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Review

The novel mechanisms and applications of exosomes in dermatology and cutaneous medical aesthetics

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ABSTRACT

Exposure to the external environment may lead to instability and dysfunction of the skin, resulting in refractory wound, skin aging, pigmented dermatosis, hair loss, some immune-mediated dermatoses, and connective tissue diseases. Nowadays, many skin treatments have not achieved a commendable balance between medical recovery and cosmetic needs. Exosomes are cell-derived nanoscale vesicles carrying various biomolecules, including proteins, nucleic acids, and lipids, with the capability to communicate with adjacent or distant cells. Recent studies have demonstrated that endogenic multiple kinds of exosomes are crucial orchestrators in shaping physiological and pathological development of the skin. Besides, exogenous exosomes, such as stem cell exosomes, can serve as novel treatment options to repair, regenerate, and rejuvenate skin tissue. Herein, we review new insights into the role of endogenic and exogenous exosomes in the skin microenvironment and recent advances in applications of exosomes related to dermatology and cutaneous medical aesthetics. The deep understanding of the mechanisms by which exosomes perform biological functions in skin is of great potential to establish attractive therapeutic methods for the skin.

1. Introduction

Skin is the largest physical, chemical, and immunological barrier organism of the body, which is composed of the epidermis, dermis, and subcutaneous tissue [1]. The external outermost layer is the 10–20 μm thick stratum corneum containing 10–15 layers of interdigitated dead cells. The second layer is called the viable epidermis in 100–150 μm thick, mostly composed of keratinocytes at various stages of

Abbreviations: MSCs, Mesenchymal Stem Cells; CM, Conditioned Medium; HDFs, Human Dermal Fibroblasts; HaCaTs, Human Keratinocytes; HUVECs, Human Umbilical Vein Endothelial Cells; BMSCs, Bone Marrow MSCs; uMSCs, Umbilical Cord-derived MSCs; ADSCs, adipose-derived MSCs; iPSC-MSCs, Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells; HFSCs, Hair Follicle Stem Cells; DPCs, Dermal Papilla Cells; HF, Hair Follicle; ORSCs, Outer Root Sheath Cells; ECM, Extracellular Matrix; ROS, Reactive Oxygen Species; MMP, Matrix Metalloproteinase; IFN-γ, Interferon Gamma; IFN-α, Interferon Alpha; TNF-α, Tumor Necrosis Factor Alpha; TGF-β, Transforming Growth Factor Beta; IL, Interleukin; VEGF, Vascular Endothelial Growth Factor; FGF, Fibroblast Growth Factor; Shh, Sonic Hedgehog; SA-β-gal, Senescence-Associated β-galactosidase; UV, Ultraviolet; 3D, Three-Dimensional; H2O2, Hydrogen Peroxide; I/R, Ischemia-Reperfusion; MAPKs, Mitogen-Activated Protein Kinases; AMPK, Adenosine Monophosphate Activated Protein Kinase; NF-κB, Nuclear Factor Kappa B; PI3K, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; AKT, Protein Kinase B; Dnmt1, DNA-methyltransferase1; PLA2, Phospholipase A2; MITF, Melanocyte Inducing Transcription Factor; TYR, Tyrosinase; KGF, Keratinocyte Growth Factor; IGF, Insulin-Like Growth Factor; HGF, Hepatocyte Growth Factor; PTEN, Phosphatase And Tensin Homolog; TRAF, TNF Receptor Associated Factor 6; MSCT, Mesenchymal Stem Cell Transplantation; SLE, Systemic Lupus Erythematosus; AD, Atopic Dermatitis; SSc, Systemic Sclerosis.

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differentiation [2]. In addition to the keratinocytes, melanocytes, Langerhans cells, and several other types of cells are also found in the epidermis [3]. The third layer is dermis riched in extracellular matrix (ECM) proteins and growth factors, attributed to the presence of various lineages of dermal fibroblasts [4]. The last hypodermis or subcutaneous layer is encompassed by adipocytes, mesenchymal stem cells (MSCs), and connective tissue [5]. The important cell types within the skin layers, including keratinocytes, fibroblasts, macrophages, adipocytes, are of capacity to communicate reciprocally in the skin environment, and can trigger complex responses after internal and external stimuli (Fig. 1A).

Skin diseases are considered to be threatening medical issues with increasing prevalence in recent years. Genetic make-up, lifestyle, nutrition, solar radiation and sun sensitivity, exposure to heavy metals and atmospheric particulate matter, and other environmental influence might lead to dermal cytotoxicity, impairment of skin barriers, matrix proteins, and activation of inflammation reactions [6]. The loss of skin constituents, physiological function, and normal structure damage, may cause skin abnormalities, including skin aging, pigmented dermatosis, some immune-mediated dermatoses, connective tissue diseases, and poor skin healing after injuries [7]. To improve skin condition and treat skin diseases, there are many methods such as skincare, lasers, medicines, surgery, and cell therapy [8]. Nonetheless, these methods have not achieved the ideal effect for skin repair and regeneration with respective disadvantages. Therefore, identifying the pathogenesis and establishing effective approaches are momentous to accelerate cutaneous regeneration and restore the function of the damaged skin.

Exosomes are cell-derived nanoscale vesicles with a diameter of 40–160 nm [9]. The exosomes are structures with bilayer membranes, and carry important gene information, such as proteins, carbohydrates, lipids, and nucleic acids. Proteins enriched in exosomes include membrane transport proteins (GTPases and annexins), tetraspanins (CD63, CD81, CD82, and CD9), biogenesis-related proteins (ESCRT complex, ALIX, and TSG101), and heat shock proteins (HSP60, 70, and 90), which are generally recognized as characteristic biomarkers of exosomes [10]. Exosomes possess the capacity to function as intercellular transmitters to impact neighboring cells, while retaining some of the biological properties of their parent cells. The exosome can modulate essential cellular processes, such as proliferation, differentiation, migration, and cell death, varying depending on the exosome origin, the physiological and pathological state, and even the precise cellular release site [11]. Emerging evidence has confirmed that exosomes involve in various disease progression, showing the potential of exosome and exosome cargoes as diagnostic and therapeutic biomarkers [12] (Fig. 1B).

In the skin, exosomes-mediated information transfer and intercellular communication are necessary to maintain cellular functions and tissue homeostasis [13]. Studies have shown that the endogenic exosomes shuttling in multiple types of skin cells, participated in complex molecular mechanisms of chronic inflammatory skin diseases [14]. Therefore, the exosome contents can be potential biomarkers for diagnosing and treating skin dysfunction and diseases. More importantly, the exosomes from stem cells and other cell types, can be therapeutic options in regenerative medicine and aesthetics, especially in scars prevention and reduction, pigmentation regulation, and hair growth. For instance, exosomes secreted by melanocytes could regulate skin pigmentation, and exosomes originated from other cell types residing in the skin can also influence the melanin production in melanocytes [15]. Exosomes derived from MSCs were also classified as a potential non-sensitizer in the skin sensitization test, and safe for use as a topical treatment with no adverse effects [16]. These demonstrated the potential of exosomes as therapeutic agent, cosmetic ingredients, or for other

