sequencing further confirmed macrophage differentiation following the application of EVs from HUMSCs, leading to a shift from M1 macrophages to M2a and M2c phenotypes with enhanced anti-inflammatory capacities.[51] Xuan et al identified miR-181c within these EVs as a key mediator of the anti-inflammatory effect, achieved by inhibiting Toll-like receptor 4 (TLR4) signaling in macrophages.[52] Additionally, these EVs activated endothelial cells and alleviated oxidative stress-driven senescence, ultimately enhanced angiogenesis in chronic wounds.[53,54,57,102,103] Notably, EVs derived from white adipose tissue exhibited functions similar to those of ADMSCs-EVs.[58] Apart from MSCs-EVs, EVs produced by other mammalian sources, such as EVs from endothelial cells,[59] epidermal stem cells (ESCs)[60] and young fibroblasts[61] have also been demonstrated to promote the healing of wounds. However, research on the application of PEVs and BEVs in cutaneous wound healing is still scarce. We have revealed the beneficial effects of gut probiotic *Lactobacillus rhamnosus* GG derived EVs in accelerating reepithelization and angiogenesis via activating PI3K/AKT signaling pathway.[24] Especially, probiotic *Lactobacillus druckerii*-derived EVs seemed to have the ability to promote wound regeneration and reduce skin scar formation.[62] However, the potential mechanisms are not clear. The PEVs from *Dandelion* showed anti-virulence activity by binding to *Staphylococcus aureus* (*S. aureus*) exotoxins, thus facilitating *S. aureus* infected wound healing.[63] Due to their promising effects, the therapeutic capabilities of BEVs and PEVs in wound healing merit further investigation in future studies.

Of note, nearly 250 EVs-related clinical trials are documented on ClinicalTrials.gov, spanning both therapeutic and diagnostic applications for multiple disease states, including 9 dedicated to wound healing (ClinicalTrials.gov). A recent Phase I clinical trial (Plexoval II, ACTRN12620000944932) assessed the safety of platelet-derived EVs in wound healing using healthy adult volunteers. Results confirmed a favorable safety profile, however, no significant difference in wound closure time was observed between treated and untreated wounds, which possibly attributed to inherently rapid healing capacity of healthy volunteers, thus the therapeutic efficacy in patients with impaired healing remains to be established.[104] Another clinical pilot study to investigate the therapeutic efficacy of human adipose tissue derived EVs in wound healing has been completed, but the results have not been posted (NCT05475418). Other clinical trials remain primarily in recruitment phases, and no EV-based products have received regulatory approval for wound management.

EVs and Hair Growth

Hair growth is vital for health maintenance, physical appearance, and personal identity.[12,105] Hair growth and regeneration are fueled by hair follicle stem cells (HFSCs) situated at the outer layer of the follicle called bulge, cycling between activation and dormancy.[106–109] Correspondingly, the hair follicles undergo three consecutive phases of rest (telogen), growth (anagen), and regression (catagen).[110] During telogen, HFSCs receive inhibitory signals, such as bone morphogenetic proteins (BMPs) produced by DP cells and remain quiescent. Upon entry into anagen, activation signals such as Wnt and Shh overwhelm inhibitory signals, leading dormant HFSCs to exit quiescence. Then, the HFSCs divide asymmetrically to produce transient amplifying cells, which generate hair matrix and sheath of the hair shaft at the follicle bulb. Simultaneously, the HFSCs also generate outer root sheath (ORS) cells. This process is governed by an intricate interaction among diverse cellular components and signaling pathways. Especially, the Wnt signaling pathway is prerequisite for the telogen-to-anagen transition.[111] Disruptions in these regulatory mechanisms can lead to hair loss. Currently, the primary approaches to treating hair loss include pharmacological interventions and surgical procedures.[112,113] However, conventional therapies are limited by potential side effects, suboptimal results and high costs, putting forward a critical need for innovative strategies.

Recent years have seen growing interest in EVs for their ability to influence hair growth cycles and enhance hair growth[114] (Figure 2). DP cells are critical to inducing the hair cycle and regeneration via interacting with surrounding environment. For this reason, it is not surprising that the DP-derived EVs (DP-EVs) have a role in promoting hair growth. Human DP-EVs induced the proliferation of ORS cells and HFSCs through Wnt pathway, ultimately triggering hair cycle progression in mice.[64–66] miRNAs within EVs are pivotal for cell-to-cell communication, as evidenced by the fact that miRNAs can directly

control gene expression via either translational repression or mRNA degradation.[115,116] miR-140-5p in DP-EVs directly targeted and suppressed BMP2, an established inhibitor of HFSCs, therefore promoting hair growth.[66] Notably, EVs derived from spheroid-cultured DP cells exhibited significantly greater efficacy in accelerating hair regrowth and angiogenesis compared to those from 2D-cultured DP cells, underscoring the enhanced biological activity of EVs produced in 3D culture systems.[40,117] Topical injection of 3D DP-EVs surpassed the pro-hair growth efficacy of 5% minoxidil, the first-line therapy for hair loss, while 2D DP-EVs showed comparable efficacy to minoxidil. No obvious toxicity was reported. Mechanistically, EVs derived from spheroid-cultured DP cells exhibited higher levels of miR-218-5p, which inhibited Wnt antagonist secreted frizzled-related protein 2 (SFRP2), thereby activating Wnt/β-catenin pathway and promoting hair follicle regeneration.[40] Critically, 3D DP-EVs showed higher yields and enhanced therapeutic efficacy than that of 2D,[117,118] supporting their scalability for clinical translation. Advancements in EV engineering address key clinical barriers, including rapid clearance and nontargeted distribution. Chen et al developed an innovative approach using degradable and injectable microgels to encapsulate DP-derived EVs (OSA-EVs). Compared to free DP-EVs, OSA-EVs demonstrated sustained release and improved retention in the skin, significantly enhancing therapeutic efficacy.[119]

Apart from DP-EVs, EVs derived from various cell types also demonstrated potential for hair regeneration. For instance, EVs from human fibroblasts enhanced ORS and DP cell proliferation in vitro and stimulated elongation of human hair shafts in cultured hair follicles.[67] These effects are mediated through Wnt3a-induced stimulation of the Wnt signaling pathway. Similarly, macrophage-derived EVs are also enriched with Wnt3a, thus harboring hair-inductive capabilities.[68] Furthermore, MSCs-EVs have been demonstrated to significantly stimulate hair growth.[69] Interestingly, MSC transplantation, a widely recognized strategy for tissue regeneration, is accompanied by the production of a substantial number of apoptotic EVs (apo-EVs). Latest research showed that MSC-originated apo-EVs are essential in boosting hair development via activating Wnt/β-catenin in hair follicle MSCs.[70] These results underscore the profound hair promoting capabilities of EVs, not only as carriers of regenerative molecules but also as key mediators of cellular signaling pathways essential for hair follicle regeneration.

EVs and Skin Aging

Aging involves a series of gradual transformations across cellular, tissue, organ, and systemic levels.[120] With increasing global prevalence, aging has emerged as a significant public health challenge.[121–123] Among its many manifestations, cutaneous aging has garnered particular attention from researchers due to its visible and impactful nature. Clinically, skin aging is characterized by wrinkles formation, a rough and uneven texture, impaired barrier function, and pigmentation. The skin aging process results from intrinsic factors like genetics and hormones, as well as extrinsic influences such as ultraviolet (UV) exposure (also known as photoaging), oxidative stress, smoking, dietary habits and the use of cosmetics.[124,125] Since skin is frequently exposed to environmental insults, preventive measures against extrinsic aging factors, particularly UV radiation and pollution, are an essential part of routine skin care to reduce skin ageing.[126]

During skin aging, there are fewer key cell populations including fibroblasts and keratinocytes.[127] Meanwhile, these senescent cells display irreversible growth arrest and develop senescence-associated secretory phenotypes, such as the production of inflammatory mediators that compromise tissue function. Recent research has shown that aged cells tend to produce more EVs, which disturbed the processes of cell growth and differentiation, ultimately skin homeostasis.[128–131] Keratinocyte proliferation and differentiation constitute the key elements of epidermal homeostasis. Choi EJ et al suggested that, relative to those from youthful fibroblasts, EVs from senescent fibroblasts induced proinflammatory cytokines and exerted a reduced support on keratinocyte differentiation and wound closure.[128–131] This effect seems at least in part associated with miR-23a-3p/ E-cadherin axis.[130] The cargos of EVs originating from senescent cells vary significantly from those of non-senescent cells.[132,133] For instance, senescent fibroblasts exhibited altered levels of proteins associated with wound healing and cell adhesion, highlighting the functional impacts.[131]

Extensive studies have underscored the anti-aging benefits of EVs[134] (Figure 2). In vitro research indicated that ADSCs-EVs can reduce oxidative stress-triggered endothelial cell aging and recover endothelial cell functions, as evidenced by enhanced angiogenesis and migration capabilities. This protective effect appeared to be mediated through miR-146a-induced inhibition of Src kinase signaling.[57] Furthermore, topical application of these EVs in a photoaging rat model significantly improved skin conditions by reducing epidermal thickness and increasing dermal thickness, emphasizing their therapeutic

potential for treating photoaged skin.[71] Similarly, Yang et al reported that BMSCs-EVs effectively suppressed UVB-induced senescent signals, such as matrix metalloproteinase-1 (MMP1), while restoring levels of type I procollagen and mitigating skin senescence.[72] Further comparative studies have shown that EVs originating from 3D-cultured dermal fibroblast spheroids possess enhanced anti-aging effects on the skin relative to BMSCs-EVs, likely due to their enhanced bioactive cargo and functional potency.[73] Herein, we propose that combination of EVs-based therapies with preventive measures, which provide additional anti-aging protection, would yield significant clinical benefits. Although limited evidence exists for this synergistic strategy, therapeutic potential of combinational therapy warrants further investigation.