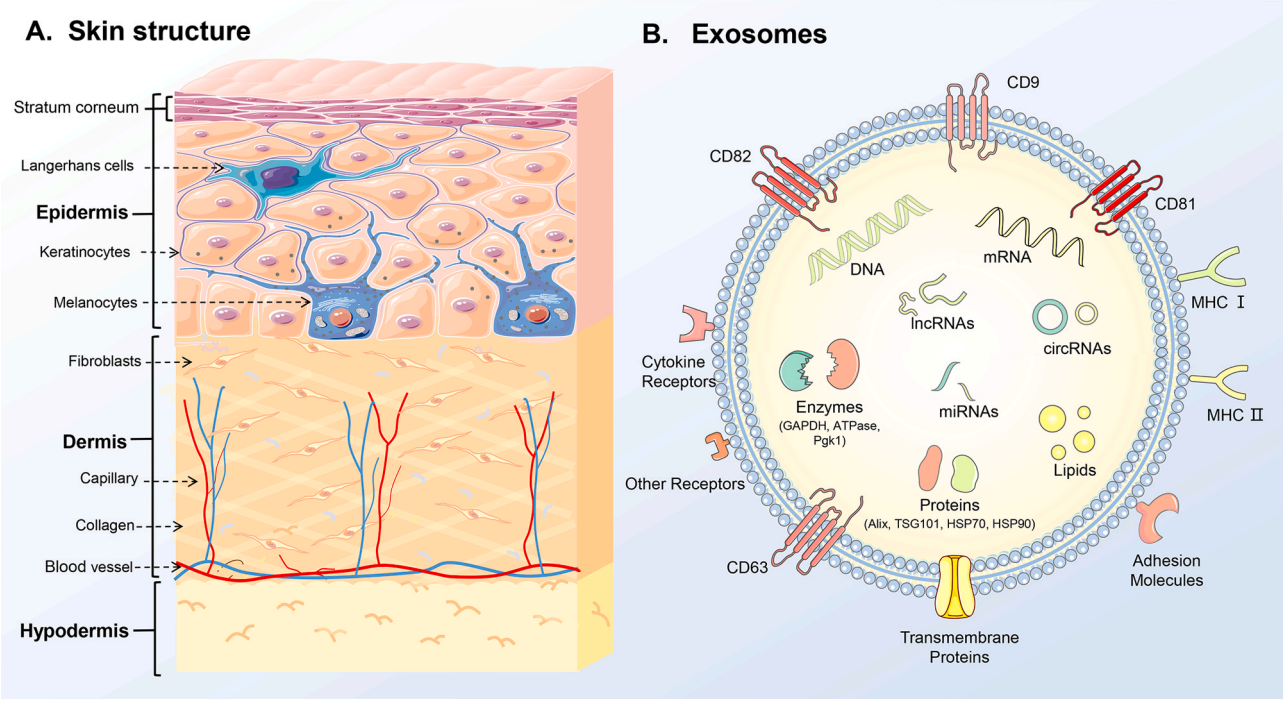

Fig. 1. Diagrammatic representation of the skin structure and the molecular composition of exosomes. (A) The skin has three layers from outside to inside: epidermis, dermis, and subcutaneous tissue. The epidermis consists of keratinocytes forming stratified corneum, with melanocytes and Langerhans cells interspersed. The outer layer of the epidermis is the stratum corneum of the skin by keratinized dead cells, which has abrasion resistance. The dermis is filled with fibroblasts, contributing to the formation of rich fibrous extracellular matrix components, including elastin, fibrillin, collagens as well as blood vessels and nerve endings. The last hypodermis is comprised of adipocytes and connective tissue. (B) As membrane-derived nanovesicles with lipid bilayer structure, exosomes pack a variety of cellular components, including nucleic acids (DNA, mRNAs, miRNAs, circRNAs, lncRNAs), biogenesis-related proteins (ALIX, TSG101), heat shock proteins (HSP70, HSP90), enzymes (GAPDH, ATPase, Pgk1), lipids, adhesion molecules, receptors, and various tissue-specific proteins involved in antigen presentation as transmembrane proteins (CD9, CD63, CD81, CD82) and MHC-I and MHC-II (Major Histocompatibility Complex).

biological uses.

Herein, we mainly summarize the latest research about the mechanisms and applications of exosomes in dermatology and cutaneous medical aesthetics, including wound healing, skin flaps reconstruction, systemic lupus erythematosus, psoriasis, atopic dermatitis, systemic sclerosis, scar removal, facial rejuvenation, pigmentation regulation, and hair growth. The in-depth understanding of the pivotal roles will provide further insights into exosomes in dermatology and cutaneous medical aesthetics. This scenario opens the possibility for the applications of exosomes as new diagnostic biomarkers and therapeutic agents in the skin. For these goals, we searched the exosomes and the above fields as keywords on Pubmed in the recent 5 years. These related studies are involved in cell, animal experiments, and tissue samples, and the original articles were included according to relevance to the topic.

2. Exosomes in dermatology

The skin is a vital organ that not only serves as a protective barrier against environmental factors, but also plays a role in the synthesis, processing, and metabolism of structural biomolecules. Skin injuries, such as chronic wounds, skin flaps necrosis, and inflammatory skin diseases, can repress the ability of skin regeneration. As exosomes are emerging bioactive substances in multiple biochemical and cellular processes of skin, the further understanding of the exosomes mechanism in dermatology will help to dig cell-free treatments in skin regeneration and repair.

2.1. Wound healing

2.1.1. Wound healing characteristics

Skin wound healing is a complex process involving several highly coordinated steps, mainly divided into inflammatory response, epithelialization, wound contraction, collagen deposition, and remodeling [17]. Trauma, surgery, acute illness, or chronic disease conditions are likely to cause poor wound healing, clinically characterized by scar formation, hyperpigmentation, prolonged healing, long-lasting ulceration, and other morphological and functional abnormalities [18]. Mechanistically, the abnormal migration, proliferation, differentiation, and apoptosis of dermal fibroblasts and epidermal keratinocytes with injury repair function are the main causes in wounds healing [11]. The emerging treatments for wound healing include physical therapy, cell therapy, biological dressings, growth factors delivery, and engineered skin equivalents [19]. Exosomes are able to affect angiogenesis, cell proliferation and differentiation, apoptosis, and inflammation, which have gained interest in wound healing [20].

2.1.2. Exosomes from skin cells in wound healing

Skin wound healing partially comes down to intercellular interaction via exosomes among various skin cells, including keratinocytes, fibroblasts, endothelial cells, adipocytes, macrophages, and other immune cells (Fig. 2) [21]. For example, Li et al. explored that macrophage-derived exosomes were capable of promoting diabetic wound healing with intense angiogenesis-promoting and proliferation effects, by attenuating the secretion of pro-inflammatory cytokines and enzymes [22]. Kim et al. found that the subcutaneous administration of M2 macrophage-derived exosomes (M2-exos) into the mouse wound could markedly decrease and increase the local populations of M1 and M2 macrophages respectively, thus contributing to the successful conversion of M1 to M2 macrophage [23]. The exosome-guided reprogrammed M2 macrophages enhanced fibroblast migration, collagen deposition, and endothelial cells tube formation in wound healing. Interestingly, the mesoglycan-treated keratinocytes-derived exosomes,

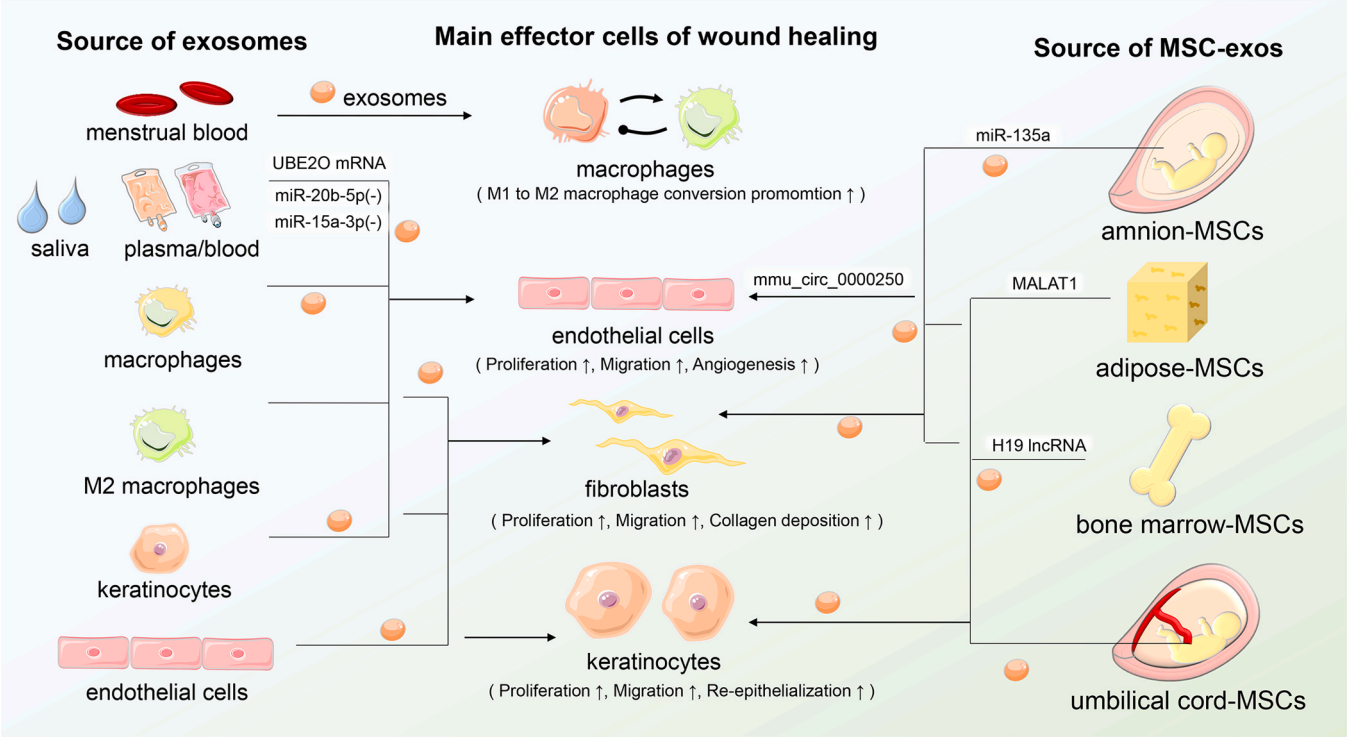

Fig. 2. The exosomes derived from multiple sources could regulate wound healing by affecting effector cells. The exosomes from various sources, including MSCs, keratinocytes, endothelial cells, immune cells, and body fluid, could regulate the wound healing process through different mechanisms.Especially, the UBE2O mRNA in saliva-exos, the miR-135a in amnion-derived MSC-exos, the MALAT1 and mmu_circ_0000250 in adipose-derived MSC-exos, and the H19 lncRNA in bone marrow-derived MSC-exos played positive roles in enhancing the functions of main effector skin cells to accelerate wound healing. The miR-20b-5p in exosomes of patients plasma and miR-15a-3p in exosomes from patients blood inversely impaired the functionality of the endothelial cells, exerting healing delay effects. Mesenchymal Stem Cells, MSCs.

which contained exosomes, could induce the increased expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) in human fibroblasts and endothelial cells, thus enhancing the angiogenesis and the formation of stress fibers in vitro [24]. This finding revealed an autocrine loop with a positive action of re-epithelialization for wound healing. Besides, Zhao et al. found that exosomes derived from human umbilical vein endothelial cells (HUVECs) could accelerate wound healing both in vitro and in vivo, and promote the proliferation and migration activities of keratinocytes and fibroblasts, which were two important effector cells for skin regeneration [25]. Then they developed a gelatin methacryloyl hydrogel as a scaffold to afford sustained release of HUVEC-exos, which promoted re-epithelialization, collagen deposition, and angiogenesis, for accelerating the wound healing process.

2.1.3. Exosomes from MSCs in wound healing

MSC-derived exosomes (MSC-exos), with excellent functions over the corresponding MSCs, might be a compelling alternative for skin regeneration, and are safer and easier to handle than cell-based products [26]. Jiang et al. found that human bone marrow MSC (BMSCs)-derived exosomes down-regulated transforming growth factor-beta (TGF-β)1, Smad2, Smad3, and Smad4, and up-regulated TGF-β3 and Smad7 expression to inhibit the TGF-β/Smad signal pathway, thus promoting the human keratinocytes line HaCaTs and human dermal fibroblasts (HDFs) proliferation, showing the potential for accelerating the mouse wound healing [27]. Zhao et al. proved that the exosomes from human umbilical cord-derived MSCs (uMSC-exos) might effectively treat the cutaneous wound in vivo by enhancing epidermal re-epithelialization and dermal angiogenesis [28]. The hucMSC-exos could inhibit apoptosis-inducing factor (AIF) and up-regulate poly ADP ribose polymerase 1 (PARP-1) and poly (ADP-ribose) (PAR) for the increased proliferation, migration, and suppressed apoptosis of HaCaTs. During wound healing in diabetic mice, the exosomes derived from menstrual blood-derived MSCs could reduce inflammation via induced M1-M2 macrophage polarization [29]. For better curative effect, combining exosomes with advanced biological materials is a favorable method to sustain the release of exosomes continuously for promoting wound healing. As Shafei et al. reported that, the loaded exosomes from adipose-derived MSCs (ADSC-exos) in the alginate-based hydrogel could function as a bioactive scaffold to maintain the ADSC-exos constantly releasing in the wound site in the animal model [30]. This bioactive wound dressing technique significantly promoted wound closure, collagen synthesis, and angiogenesis in the wound area.

The regulatory RNAs enriched in exosomes, such as microRNAs (miRNAs), lncRNAs, and circRNAs, can regulate angiogenesis, cellular transport, apoptosis, proteolysis, adipogenesis, and extracellular matrix turnover [31]. At the cellular level, ADSC-exos containing MALAT1 attenuated the suppression of cell proliferation, migration, and the promotion of cell apoptosis in HaCaTs and HDFs treated with H_2O_2, via sponging microRNA (miR)−124a and activating Wnt/β-catenin pathway [32]. Gao et al. found that local injection of miR-135a in exosomes derived from human amnion MSCs into the wounds in rats, could promote wound healing via down-regulating large tumor suppressor 2 (LATS2) levels to increase the migration of epidermal cells [33]. Li et al. found that BMSC-derived exosomal lncRNA H19 could bind to miR-152–3p, which inhibited miR-152–3p and promoted phosphatase and tensin homolog (PTEN) and expression to suppress the apoptosis and inflammation of fibroblasts, leading to the accelerated wound healing process in diabetic foot ulcer [34]. Shi et al. verified that ADSC-exos contained a high concentration of mmu_circ_0000250 and could enhance the therapeutic effect on full-thickness skin wound repair in diabetic rats by miR-128–3p absorption and sirtuin 1 (SIRT1) upregulation [35].

2.1.4. Exosomes from body fluid in wound healing

Exosomes in body fluid can also participate in skin wound healing. Xiong et al. found that exosomes from type 2 diabetes mellitus patients hindered wound healing in mice, and transferred high levels of miR-20b-5p to HUVECs to exert negative regulation of cell functionality and angiogenesis by inhibiting the Wnt9b/β-catenin pathway [36]. Similarly, Xiong et al. also found that miR-15a-3p was up-regulated in the extracted exosomes from diabetic patient blood, which was proved to impair HUVECs angiogenesis and survival by suppressing the NADPH oxidase NOX5/reactive oxygen species (ROS) signaling pathway, resulted in hindering wound healing in vitro and in vivo. Therefore, the inhibition of circulating exosomal miR-15a-3p might be a novel therapeutic target for diabetic foot ulcer therapy [37]. In addition, as one of the main mRNAs of saliva-derived exosomes, the UBE2O mRNA mediated HUVECs proliferation, migration, and angiogenesis in vitro, and promoted cutaneous wound healing in vivo via SMAD6/BMP2 pathway [38].

2.2. Skin flaps reconstruction

2.2.1. Skin flaps characteristics

The closure of skin defects routinely requires the use of cutaneous flaps borrowed from the surrounding skin or artificial flaps to obtain satisfactory functional and aesthetic outcomes [39]. Partial and complete necrosis of skin flaps remains a significant problem in plastic and reconstructive surgery. Inadequate blood perfusion and ischemia-reperfusion injury are considered to be the main factors [40]. Extensive research has been performed on enhancing skin flap viability by various pharmacological manipulations, growth factor applications, and physiotherapeutic [41]. However, these studies have failed to display dramatic or consistent improvements in flap survival. Exosomes containing a variety of proangiogenic factors exhibit the ability of tissue damage repair due to neovascularization.

2.2.2. Exosomes in skin flaps reconstruction

Exosomes were shown to induce the proliferation and migration of vascular endothelial cells and reduce cell apoptosis for injury repair and vascularization [42]. For instance, Xie et al. confirmed that local injection of exosomes derived from BMSCs could stimulate the expression of VEGF to induce angiogenesis and enhance the survival of random pattern dorsal skin flaps in rats [43]. The exosomes derived from ADSC pre-conditioned with H_2O_2 significantly improved the migration and tube formation of HUVECs for flap neovascularization and relieved inflammatory reactions and apoptosis in ischemia/reperfusion (I/R) injury of flap transplantation [44]. Pu et al. found that the injection of ADSC-conditioned medium (CM) or ADSC-exos into the flaps significantly improved flap survival and capillary density [45]. Following I/R injury, the ADSCs secreted interleukin 6 (IL-6) and then stimulated angiogenesis and enhanced recovery by the classic signaling pathway. In another research, the bioinformatics analysis verified that significantly up-regulated hsa-miR-760 and down-regulated hsa-miR-423–3p in ADSC-exos could regulate the expression of genes ITGA5 and HDAC5, respectively [46]. Therefore, given that the ability of the vascularization of skin flaps, ADSC-exos was able to resolve the problem of insufficient formation of new blood vessels in artificial dermal prefabricated flaps.

2.3. Immune-mediated dermatoses

Inflammatory skin diseases, such as systemic lupus erythematosus (SLE), psoriasis, atopic dermatitis (AD), and systemic sclerosis (SSc), are considered major public issues with increasing prevalence [47]. The symptoms of these diseases can deteriorate the quality of life of patients as a result of an impaired skin barrier, itch, insomnia, and social stigma over a long period. There is increasing interest in the pathogenesis and therapeutic application of exosomes for inflammatory skin conditions. Effective communication between immune cells, which is done by exosomes to some extent, is critical for a coordinated immune response. The functions of exosomes include immunoregulatory mechanisms such

as modulation of antigen presentation, immune activation, immune suppression, immune surveillance, and intercellular communication (Table 1).

2.3.1. Systemic lupus erythematosus

2.3.1.1. SLE characteristics. The systemic lupus erythematosus (SLE) is a chronic relapsing autoimmune disease illness. SLE affects not only vital organs such as the heart, lung, and kidney, but also the nerves and skin, resulting in poor quality of life and serious mortality [48]. Although many factors appear to be important in SLE etiology, such as gender, age, geography, ethnicity, and genetic ancestry, the exact pathogenesis is not fully elucidated [48]. Exosomes, as triggers of regenerative effects in target cells, can regulate physiological responses and the pathogenesis of some diseases, including SLE. This characteristic makes exosomes not only potential diagnostic or prognostic biomarkers of disease but also possible therapeutic targets [49].

2.3.1.2. Exosomes in SLE pathogenesis. The circulating exosomes are proved to be immunologically active and their levels correlate with disease activity in SLE patients. Lee et al. found that SLE exosomes were enriched in the serum of SLE patients and were correlated with disease activity in SLE patients [50]. Besides, SLE exosomes mediated a higher production of tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6, which might play a role in the inflammatory process of SLE. Circulating miRNAs have been investigated to be encapsulated by exosomes and microvesicles, and circulate in a relatively stable state in peripheral blood [51]. The exosomes isolated from the plasma of SLE patients could promote the human blood plasmacytoid DCs (pDCs) to secret interferon-alpha (IFN-α) in vitro [52]. The exosome-delivered miRNAs containing an IFN induction motif, could mediate the human pDCs activation, maturation, and survival via toll-like receptor 7 (TLR7) triggering. Hernandez et al. investigated that the miRNAs in urine were mainly contained in the exosomes of SLE and were mainly found in the case of active lupus nephritis, with miR-146a being the most augmented [53]. Therefore, these new findings prompted the importance of exosomal miRNAs network regulation in SLE. Isolation and detection of circulating miRNAs from the blood of SLE patients may help achieve SLE surveillance [54].