EVs and Inflammatory Skin Diseases

Diverse inflammatory dermatopathies are marked by pathological deterioration of skin tissue driven by immune imbalance. Among the most prevalent chronic inflammatory skin diseases are atopic dermatitis (AD), vitiligo, and psoriasis (Figure 3). Key cytokines implicated in these inflammatory responses include interleukin-4 (IL-4), IL-13, IL-17, and tumor necrosis factor-alpha (TNF-α), which collectively shape the intricate immunological landscape of these diseases.[135,136]

AD

AD is a chronic inflammatory skin disorder marked by dry, scaly skin, intense itching and recurrent eczematous lesions.[137–139] The pathogenesis of AD mainly involves epidermal barrier dysfunction, Th2-type immune responses, microbial dysregulation, and neuroimmune interactions.[139] The beneficial effects of MSCs from ADMSCs, BMSCs and HUMSCs have been reported.[140] Therefore, the application of MSC-EVs for AD treatment also gained significant attention as a novel cell-free therapeutic approach[25,79] (Figure 3). In two independent studies, EVs derived from ADMSCs were shown to alleviate AD symptoms in mouse models, as evidenced by reduced clinical scores, downregulated levels of inflammatory cytokines and reduced mast cells.[74,75] These therapeutic effects were associated with the restoration of epidermal barrier function through the promotion of de novo ceramide synthesis, a critical component of the skin protective barrier.[75] Approaches to pre-treatment have been applied to enhance the therapeutic efficiency and reliability of EVs. For instance, EVs derived from interferon-gamma (IFN-γ)-primed MSCs were found to downregulate the expression of Th2 cytokine receptors, including IL-4Rα, IL-13Rα1, and IL-31Rα, as well as their downstream signaling mediators JAK1 and STAT, thereby mitigating AD symptoms in mice.[76,77] Furthermore, these EVs appeared to recover epidermal barrier function through increasing lipid production, further highlighting their therapeutic potential.[76,77] Both *S. aureus* and *Lactobacillus plantarum* are naturally present on the skin, but their roles in skin health and disease are markedly different. EVs released by *S. aureus* have been shown to induce and exacerbate AD-like skin inflammation, whereas EVs derived from *Lactobacillus plantarum* have demonstrated protective effects, such as reducing epidermal thickening and lowering IL-4 levels in *S. aureus*-induced mouse models of AD.[78] The study underscored the intricate function of EVs from skin microbiome bacteria in modulating skin inflammation and suggested that focusing on certain bacterial EVs might offer an innovative therapeutic approach to AD. While the impact of BEVs on skin health has been increasingly studied, research on PEVs remains limited. Recently, an interesting study investigated the healing possibilities of EVs isolated from grapefruit, revealing the significant anti-inflammatory and antioxidant properties in vitro. These grapefruit-EVs were shown to reduce reactive oxygen species (ROS) levels and suppress the proliferation of $CD4^+$ T cells, leading to alleviated AD symptoms in vivo.[79] Notably, lipidomic analysis revealed that the lipid composition of grapefruit-EVs closely resembled that of the parent plant tissue, suggesting that EVs retain key bioactive components of their sources. This finding supports the view that EVs can serve as a natural and effective treatment option for inflammatory skin diseases.

Vitiligo

Vitiligo is an autoimmune disorder characterized by the destruction of pigment-producing melanocytes in the skin, resulting in depigmented patches.[141–143] It affects approximately 1% of the global population, posing significant psychological and social challenges for patients. The pathogenesis of vitiligo is primarily driven by autoimmune dysfunction, particularly an imbalance in the adaptive immune system involving $CD8^+$ T cells, regulatory T cells (Tregs), and dendritic cells, which attack and destroy melanocytes.[144–146] In addition, oxidative stress is believed to be an initiating factor in melanocyte loss. Excessive ROS induces DNA damage and protein misfolding, ultimately leading to melanocyte deficiency. Current therapies, including topical corticosteroids, phototherapy and immunosuppressants, often fail to meet clinical