2.3.1.3. Exosomes in SLE application. The senescence of MSC damages the immune regulation and regeneration characteristics of MSC, and it also plays a vital role in the occurrence and development of SLE. For instance, the expression of miR-146a was declined significantly in serum exosomes of SLE patients, and could be internalized into MSCs mediated by exosomes to participate in MSCs senescence through targeting TNF receptor-associated factor 6 (TRAF)/nuclear factor kappa B (NF-κB) signaling [55]. With the ability to support the repair of damaged tissues, systemic mesenchymal stem cell transplantation (MSCT) has been successfully applied to treat SLE. MSCs do not necessarily replace diseased tissues, but play a complex paracrine function, which is mediated by its extracellular secretion products [56]. Liu et al. found that exosomes secreted by MSCT significantly reduced the intracellular level of miR-29b, up-regulated the expression of DNA-methyltransferase1 (Dnmt1), and down-regulated the expression of Notch1 and Notch intracellular domain (NICD) to transfer Fas to rescue the receptor MRL/lpr BMSCs function, thereby increasing in vivo bone formation [57].

2.3.2. Psoriasis

2.3.2.1. Psoriasis characteristics. Psoriasis is a chronic, immune-mediated inflammatory skin disease, consisting of red and scaly plaques most commonly found on the elbows, knees, scalp, and lower back [58]. Psoriasis is considered a systemic disease, combined with

Table 1
The pathogenesis of exosomes in chronic inflammatory skin diseases.

Disease	Source	Model	Mechanism	Ref.
SLE	Plasma of SLE patients	SLE patients	Secrete increased IFN-α by TLR7-dependent activation, maturation, and survival of human pDCs	[52]
	Serum of SLE patients	SLE patients	Induce a higher production of IFN-α, TNF-α, IL-1β, and IL-6, amplifying the abnormal immune response	[50]
	Serum of SLE patients	SLE patients	miR-146a in exosomes could be internalized into MSCs and induce MSCs senescence through targeting TRAF6/NF-κB signaling	[55]
	BMSCs of C3H/HeJ mice	Fas-deficient-MRL/lpr mice	Transfer Fas to recipient MRL/lpr BMSCs to reduce intracellular miR-29b, resulting in recovery of Dnmt1-mediated Notch1 promoter hypomethylation, and improving MRL/lpr BMSCs function	[57]
Psoriasis	Psoriatic keratinocytes	Neutrophils and psoriasis-like mice	Induce expressions of IL-6, IL-8, and TNF-α in neutrophils in vitro, and exacerbate skin lesions in psoriasis-like mice	[61]
	Neutrophils of GPP patients	Keratinocytes	Increase the expression of IL-1b, IL-36 G, IL-18, and TNF-α in keratinocytes, via activating NF-κB and MAPK signaling pathways	[62]
	IFN-α-induced mast cell	CD1a-expressing cells	Transfer cytoplasmic PLA2 activity to neighboring CD1a-expressing cells, leading to the generation of neolipid antigens and subsequent recognition by lipid-specific CD1a-reactive T cells to induce production of IL-22 and IL-17A	[63]
AD	S. aureus	Mice	Increase the production of pro-inflammatory mediators by dermal fibroblasts, and cause epidermal thickening with infiltration of the dermis by mast cells and eosinophils in mice, inducing the production of IL-4, IL-5, IFN-γ, and IL-17	[118]
	ADSCs	AD mice	Reduce the levels of serum IgE, the number of eosinophils in blood, and the infiltration of mast cells, $CD86^+$, and $CD206^+$ cells in skin lesions, and decreased the expression of inflammatory cytokines	[66]
	ADSCs	AD mice	Reduce trans-epidermal water loss, enhance stratum corneum hydration, decrease	[67]

(*continued on next page*)

Table 1 (*continued*)

Disease	Source	Model	Mechanism	Ref.
			inflammatory cytokines secretion, and increase the production of ceramides and dihydroceramides	
SSc	SSc neutrophils	HDFs and ECs	22 dysregulated miRNAs and 281 dysregulated lncRNAs in exosomes could change many fibrosis related genes in the Wnt, AMPK, IL-23 and Notch signaling pathways	[71]
	SSc fibroblasts	SSc patients	Collagen-related microRNA levels in exosomes were dysregulated, resulting in the increased frequencies of vascular involvements, including skin ulcers or pitting scars	[69]
	Serum of SSc patients	HDFs	Cause dose-dependent stimulation of profibrotic gene expression and type I collagen and fibronectin production and secretion	[73]
	Plasma of SSc patients	ECs	High levels of S100A8/A9 in exosomes from SSc PBMCs and neutrophils could suppress the proliferation and migration of human dermal microvascular endothelial cells	[72]
	BMSCs	SSc mice	Transfer miR-151–5p to the recipient BMSCs to inhibit IL4Rα expression, downregulate mTOR pathway activation to enhance osteogenic differentiation and reduce adipogenic differentiation, rescuing osteopenia, impaired BMSCs, tight skin, and immune disorders in SSc mice	[74]

Abbreviations: Systemic Lupus Erythematosus, SLE; Atopic Dermatitis, AD; Systemic Sclerosis, SSc; Generalized Pustular Psoriasis, GPP; Mesenchymal Stem Cells, MSCs; Adipose-derived MSCs, ADSCs; Bone Marrow-derived MSCs, BMSCs; Human Dermal Fibroblasts, HDFs; Human Keratinocytes, HaCaTs; Endothelial Cells, ECs; Peripheral Blood Monocytes, PBMCs; Interferon Alpha, IFN-α; Interferon Gamma, IFN-γ; Tumor Necrosis Factor Alpha, TNF-α; Interleukin, IL; Mitogen-Activated Protein Kinases, MAPKs; Adenosine Monophosphate Activated Protein Kinase, AMPK; Nuclear Factor Kappa B, NF-κB; TNF receptor-associated factor, TRAF; DNA-methyltransferase1, Dnmt1; Phospholipase A2, PLA2

psychological, metabolic, arthritic, and cardiovascular comorbidities [59]. For a long time, the pathogenesis of psoriasis has been a hotspot for dermatological research. Exosomes derived from both immune and nonimmune cells can participate in suppressing or stimulating the immune responses depending upon the context of inflammatory and autoimmune diseases.

2.3.2.2. Exosomes in psoriasis pathogenesis. Keratinocytes are the main constituents of the epidermis and relate to the formation of psoriatic lesions. The dysregulations of the proliferation and differentiation of keratinocytes are the key characteristics of psoriasis [60]. Jiang et al. found that psoriatic keratinocyte-derived exosomes activated the NF-κB and p38 mitogen-activated protein kinase (MAPK) pathway, and induced expressions of neutrophil pro-inflammatory factors IL-6, IL-8, and TNF -α [61]. The keratinocyte-derived exosomes from imiquimod-induced epidermis exacerbated skin lesions in psoriasis-like mice, contributing to the psoriasis progression. Besides, keratinocytes interact with infiltrating immune cells (such as neutrophils and mast cells) through exosomes, thereby positively affecting the epidermal microenvironment of psoriasis. Shao et al. verified that the exosomes secreted by neutrophils of patients with generalized pustular psoriasis could be internalized by keratinocytes, and then increased the expression of inflammatory molecules in keratinocytes via activating NF-κB and MAPK signaling pathways, such as IL-1β, IL-36 G, IL-18, and TNF-α [62]. Cheung et al. found that IFN-α-induced mast cell transferred cytoplasmic phospholipase A2 (PLA2) activity to neighboring CD1a-expressing cells via exosomes, leading to a CD1a-reactive T cell response by inducing the production of IL-22 and IL-17A in psoriasis patients [63].

2.3.3. Atopic dermatitis

2.3.3.1. AD characteristics. Atopic dermatitis (AD) is a chronic inflammatory skin disorder possessing complex pathogenesis characterized by barrier dysfunction, immune dysregulation, and skin microbiota dysbiosis [64]. Therapeutic methods require a multistep approach, including reducing pruritus and establishing disease control, such as the use of topical anti-inflammatory agents, phototherapy, systemic immunosuppressants, or dupilumab [65]. However, the treatment of AD is still challenging, and there is an urgent need for effective and safe treatments.