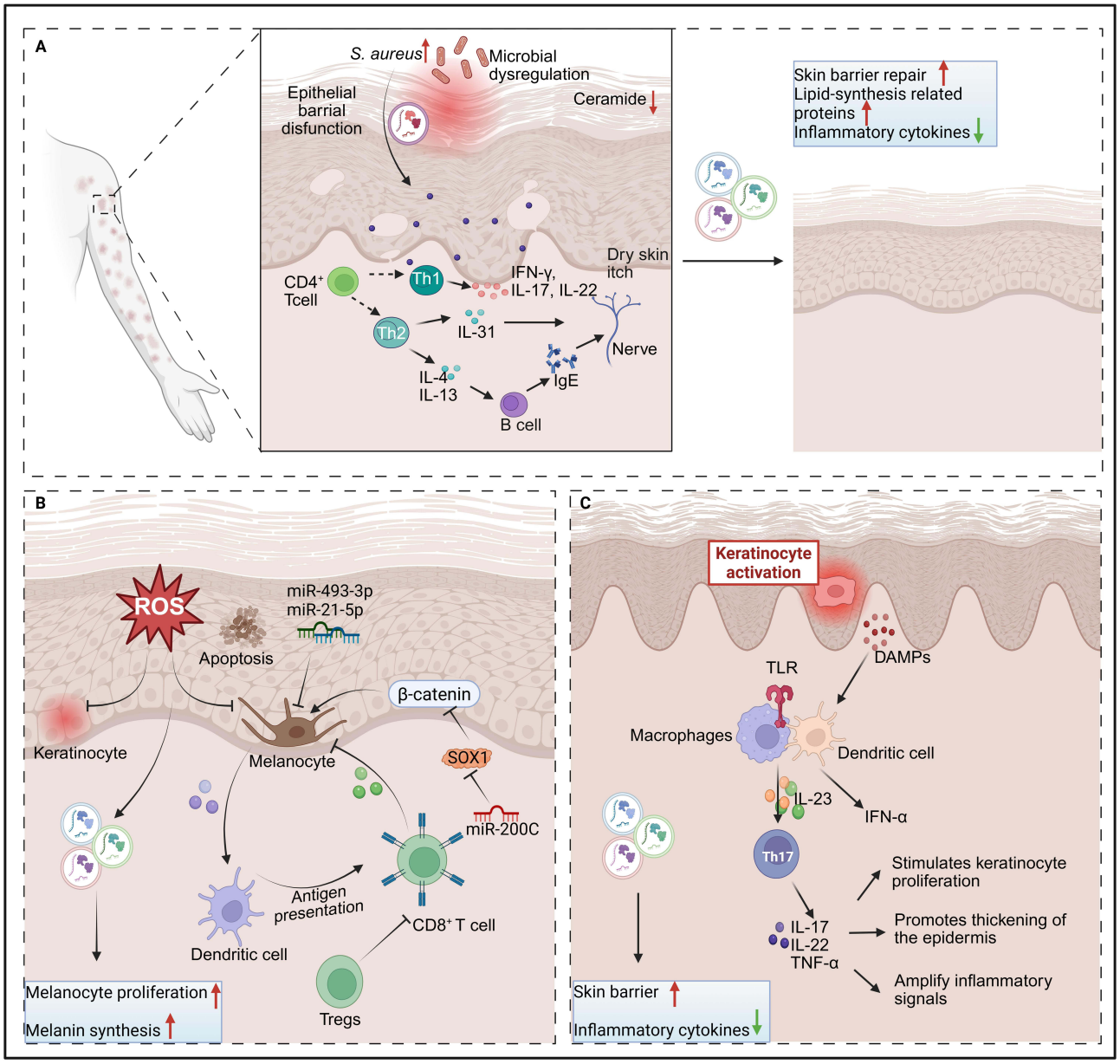


Figure 3 The role of EVs in inflammatory skin diseases. (**A**) EVs can promote de novo ceramide synthesis, restore epidermal barrier function and downregulate inflammatory responses, thereby alleviating AD. In addition, the EVs released by *S. aureus* upregulate inflammatory factor levels in keratinocytes. (**B**) EVs from keratinocytes stimulate the proliferation and melanin synthesis of melanocytes, thereby alleviating vitiligo. (**C**) EVs exert beneficial effects on psoriasis via regulating skin barrier and inflammatory responses. Tregs, regulatory T cells. Upward red arrows represent promotion; downward green arrows represent repression. Created with Biorender.com.
Abbreviations: AD, atopic dermatitis; ROS, reactive oxygen species; *S. aureus*, *Staphylococcus aureus*.

requirements.[142] Recently, EVs have attracted considerable interest within vitiligo research studies, offering new insights into disease progression and therapy[147,148] (Figure 3). For example, EVs isolated from vitiligo patients exhibited high levels of miR-493-3p and miR-21-5p, which increased ROS, promoted melanocyte apoptosis, and inhibited the melanogenesis of melanocytes, underscoring their detrimental effects.[149,150] Conversely, miR-200c was downregulated in EVs keratinocytes in vitiligo lesions. This downregulation promotes the expression of melanogenesis-related genes by suppressing SOX1, which leads to β-catenin activation.[80] In addition, EVs from keratinocytes of healthy individuals can be taken up by melanocytes and stimulate their proliferation and melanin synthesis.[151] These results emphasize the promise of EVs and their molecular contents as therapeutic targets and biomarkers for vitiligo.

Psoriasis

Psoriasis is a widespread, chronic skin condition marked by papulosquamous features, exhibiting notable genetic susceptibility and autoimmune mechanisms.[152] Immunological and genetic research has pinpointed IL-17 and IL-23 as crucial triggers in the pathogenesis of psoriasis.[152,153] In recent years, EVs have gained attention as a potential treatment option for psoriasis (Figure 3). Among the most studied are MSCs-derived EVs, particularly those sourced from HUMSCs, IFN-γ primed HUMSCs, embryonic stem cells, and gingival, which have demonstrated significant anti-inflammatory and immunomodulatory effects. Notably, these EVs significantly reduced key inflammatory cytokines, such as IL-17, IL-23 and TNF-α in psoriasis-like mouse models.[81–84] It was also reported that EVs from skin commensal bacteria (*Cutibacterium acnes, Staphylococcus Epidermidis ATCC12228* strain) and gut commensal bacteria (*Parabacteroides goldsteinii*) restored skin barrier function and attenuated the infiltration of pro-inflammatory cells, thereby downregulating the level of inflammatory cytokines, consequently alleviating psoriasis progression.[85–87] Of note, *Cutibacterium acnes*-derived EVs also restored the microbiota diversity on the skin of mice, reduced the colonization of *S. aureus*.[85] EVs from *Parabacteroides goldsteinii* have shown good stability, and upon oral administration, they can travel to the colon, cross the intestinal barrier, and reach inflamed skin,[87] indicating a novel therapeutic option based on the EV-mediated gut-skin axis.

Beyond naturally occurring EVs, engineered EVs loaded with specific therapeutic cargos via gene transfection have also shown promising results in psoriasis treatment.[88,154,155] Programmed cell death-ligand 1 (PD-L1) is one of the key components to inhibit immune responses and prevent immune cells from indiscriminately attacking self-tissue.[156] MSCs-EVs with PD-L1 over-expression effectively remodeled the inflammatory ecosystem in the affected skin tissues, suppressing key inflammatory cytokines in both skin and system, including IL-17A, TNF-α, IL-4 and IFN-γ via PD-1/PD-L1 axis. Notably, these EVs displayed enhanced efficacy than conventional MSCs-EVs in imiquimod-induced psoriasis.[88]

In summary, existing research on EVs in inflammatory skin conditions represents just a small fraction of the potential knowledge, and there is still a huge potential to be explored.

EVs and Skin Cancers

By facilitating cell-to-cell communication, EVs critically influence tumor development and progression, positioning them as promising therapeutic agents. Additionally, their inherent stability, easy accessibility and dynamic cargo alterations across distinct pathologic states render them as attractive diagnostic tools via comprehensive omics techniques (Figure 4). While EV research is well-established in many cancers, investigations into their functions in skin malignancies remain at an early stage. In this part, we discuss the role of EVs in skin cancers, including melanoma and non-melanoma skin cancers (NMSCs), focusing on their diagnostic and therapeutic potential.

Melanoma

Melanoma is one of the most dangerous and aggressive cutaneous malignancies, causing 75% of skin cancer-related deaths, even though it constitutes only 4% of all skin cancers.[157–159] Even with modern therapies, overall survival rates remain suboptimal, partly due to delayed diagnosis, metastasis and therapeutic resistance. Consequently, there is an urgent need to identify novel biomarkers and develop effective therapeutic strategies.

To date, several studies have revealed the pro-tumorigenic properties of melanoma EVs, including their role in immunosuppression, tumor metastasis, angiogenesis, and drug resistance.[160,161] Ma et al reported that tumor EVs were enriched in PD-L1, which facilitated T cell senescence and conferred immunotherapy resistance in melanoma models. Conversely, inhibiting EV synthesis reversed these effects.[89] In addition, melanoma cell B16F10-derived EVs induced the proliferation of lymphatic endothelial cells in draining lymph nodes, a process associated with lymphatic metastasis, while simultaneously induced apoptosis of $CD8^+$ T cells to facilitate tumor immune evasion and therapy resistance.[90] These findings highlight the potential of EVs as therapeutic targets.