2.3.3.2. Exosomes in AD application. ADSCs can exert a strong paracrine effect by secreting active soluble factors and exosomes to modulate the inflammation, showing the potential treatment option for AD. Cho et al. found that the injection of ADSC-exos could ameliorate AD in the NC/Nga mice treated with house dust mite antigens, by reducing the level of serum IgE, eosinophils, and pro-inflammatory cytokines, such as IL-4, IL-23, IL-31, and TNF-α [66]. This result indicated the value of ADSC-exos in improving pathological symptoms in AD skin lesions. Shin et al. found that in an oxazolone-induced dermatitis model, the subcutaneous injection of ADSC-exos remarkably reduced trans-epidermal water loss while enhancing stratum corneum hydration and markedly decreasing the levels of inflammatory cytokines such as IL-4, IL-5, IL-13, TNF-α, IFN-γ, IL-17, and thymic stromal lymphopoietin (TSLP) [67]. This meant that ASC-exos effectively restored epidermal barrier functions in AD by promoting the de novo synthesis of ceramides.

2.3.4. Systemic sclerosis

2.3.4.1. SSc characteristics. Systemic sclerosis (SSc) is an autoimmune disease of unknown etiology characterized by vascular abnormalities, immune system activation, and disturbances in the fibroblast function of skin and internal organs [68]. The SSc pathogenesis is complex and not fully understood, and is difficult to classify patients and choose the most appropriate treatment. The miRNAs and proteins are selectively packaged in exosomes that differ in terms of their physiological and SSc conditions. Nakamura et al. found that SSc showed decreased serum exosome levels, which could present lots of vascular abnormalities, leading to the higher susceptibility to pitting scars and ulcers [69]. These exosome cargoes are potential biomarkers for diagnosing, monitoring the disease evolution, and treatment responses.

2.3.4.2. Exosomes in SSc pathogenesis. Neutrophils are critical players in

autoimmunity, inflammation, vasculopathy, and fibrosis during the pathology of SSc [70]. Li et al. found that human dermal microvascular endothelial cells and human primary skin fibroblasts stimulated with dSSc neutrophils-exos showed different fibrosis-related gene expression in the Wnt, adenosine monophosphate-activated protein kinase (AMPK), IL-23, and NOTCH signaling pathways [71]. Furthermore, the high levels of S100A8/A9 in SSc exosomes derived from plasma, peripheral blood monocytes, and neutrophils, separately could suppress the proliferation and migration of human dermal microvascular endothelial cells [72]. Meanwhile, the serum exosomes from SSc patients contain miRNAs that showed a markedly profibrotic profile and induced a profibrotic phenotype in target normal fibroblasts in vitro. Wermuth et al. found that SSc serum exosomes showed 6 profibrotic miRNAs up-regulation and 10 antifibrotic miRNAs down-regulation compared to normal serum exosomes [73]. Exosomes isolated from SSc patients promoted normal human dermal fibroblasts to express the profibrotic gene, type I collagen, and fibronectin. Thus, exosomes were involved in the pathogenesis of SSc and may be a promising therapeutic target for SSc patients.

2.3.4.3. Exosomes in SSc application. Recently, the exosome-mediated transfer may be a new mechanism to provide therapeutic effects in MSCT. Chen et al. investigated that the miR-151–5p derived from donor MSC-exosomes could inhibit IL4Rα expression in the recipient BMSCs of SSc mice, thereby enhancing osteogenic differentiation, rescuing osteopenia, and immune disorders [74]. The analysis of the complicated content of exosomes and other vesicles, which are released into the extracellular space and circulation, will undoubtedly enable the development of personalized and individualized medicine for patients with SSc.

3. Exosomes in cutaneous medical aesthetics

With the development of society and the change of human aesthetic, the scar, facial aging, pigmentation, hair loss and other skin problems are attracting increasing attention. Medical cosmetic intervention is beneficial to change the personal impression and improve mood and self-esteem. Exosomes provide a multifaceted strategy for promoting cutaneous regeneration and repair in skin cosmetology (Fig. 3).

3.1. Scar removal

3.1.1. Scar formation characteristics

Scar formation is the biological process of wound healing after skin defect extending to the reticular dermis. Pathological or inflammatory scars include atrophic, hypertrophic, and keloids with variable degrees

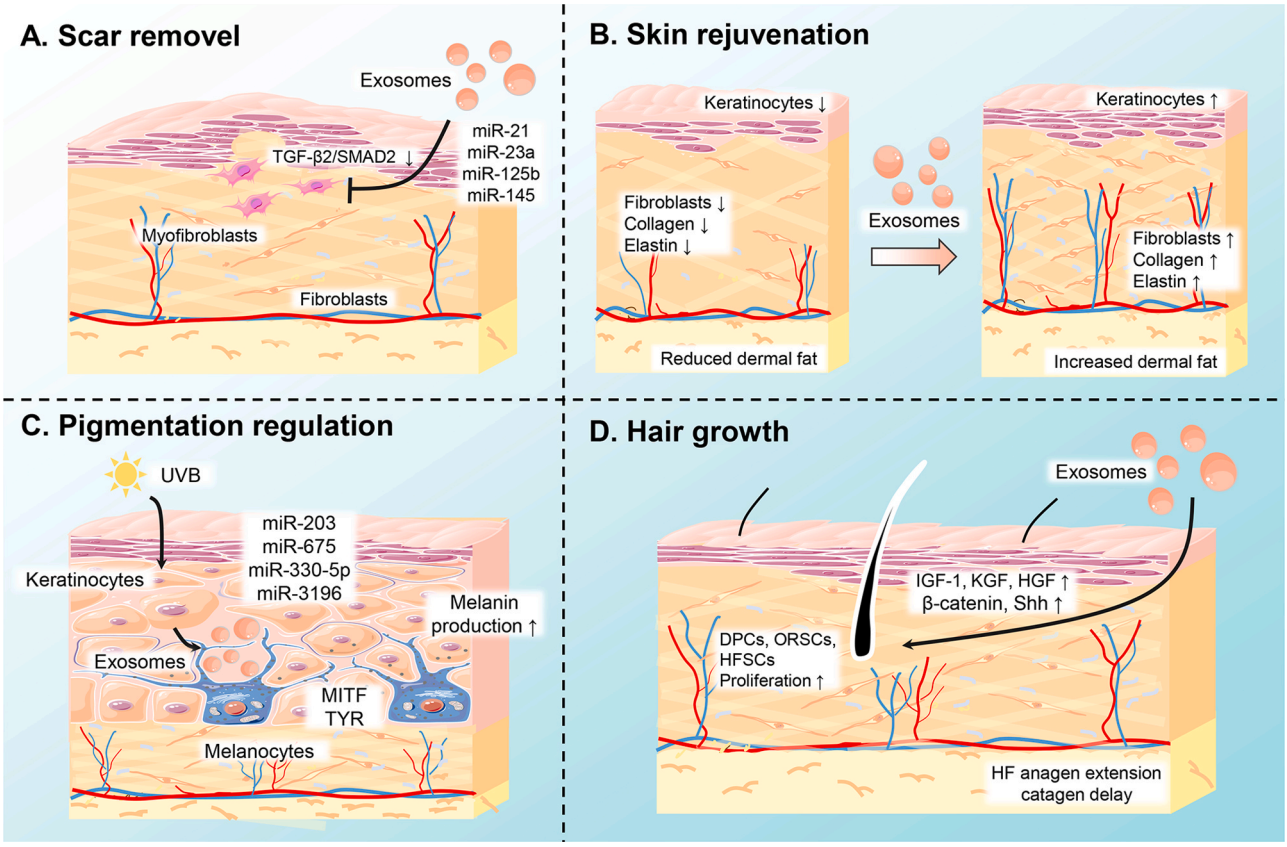

Fig. 3. The mechanisms of exosomes in cutaneous medical aesthetics. (A) Exosomes from umbilical cord-derived MSCs, enriched in miR-21, miR-23a, miR-125b, and miR-145, targeted the TGF-β2/SMAD2 pathway to inhibit the differentiation of fibroblasts to myofibroblasts, resulting in reduced excessive fibrosis and scar formation. (B) Exosomes could improve keratinocytes and fibroblasts function, enhance collagen and elastin synthesis, and increase dermal fat, thus promoting the regenerative and restorative capacity for skin anti-aging. (C) After exposure to the UVB, the keratinocyte-derived exosomes modulated their miRNA content to increase melanocyte pigmentation via miR-3196 and MITF-dependent signaling pathways or miR-203 and MITF-independent signaling pathway. The miR-330–5p overexpressing in keratinocyte-derived exosomes decreased the melanin production and TYR expression in melanocytes. And the miR-675 from keratinocyte exosomes involved in H19 lncRNA downregulation-stimulated melanogenesis, by inhibiting MITF expression. (D) The dermal papilla cells-derived exosomes promoted the viability of DPCs, ORSCs, and HFSCs, increased the expression of IGF-1, KGF, HGF, β-catenin, and Shh, and also accelerated the onset of HF anagen, postponed catagen, longer hair shafts in the skin of mice. Hair Follicle Stem Cells, HFSCs; Dermal Papilla Cells, DPCs; Hair Follicle, HF; Outer Root Sheath Cells, ORSCs; Transforming Growth Factor Beta, TGF-β; Keratinocyte Growth Factor, KGF; Insulin-Like Growth Factor, IGF; Hepatocyte Growth Factor, HGF; Sonic Hedgehog, Shh; Ultraviolet B, UVB; Melanocyte Inducing Transcription Factor, MITF; Tyrosinase, TYR.

of redness or hyperpigmentation. The popular reasons include trauma, burn, surgery, vaccination, skin piercing, folliculitis, acne, and herpes zoster infection [75]. The emergence and evolution of scars vary from different risk factors, including reduced apoptosis of fibroblasts, excessive collagen deposition, enhanced expression of TGF-β1, delayed keratinocyte function, prolonged inflammation, excessive angiogenesis, and even aging [76]. Exosomes are new kind of mediators released by multiple cell types in scar formation, including macrophages, fibrocytes, and fibroblasts/myofibroblasts [77]. For instance, Chen et al. investigated that lncRNA-ASLNCS5088 was enriched in M2 macrophage-derived exosomes, which could be transferred to fibroblasts efficiently, and then acted as an endogenous sponge to adsorb microRNA-200c-3p, resulting in increased glutaminases and alpha-smooth muscle actin (α-SMA) expression, to induce hypertrophic scar progression [78]. Thus, M2 macrophages are critical for persistent scar formation via exosome-mediated intercellular communication.

3.1.2. Exosomes in scar removel

There are several complementary therapies such as surgery, laser therapy and cell therapy to minimize and improve scars appearance (Table 2) [79]. ADSC-exos can accelerate the repair process of scars after wounds. Very interestingly, the study of Hu et al. showed the increased collagen I and III production by systemic administration of ADSC-exos in the early stage of mouse wound healing, while ADSC-exos might inhibit collagen expression to reduce scar formation in the late stage [80]. They provided a new perspective of ADSC-exos to optimize the fibroblast characteristics for soft tissue repair. Wang et al. confirmed that ADSC-exos promoted ECM remodeling and scarless repair in a mouse model [81]. The underlying mechanism might relate to the regulation of the ratios of collagen III: collagen I, TGF-β3: TGF-β1, matrix metalloproteinase (MMP) 3: tissue inhibitor of metalloproteinases 1, and the prevention of myofibroblast differentiation. Besides, in a mouse model of full-thickness skin wounds, ADSC-exos could promote collagen synthesis and optimize collagen deposition by activating the PI3 Kinase Akt (PI3K/Akt) signaling pathway to shorten healing time and reduce scar formation in the mouse model [82]. Wang et al. showed that the use of ADSC-exos in combination with multifunctional FEP scaffold dressing, consisting of F127-PEI and APu, could speed up the healing with less scar tissue formation and skin appendage regeneration through enhanced cell proliferation, granulation tissue formation, collagen deposition, remodeling, and re-epithelialization [83]. This study showed that combining bioactive ADSC-exos into multifunctional dressing was of great potential in repressing scar formation and generating skin appendages in the healed tissue.

Other types of MSC-exos also exhibit the ability to repair scar. Zhang et al. observed that exosomes from human induced pluripotent stem cell-derived mesenchymal stem cells (iPSC-MSCs) could promote re-epithelialization and angiogenesis, promotion of collagen maturity, and reduce scar widths [84]. During wound healing in diabetic mice, the exosomes from menstrual blood-derived mesenchymal stem cells enhanced neoangiogenesis through VEGF-A upregulation, accelerated re-epithelialization, possibly through the NF-κB p65 subunit upregulation, resulting in less scar formation [29]. Fang et al. found that exosomes from umbilical cord-derived MSCs (uMSCs), were enriched in specific miR-21, miR-23a, miR-125b, and miR-145 [85]. In a skin-defect mouse model, uMSCs-exos could interfere with the activity of the TGF-β2/SMAD2 pathway to suppress myofibroblast differentiation and over-aggregation, leading to reduced excessive fibrosis and scar formation (Fig. 3A). In addition, Hu et al. demonstrated that the local transplantation of exosomes from human umbilical cord blood plasma with a high content of miR-21–3p accelerated re-epithelialization, reduced scar widths, and enhanced angiogenesis by inhibiting PTEN and sprouty homolog 1 (SPRY1) in the mouse skin wounds [86]. These results indicated that MSC-Exos, including ADSC-exos, could regulate the function of fibroblasts, and the deposition or arrangement of collagen to promote a scarless pattern. ADSC-exos are a promising therapeutic approach for enhancing wound healing and preventing scars.

3.2. Skin rejuvenation

3.2.1. Skin aging characteristics

The skin undergoes physiological changes and inevitably loses its structural and functional characteristics as a consequence of the intrinsic and extrinsic aging process. Extrinsic hostile factors, such as air pollution, lifestyle choices, and particularly ultraviolet (UV) radiation, contribute to skin aging [87]. Photoaging, induced by UV exposure, is

Table 2
The mechanism of exosomes in reducing scar formation.

Source cells	Model	Mechanism	Potential application	Ref.
Human ADSCs	Mice skin wound	ADSC-exos increased collagen I and III production in the early stage of wound healing, and inhibited collagen expression to reduce scar formation in the late stage	Reduced scar formation	[80]
Human ADSCs	Mice full-thickness dorsal wounds	ADSC-exos promoted ECM reconstruction by regulating the ratios of collagen type III: type I, TGF-β3:TGF-β1 and MMP3:TIMP1, and by regulating fibroblast differentiation to mitigate scar formation	Reduced scarring extent	[81]
Human ADSCs	Mice full-thickness wounds	ADSC-exos promoted fibroblast proliferation and migration and optimized collagen deposition via the PI3K/Akt signaling pathway	Reduced scar formation	[82]
Mice ADSCs	Diabetic mice full-thickness wound	ADSC-exos in combination with multifunctional dressing enhanced cell proliferation, granulation tissue formation, collagen deposition, remodeling, and re-epithelialization	Less scar tissue formation, skin appendage regeneration	[83]
Human iPSC-MSCs	Rat skin wound	iPSC-MSC-exos promoted the proliferation and migration of human fibroblasts and HUVECs, enhance fibroblasts collagen and elastin secretion, and increased tube formation by HUVECs	Reduced scar widths	[84]
Human menstrual blood-MSCs	Diabetic mice full-thickness excisional wound	MenSC-exos enhanced neoangiogenesis through VEGFA upregulation, accelerated re-epithelialization through activating NF-κB signaling pathway, caused less scar formation through decreased Col1:Col3 ratio	Less scar formation	[29]
Human umbilical cord-MSCs	Mice full-thickness skin defects	uMSC-exos containing miR-21, miR-23a, miR-125b, and miR-145 suppressed myofibroblast formation by inhibiting excess α-SMA and collagen deposition through the TGF-β/SMAD2 signaling pathway	Fibroblasts to myofibroblasts differentiation suppression, prevented scar formation	[85]
Human umbilical cord blood plasma	Mice skin wounds	UCB-exos containing miR-21–3p accelerated re-epithelialization, reduced scar widths, and enhanced angiogenesis, through inhibition of PTEN and SPRY1	Less scar formation	[86]

Abbreviations: Mesenchymal Stem Cells, MSCs; Adipose-derived MSCs, ADSCs; Umbilical Cord-derived MSCs, uMSCs; Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells, iPSC-MSCs; Extracellular Matrix, ECM; Menstrual Blood-MSCs, MenSC-exos; Transforming Growth Factor-Beta, TGF-β; Human Umbilical Vein Endothelial Cells, HUVECs; Nuclear Factor Kappa B, NF-κB; Vascular Endothelial Growth Factor, VEGF; Interleukin, IL; Phosphatase And Tensin Homolog, PTEN; Sprouty Homolog 1, SPRY1

characterized by sunburn, irregular pigmentation, dryness, sallowness, roughness, fine and coarse wrinkles, which are mainly due to changes in the ECM materials [88]. Dermal fibroblasts are the cell types majoring in the synthesis of structural components such as procollagen and elastic fibers [89]. Aging changes the number and proliferation of HDFs, reduces collagen synthesis and repair, and accelerates the degradation of the existing skin matrix by MMPs. The beneficial effects of paracrine substance secreted from various cells, especially stem cells-CM and exosomes, can consequently maintain the homeostasis and juvenescence of skin.

3.2.2. Exosomes in skin rejuvenation

As exosomes can mediate intercellular communication and regulate the properties of HDFs, exosomes have recently received tremendous attention in anti-aging skin rejuvenation (Fig. 3B) (Table 3). The exosomes derived from the three-dimensional culture of HDFs spheroids (3D-HDF-exos) caused increased procollagen type I and decreased MMP-1 expression, through down-regulating TNF-α and up-regulating TGF-β [90]. The 3D-HDF-exos resulted in a higher level of dermal collagen deposition than BMSC-derived exosomes in vitro and in a nude mouse photoaging model. Therefore, 3D-HDF-exos might regulate dermal fibroblasts to induce efficient collagen biosynthesis and ameliorate inflammation, possessing anti-skin-aging properties. Pluripotent stem cells (PSCs) were cultured under well-established conditions and could maintain the physiological characteristics regardless of promising potential for self-renewal [91]. In the UVB-induced photoaging and natural senescence model, Oh et al. demonstrated that human induced pluripotent stem cell-derived exosomes (iPSC-exos) ameliorated genotypic and phenotypic changes of photoaging HDFs [92]. Mechanically, the beneficial effects of iPSC-Exo were realized by reducing the expression level of senescence-associated β-galactosidase (SA-β-gal) and MMP1/3, and restoring the collagen type I expression in senescent HDFs. Senescent cells accumulate in various tissues over time and contribute to tissue dysfunction and aging-associated phenotypes. Bae et al. investigated the anti-senescence property of exosomes originated from embryonic stem cells and found that this exosome-containing mmu-miR-291a-3p reversed the senescence in HDFs, mechanically through the TGF-β receptor 2 pathway [93]. This result suggested that ESC-derived exosomal mmu-miR-291a-3p was of potential for cell-free intervention against skin aging.