EVs have gained significant attention as novel diagnostic biomarkers in melanoma (Table 2). Patients with melanoma showed upregulated EV concentrations compared to healthy individuals.[169] Through omics profiling, several bioactive molecules in EVs have been identified as valuable biomarkers, enabling both early diagnosis and treatment in melanoma. Among those, miRNAs represent the most extensively investigated diagnostic biomarkers for melanoma.[170,171] Xiong

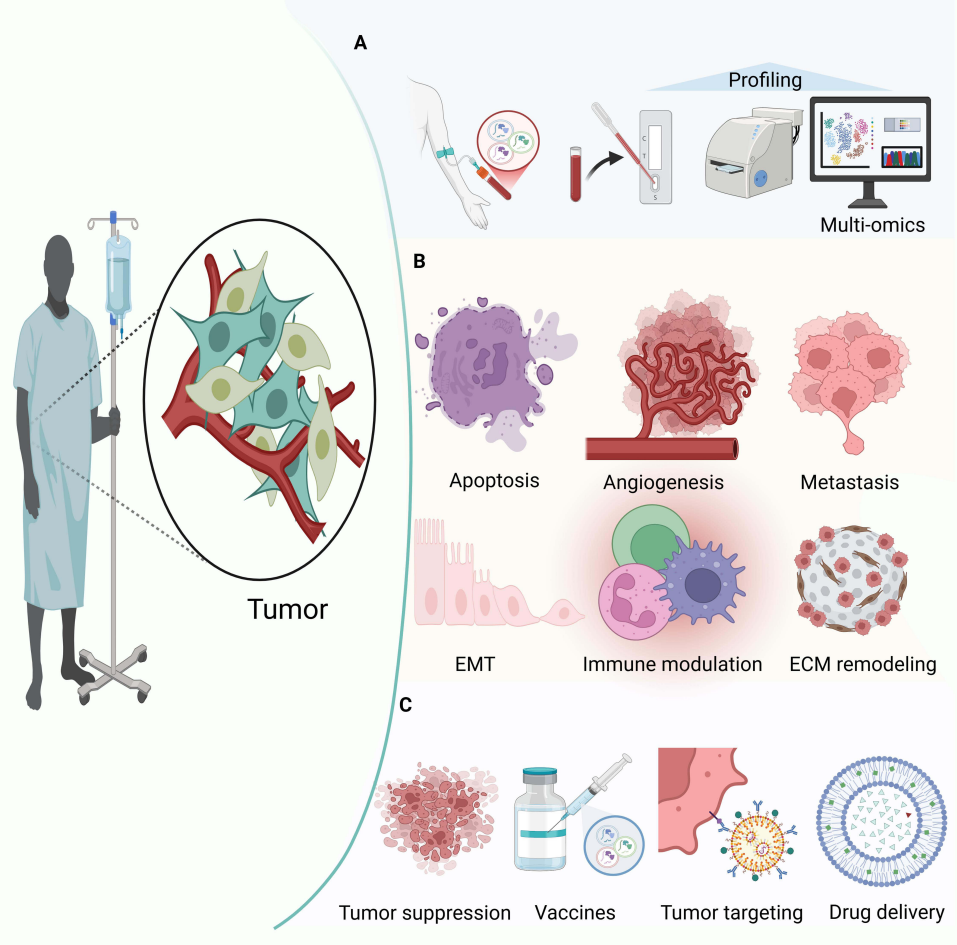


Figure 4 The role of EVs in cancers. (**A**) EVs function as diagnostic tools in tumor research fields. (**B**) EVs modulate multiple biological processes, including apoptosis, angiogenesis, metastasis, EMT, immunity, and ECM remodeling. (**C**) EVs function as therapeutic agents. Created by biorender.
Abbreviations: ECM, extracellular matrix; EMT, epithelial-mesenchymal transition.