Table 3
The mechanism of exosomes in combating skin aging.

Source cells	Model	Mechanism	Potential application	Ref.
3D culture of HDFs spheroids	UVB-induced HDFs, photoaging mouse	Exosomes increased procollagen type I and decreased MMP-1 expression, through down-regulating TNF-α and up-regulating TGF-β	Induced collagen biosynthesis, ameliorated inflammation and skin-aging	[90]
Human iPSCs	UVB-exposed HDFs	Exosomes reduced the SA-β-Gal and MMP-1/3 expression and restored the collagen type I expression	Inhibited photo-aged HDFs damages	[92]
Embryonic stem cells	Senescent HDFs	ESC-exos containing mmu-miR-291a-3p reversed the HDFs senescence, through the TGF-β receptor 2 pathway	Anti-senescence of HDFs	[93]

Abbreviations: Human Dermal Fibroblasts, HDFs; Senescence-Associated β-galactosidase, SA-β-gal; Ultraviolet, UV; Three-Dimensional, 3D; Induced Pluripotent Stem Cells, iPSCs; Matrix Metalloproteinase, MMP; Tumor Necrosis Factor Alpha, TNF-α; Transforming Growth Factor Beta, TGF-β

3.3. Pigmentation regulation

3.3.1. Skin pigmentation characteristics

In the thin outermost layer of the skin, solar irradiation activates various regulatory agents and pathways that lead to increased melanin synthesis in melanocytes. Melanocytes convey melanin into epidermal cells and combine with epidermal cells to form a functional epidermal melanin unit, which plays a key role in regulating pigmentation and homeostasis of the epidermis [94]. One of the first lines of cutaneous photoprotective defense is the synthesis of melanin [95]. However, after exposure to damaging agents, excessive melanin production and irregular accumulation in skin cells also result in skin burning, tanning, and pigmentation, including solar lentigines, freckles, age spots, and melisma [96]. Skin pigmentation depends on interactive influences between keratinocytes and melanocytes in the epidermis. The exosomes carry multiple membrane proteins and cytosolic components to melanocytes and regulate pigmentation in both healthy and diseased status by modulating gene expression and enzyme activity (Table 4) [97].

3.3.2. Exosomes in pigmentation regulation

Keratinocytes, occupying the important position on the epidermal melanin unit, have been reported to secrete exosomes containing soluble factors and miRNAs, to participate in pigmentation modulation and the homeostasis of the skin [98]. Takano et al. found that the exosome fraction isolated from UVB-irradiated keratinocytes significantly activated melanocytes, suggesting the validity of quantitative changes in exosome secreted by keratinocytes on the substantial regulation of human skin color development [99]. Liu et al. suggested that keratinocytes crosstalked with melanocytes in the epidermal melanin unit via exosomal miRNAs [100]. They found that keratinocyte exosomes overexpressed miR-330–5p and induced a significant decrease in the production of melanin and expression of tyrosinase (TYR) in melanocytes. Cicero et al. reported that the miRNA profile of keratinocyte exosomes was modified stimulated by UVB [15]. They found that the exosomes from keratinocytes containing miR-3196 increased the intracellular melanin content of human melanocytes via melanocyte inducing transcription factor (MITF)-dependent signaling pathways. Additionally, keratinocytes-derived exosomes highly expressed miR-203 to regulate melanogenesis in melanoma cells, increasing pigmentation and TYR protein levels. Kim et al. showed that miR-675 released from keratinocyte exosomes involved in H19 lncRNA downregulation-stimulated melanogenesis, by inhibiting MITF expression through targeting its 3'-untranslated region [101]. Exosomes, as communication for pigment transfer from melanocytes to keratinocytes, continue to be explored for preventing unusual pigmentation (Fig. 3C). Studies on exosomes between keratinocytes and melanocytes will open the path for new strategies to manipulate pigmentation in healthy and diseased states.

3.4. Hair growth

3.4.1. Hair loss characteristics

Hair loss, also known as alopecia or baldness, is the most readily visible human trait due to various reasons, such as aging, diseases, and medications [102]. Hair follicle behavior is characterized by a succession of active (anagen) and dormant (telogen) phases, separated by intense tissue remodeling processes of regression (catagen) and regeneration (neogen) [103]. Hair follicle stem cells (HFSCs) are the epithelial stem cells with features of the slowly cycling and quiescent nature, proliferation at the onset of hair growth, persistence throughout the lifetime of the organism, and distinct biochemical makeup and their

Table 4
The mechanism of exosomes in pigmentation regulation.

Source cells	Model	Mechanism	Potential application	Ref.
Mouse keratinocytes	melanocytes	Keratinocytes exosomal miR-330–5p reduced melanin production, suppressed TYR expression in melanocytes to suppress pigmentation	Pigmentation inhibition	[100]
Human keratinocytes	melanocytes	Keratinocytes exosomes containing miR-3196 increased the intracellular melanin content of melanocytes via MITF-dependent signaling pathways, and highly expressed miR-203 to regulate melanogenesis, increasing pigmentation and TYR protein levels	Pigmentation regulation	[15]
Human keratinocytes	Melanocytes and mouse skin	miR-675 released from keratinocyte exosomes involved in H19 lncRNA downregulation-stimulated melanogenesis, by inhibiting MITF expression through targeting its 3'UR	Melanogenesis regulation	[101]

Abbreviations: Tyrosinase, TYR; Melanocyte Inducing Transcription Factor, MITF; 3'-Untranslated Region, 3'UR

location in a well-protected niche [104]. Hair dermal papillae are rich in pluripotent stem cells [105]. Dermal papilla cells (DPCs) are mesenchyme-derived fibroblasts that interact with various types of epithelial cells, hair germ cells, and stem cells in the hair follicles [106]. HFSCs and DPCs play important roles in hair growth and regeneration, especially in maintaining hair follicles during the growth phase. There are some available intervention strategies, including the medications minoxidil or finasteride and hair transplant surgery. Recent studies have focused on altering the composition and up-regulating the secretome of the stem cells, especially exosomes, to recover or replenish the signals of hair regrowth (Table 5).

Table 5
The mechanism of exosomes in hair growth.

Source cells	Model	Mechanism	Potential application	Ref.
Human DPCs	ORSCs, Shaved mice	DPC-exos accelerated the onset of HF anagen and delayed catagen in mice, enhanced ORSCs proliferation and migration, and stimulated the β-catenin and Shh expression	HF growth and development	[107]
3D-cultured human DPCs	DPCs, ORSCs, HFs, Shaved mice	3D-DPC-exos promoted the DPCs and ORSCs viability, increased the IGF-1, KGF, and HGF expression in DPCs, and facilitated hair shaft elongation in cultured human HFs, and induced anagen from telogen and also prolonged anagen in mice	Hair growth, hair regeneration	[108]
Goat DPCs	HFSCs	miR-22–5p produced by DPCs-exos inhibited HFSCs proliferation by targeting LEF1	HFSCs proliferation regulation	[109]
Rat ADSCs	Diabetic rat wound model	OxOBand loading ADSC-exos facilitated the hair follicles formation and promoted the epidermal morphology	Hair follicle formation	[110]
Human BMSCs	Shaved mice	The microneedle device integrated with MSC-exos and UK5099, enhanced the treatment efficiency at a reduced dosage, leading to promoted pigmentation and hair regrowth	Hair growth	[111]

Abbreviations: Three-Dimensional, 3D; Hair Follicle Stem Cells, HFSCs; Dermal Papilla Cells, DPCs; Hair Follicle, HF; Outer Root Sheath Cells, ORSCs; Mesenchymal Stem Cells, MSCs; Bone Marrow MSCs, BMSCs; Adipose-Derived MSCs, ADSCs; Fibroblast Growth Factor, FGF; Sonic Hedgehog, Shh; Keratinocyte Growth Factor, KGF; Insulin-Like Growth Factor, IGF; Hepatocyte Growth Factor, HGF

3.4.2. *Exosomes in hair growth*

DPC-exos can regulate hair follicle (HF) growth, cycle stages for hair growth, and stimulate the proliferation and differentiation of outer root sheath cells (ORSCs). As Zhou et al. reported, the cutaneously injected DPC-exos into HFs at different HF cycle stages, resulted in the accelerated onset of HF anagen, delayed catagen, longer hair shafts, and larger bulges in the skin of mice [107]. This was mainly mediated by up-regulated β-catenin and sonic hedgehog (Shh) levels. Kwack et al. found that the three-dimensional cultured dermal papilla cells-derived exosomes (3D-DPC-exos) promoted the viability of DPCs and ORSCs, increased the expression of insulin-like growth factor (IGF) 1, keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) in DPCs, and also facilitated hair shaft elongation in cultured human hair follicles [108]. Besides, local injections of 3D-DPC-exos accelerated the onset of HF anagen and postponed catagen in mice [108]. Yan et al. found that DPC-exos attached to the surface of HFSCs co-cultured with DPCs, and were essential for HFSC proliferation and differentiation [109]. A total of differentially expressed 111 miRNAs were presented in the DPC-exos compared with DPCs. Among them, miR-22–5p produced by DPCs-exos inhibited HFSC proliferation by targeting LEF1. DPC-exos might be a promising candidate agent for the prevention and treatment of hair loss (Fig. 3D).