et al revealed that the elevated miR-550a-3p and reduced miR-150-5p levels in plasma-derived EVs from melanoma patients were significantly associated with decreased overall survival.[162] Additionally, high enrichment of miR-92b-3p, miR-182-5p, miR-183-5p, miRNA-532-5p and miRNA-106b in serum-derived EVs from melanoma patients was also identified, but not the healthy ones.[163,164] Bioinformatics analyses confirmed the strong association between miR-92b-3p, miR-182-5p, miR-183-5p, and oncogenic pathways and tumor progression.[163] Meanwhile, miR-532-5p and miR-106b panel also differentiated metastatic melanoma patients from non-metastatic subjects, and stratified disease stages.[164] In patients with metastatic sporadic melanoma, EV miR-17, miR-19a, miR-21, miR-126, and miR-149 in plasma had higher levels than in unaffected individuals and familial melanoma patients, supporting their utility as metastasis-predictive biomarkers.[165] EV-enriched proteins have also emerged as promising melanoma biomarkers. For example, García-Silva et al showed that nerve growth factor receptor (NGFR) was enriched in EVs from metastatic melanoma cell lines.[166] This increase was associated with lymphangiogenesis and tumor adhesion, indicative of the diagnostic metastasis. Additionally, several independent studies revealed that PD-L1 in circulating EVs can serve as a diagnostic biomarker for immunotherapy outcome and stratification of responders versus non-responders.[167,172,173] This finding is significant, since the direct detection of PD-L1 is difficult due to the unstable nature of proteins.

The therapeutic applications of EVs on melanoma have also been reported. Tumor-associated macrophages (TAMs) exhibited a biphasic nature, characterized by tumor-suppressing M1 phenotype or tumor-promoting M2 phenotype.[174] Cao et al found that ginseng-derived EVs reprogrammed M2 macrophages to M1 polarization, and therefore inhibited melanoma growth.[91] Dendritic cells are critical antigen presenting cells to boost tumor immunity.[175] Induced pluripotent

Table 2 EVs as Diagnostic Biomarkers in Skin Cancers

Caner Type	Biomarker	Sources	Clinical Value	References
Melanoma	miR-550a-3p	Plasma	Expression levels of miR-550a-3p are negatively correlated with overall survival.	[162]
	miR-150-5p	Plasma	Expression levels of miR-150-5p are positively correlated with overall survival.	[162]
	miR-92b-3p, miR-182-5p, miR-183-5p	Serum	Diagnostic biomarkers	[163]
	miR-532-5p, miR-106b	Serum	Diagnosis and stage stratification	[164]
	miR-17, miR-19a, miR-21, miR-126, and miR-149	Plasma	Diagnostic biomarker of metastasis	[165]
	NGFR	Metastatic melanoma cells	Diagnostic biomarker of metastasis	[166]
	PD-L1	Blood	Prognostic biomarker for anti-PD-1 therapies in metastatic melanoma, stratification of responders from non-responders	[167]
BCC	miR-197-5p, miR-365b-5p, miR-6503-3p, miR-5190, miR-3940-3p, miR-3909, miR-615-3p, miR-548am-5p, miR-548ah-3p	Blood	Diagnostic biomarker of metastasis	[94]
SCC	Circ-CYP24A1	Plasma	Diagnostic biomarker	[168]

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

stem cells (iPSCs) pulsed dendritic cells displayed enhanced immune response.[176] Natural killer cells-derived EVs remarkably inhibited the growth of melanoma by inducing apoptosis in vitro and in vivo.[92] Alongside natural EVs, engineered EVs with enhanced therapeutic efficacy have also been developed for melanoma. Multiple EV modification strategies have been developed, such as chemical modification and drug loading.[177] TLR3/7/8/9 participate in regulating endocytosis of EVs by dendritic cells via endosomes.[178] Using click chemistry, Tang et al developed engineered tumor EVs with the display of TLR9 agonists on the surface, which stimulated TLR signals on intracellular endosomes, consequently enhancing dendritic cell activation, improving the processing and presentation of antigens encapsulated in EVs and priming T cells.[179] This cascade led to improved antitumor efficacy against melanoma. Additionally, to overcome the aqueous insolubility and short half-life of triptolide, an anticancer agent, Gu et al developed an EV platform to load triptolide using EVs from HUMSCs, referred to as cRGD-Exo/TP. These engineered EVs displayed enhanced tumor targeting and prolonged triptolide pharmacokinetics, ultimately inhibiting tumor growth with significant survival benefit in malignant melanoma models.[93]

NMSCs

NMSCs are far more common than melanoma and primarily comprise basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[180,181] BCC is the most common skin cancer, with around 3.6 million new annual diagnoses globally.[182] Although early-stage BCC is highly treatable, managing locally advanced or metastatic BCC continues to pose significant clinical challenges.[183] A study comparing EVs from the peripheral blood of metastatic BCC and non-metastatic BCC (NMBCC) patients, revealed that NMBCC-derived EVs exhibit greater potential to promote fibroblast proliferation, migration, and invasion.[94] miRNA sequencing identified nine upregulated miRNA in metastatic BCC-derived EVs, suggesting their potential utility as prognostic biomarkers for metastatic progression (Table 2). However, the specific miRNAs or other key bioactive components responsible for mediating these distinct functions remain determined.

SCC is more invasive and prone to spreading than BCC, especially in immunocompromised patients or those with prolonged UV exposure.[184] The pathogenic functions of EVs have been studied. It has been reported that pro-oncogenic Dsg2 enhanced EV secretion from SCC cells, leading to increased IL-8 packaging in EVs and promoting SCC progression.[185] These EVs contained a high level of miRNA-31, which directly targeted RhoBTB1 and resulted in

SCC cell proliferation, migration, and invasion.[186] In addition, M2 macrophage-derived EVs promote SCC progression by inhibiting ferroptosis, a form of cell death.[95] 5-Aminolevulinic acid photodynamic therapy (ALA-PDT) is an effective therapeutic strategy for SCC. Interestingly, EVs from ALA-PDT-treated SCC cells induced dendritic cell maturation.[187] These studies reveal the complicated role of EVs in tumor microenvironment.

Compared with melanoma, the diagnostic utility of EVs in SCC is less explored. Zhang et al reported that, compared with healthy individuals, cutaneous SCC patients displayed elevated expression of circ-CYP24A1 in EVs from plasma.[168] Critically, circ-CYP24A1 promoted the proliferation, migration, and invasion of SCC cells, supporting its dual utility as both an early diagnostic biomarker and therapeutic target.

Collectively, research on EVs in skin cancers remains in its infancy. Investigating how EVs influence the tumor microenvironment and engage with immune cells could provide valuable insights into skin cancer pathogenesis and uncover novel therapeutic targets. Furthermore, the integration of multi-omics approaches, such as proteomics and transcriptomics, could deepen our understanding of EV biology and identify novel biomarkers for early detection and treatment monitoring. By leveraging these advancements, researchers and clinicians can move closer to achieving precision medicine in melanoma.

Conclusion and Perspectives

The application of EVs in dermatology is a rapidly evolving field with transformative potential for treating diverse cutaneous disorders. EVs exhibit remarkable capabilities in immune modulation and cellular activation through delivering bioactive molecules, making them a promising tool for treating diseases such as chronic wound healing, psoriasis, AD, vitiligo, and even skin cancers. However, despite their therapeutic promise, several significant challenges must be addressed to facilitate the widespread clinical adoption of EVs.

A significant obstacle is the absence of standardized procedures for EV extraction, preservation, and analysis. The present techniques for isolating particles, like ultracentrifugation, size-exclusion chromatography, and chemical precipitation, often yield a mixture of vesicles with varied sizes, which can mess with the consistency of results and complicate the follow-up analysis. Additionally, the complex and diverse composition of EVs, which includes proteins, lipids, nucleic acids, and other biomolecules, makes it difficult to pinpoint the specific mechanisms by which they exert their therapeutic effects. This heterogeneity also poses challenges for quality control and batch-to-batch consistency, which are critical for clinical translation. Moreover, most current studies are performed on cells or animal models. Despite significant preclinical efficacy, biological differences between species, such as immune responses, skin structure, and disease progression, limit the direct applicability of EV findings to humans, necessitating rigorous validation in clinical trials. However, early-phase trials with EVs concentrate predominantly on safety and effectiveness evaluations. Although EVs are already marketed in beauty/skincare and undergoing Phase III trials for pharmaceutical applications, significant uncertainties regarding their commercial viability persist. Critical considerations, including scalability, economic viability, regulatory clearance, and enduring safety concerns, must be resolved before EVs are widely adopted as a standard treatment method.

To overcome these challenges, future research should prioritize the development of standardized protocols for EV production and characterization, as well as the elucidation of their precise mechanisms of action. Advanced technologies, such as single-vesicle analysis and multi-omics approaches, could provide deeper insights into EV composition and function, enabling the design of more targeted and effective therapies. Additionally, robust preclinical models that better mimic human skin biology and disease pathology will be essential for bridging the gap between animal studies and human trials. Joint efforts by scientists, healthcare professionals, corporate partners, and governing entities are essential in progressing EV-derived treatments from research settings to clinical use. Through a structured approach to tackling these technical and translational obstacles, the sector can maximize the therapeutic utility of EVs, facilitating the development of innovative, minimally invasive, and highly effective treatments for complex dermatological conditions. Integration of cutting-edge analytical tools with enhanced mechanistic understanding will accelerate the emergence of precision-based, personalized EV therapeutics tailored to diverse patient needs.

Data Sharing Statement

Data sharing not applicable - no new data generated.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by National Natural Science Foundation of China (82204450 and 82272278), the National Key Research and Development Program of China (2023YFC2509000), and Shanghai Qiran Biotechnology Co., Ltd.

Disclosure

The authors declare that they have no competing interests in this work.

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