The traditional subcutaneous injection of exosomes often requires frequent administration due to their short-term retention in vivo. For better efficiency of exosomes release and absorption, combining exosomes with advanced biomaterials or joint drug delivery might hold promise for hair loss therapy. Shiekh et al. designed the oxygen releasing anti-oxidant wound dressing OxOBand, composed of polyurethane, to load ADSC-exos [110]. In a diabetic rat model, OxOBand facilitated the hair follicle formation with several hair follicles and promoted the epidermal morphology similar to that of healthy skin. Yang et al. invented a microneedle device, which was supported by a water-soluble hyaluronic acid (HA)-based patch base, and integrated with MSC-exos and a small molecular drug UK5099, reinforcing the hair growth treatment efficiency at a reduced dosage by transporting the loaded cargoes into the HFs microenvironment [111]. This microneedle system activated the telogen-to-anagen transition, and promoted pigmentation and hair regrowth in a painless and minimally invasive manner. This highly bioactive cell-free strategy provides a potential avenue for the treatment of hair loss.

4. Current limitation of exosomes in clinical skin application

Exosomes have gradually become multipotent and multifunctional frontiers in contemporary medicine, especially in dermatology and cutaneous medical aesthetics. However, there are still some limitations of exosomes that need to be mentioned for clinical translational application.

There are limitations of exosomes in source, isolation, purification, and identification. The quality control is strictly needed for clinical

applications, which require a high degree of standardization, involving the isolation of cells, the isolation of cultured serum and exosomes [112]. Currently, there is no standardized procedure for the isolation and storage of exosomes, as well as for the identification of exosomes which need comprehensive qualitative analysis of morphology, particle size, and protein. For skin therapy, the utilization of secretome derivatives, such as full conditioned media or purified exosomes generated in vitro, may present some disadvantages for cell manufacturing, storage, product safety, and their potential as a ready-to-go therapeutic product. In terms of the isolation techniques of exosomes, a variety of novel techniques have been or are currently being developed, including ultracentrifugation, size-based filtration, size-exclusion chromatography, polymer precipitation, and some novel combination techniques [20]. However, there is no one-size-fits-all approach among the existing techniques, and the complete isolation of exosomes from other components is unrealistic. As a result, improved protocols and standardized procedures are needed to achieve equilibrium in improving the yield and purity of exosomes. The production and concentration of exosomes in quantities sufficient for clinical administration are also challenging. To achieve the sufficient dose of exosomes in clinical application, it needs to expand the model of cell culture [113].

The other limitation is that the basic experiments related to cells and animals cannot accurately reflect the human level [114]. This is because human skin and animal skin tissue have specific species differences, and the same skin diseases and repair mechanisms are also different in humans and animals. For example, the mice skin is looser than humans, and the mice perform healing by wound contraction, which is significantly different from human wounds healing [115]. In some cases, it is not precise to directly use preclinical studies to explain the functions of exosomes in human application. This means that existing data may not be very predictive. Therefore, it is still very necessary to construct skin-related animal models that are more proximate to human skin. In addition, the existing research mainly focuses on the skin application of mouse- and human-derived exosomes, and the expression characteristics and levels of these two exosome secretomes in the genome and proteome are still unclear. Obviously, this factor may have a great impact on skin clinical trials.

The biosafety and efficacy are the priorities for the exosome application in clinical trials. At present, previous studies have been carried out on the cellular and animal levels, but accompanied by uncertain efficacy in humans. Considering that almost all cell types produce exosomes, the situation of exosome-mediated signal interaction is much more complicated and multifaceted in vivo, and strongly depends on the specific physiological and pathological environment [116]. The available sources of exosomes reported in dermatology and cutaneous medical aesthetics are complex, and exosomes from different cell sources may have similar positive effects on the same disease. So it is worth pondering to determine which cell types are safe and possess fewer side effects. More importantly, as exosomes are complicated in composition like biochemical cocktails, the biosafety and efficacy will be of effect deviations and are not very predictable to some extent. The effect of its human dose, dosing interval, administration mode on biosafety and efficacy will require more comprehensive data support compared with drugs with a single component [117]. Finally, other issues associated with the potential clinical application of exosomes in dermatology and cutaneous medical aesthetics, including follow-up, ethics, techniques, and supervision, are also very challenging (Table 6).

Table 6
The current limitation of exosomes in clinical skin application.

Exosomes-related limitation	Quality control of exosome source
	Exosomes isolation techniques and standardization, purity, yield, concentration, storage conditions
	Exosomes identification and characterization
Preclinical model-related limitation	Exosomes genomic and proteomic differences
	Different dose and concentrations in vitro and in vivo
	Model specificity in different species
	Differences in skin diseases and repair mechanisms
Clinical limitation	Immunogenicity, immunotoxicity, biodistribution persistence, metabolism, excretion
	Administration route, dosage, concentration
	Efficacy durability
	Long-term follow-up, periodic checking, side effects detection

5. Conclusion and perspectives

Many skin damages, including hair diseases, requires strict integration of medicine and aesthetics in the aspect of therapy. Exosomes, containing important paracrine mediators, are engaged in multiple physiological and pathological processes of the skin. Herein, we present the latest overview of the novel mechanisms and applications of exosomes in dermatology and cutaneous medical aesthetics. As cell-to-cell messengers, exosomes shuttle between various skin cells, like keratinocytes, fibroblasts, endothelial cells, adipocytes, and immune cells, by exerting paradox influences on tissue regeneration and repair. Specifically, the differential expression profile, immune and inflammatory responses, tissue regeneration and repair, and other regulatory mechanisms associated with exosomes, were the key points in the physiological responses and pathogenesis of some skin injuries and diseases. These endogenous exosomes can be developed as diagnostic biomarkers, due to their sensitivity and specificity of expression level in some immune-mediated dermatoses, including SLE, psoriasis, AD, and SSc. In addition, recent studies have shown that exosomes are also valuable candidates with regenerative and reconstructive potential. The exogenous exosomes generated by iPSC, uMSCs, HDFs, BMSCs, and ADSCs, exhibit impressive excellent properties to effectively repair skin or cosmetic problems. To some extent, exosomes derived from specific skin tissue cells or stem cells can not only treat various skin abnormalities, but also regulate skin homeostasis positively.

However, there are still some significant challenges in this area worth addressing. First of all, exosomes not only originate from a variety of cell types in the skin, but also transmit very complex biological information, so the mechanism of exosomes is still poorly understood in dermatology and needs to be further clarified. For example, exosomes produced by keratinocytes, fibroblasts, and immune cells can carry miRNAs and cytokines internalized into different targeted cells to regulate different processes. Exosomes are concerning with the mechanisms underlying the onset and progression of many skin diseases, involving numerous districts, different cell types, and complex interactions within the microenvironment. These make the cell-exosome-cell network of skin an intriguing but complex issue. Secondly, the skin disease-associated exosomes contain a large number of mRNAs, ncRNAs, and proteins that can reflect the physiological or pathological state of the cells of origin. Besides, due to the easy availability and non-invasive collection, the exosomes with cargo-specific patterns are sensitive and specific to predict the presence, or occurrence of dermatologic disease. The differentially expressed exosomes in saliva, blood, and skin tissue are expected to be used as biomarkers for the screening, diagnosis, and treatment of skin diseases. Thirdly, exosomes are carriers containing multi-component cargoes, like a cocktail encapsulation. Most of the existing studies focus on target screening or the phenotype and mechanism of a single cargo. More comprehensive and in-depth studies of the phenotype and function of exosomes with the complicated component are needed. Lastly, as most studies are focusing on cellular and animal levels and the clinical applications of exosomes for skin treatment is still very few, there are many unanswered questions regarding the methods

to optimize exosomes for clinical use. The safety and efficacy of exosome therapy require clinical trials to optimize treatment dose, cell resource, frequency of administration, before that exosomes will be offered as acceptable remedy for human skin treatment. Therefore, more extensive clinical trials are still urgent to further investigate the efficacy of exosomes in the field of dermatology and cutaneous medical aesthetics.

Collectively, we offer the key insights into the exosomes that are crucial orchestrators and promising candidates in dermatology and cutaneous medical aesthetics. Further studies are required to investigate the exosome-associated strategies for better clinical outcomes in the area of skin research.

CRediT authorship contribution statement

M.-C. Xiong, Q. Zhang and W.-J. Hu performed the literature search and wrote the manuscript. H.-B. Tang, M. Wu and Y.-P. Wu conceived the project and revised the manuscript. C.-R. Zhao, W.-C. Lv, Y.-C Wang and Y. Yi edited the manuscript. All authors reviewed the manuscript and all approved of the final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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