Life Sciences 357 (2024) 123066

Contents lists available at ScienceDirect

Life Sciences

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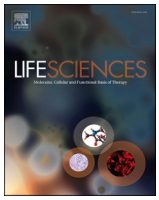

Exosomes from mesenchymal stem cells: Potential applications in wound healing

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ARTICLE INFO

Keywords:
Wound healing
Mesenchymal stem cells
Exosomes
Angiogenesis
Therapy

ABSTRACT

Wound healing is a continuous and complex process regulated by multiple factors, which has become an intractable clinical burden. Mesenchymal stem cell-derived exosomes (MSC-exos) possess low immunogenicity, easy preservation, and potent bioactivity, which is a mirror to their parental cells MSC-exos are important tools for regulating the biological behaviors of wound healing-associated cells, including fibroblasts, keratinocytes, immune cells, and endothelial cells. MSC-exos accelerate the wound healing process at cellular and animal levels by modulating inflammatory responses, promoting collagen deposition and vascularization. MSC-exos accelerate wound healing at the cellular and animal levels by modulating inflammatory responses and promoting collagen deposition and vascularization. This review summarizes the roles and mechanisms of MSC-exos originating from various sources in promoting the healing efficacy of general wounds, diabetic wounds, burn wounds, and healing-related scars. It also discusses the limitations and perspectives of MSC-exos in wound healing, in terms of exosome acquisition, mechanistic complexity, and exosome potentiation modalities. A deeper understanding of the properties and functions of MSC-exos is beneficial to advance the therapeutic approaches for achieving optimal wound healing.

1. Introduction

Skin injuries are one of the most common problems in clinical practice and pose a tremendous burden on patients [1–3]. Wound healing is divided into four phases according to current academic consensus: hemostasis, inflammation, proliferation, and remodeling [4,5]. Multiple cells and cytokines co-modulate the wound healing process and exhibit temporal and spatial specificities. Conventional wound treatment modalities include gauze dressings, continuous negative pressure therapy, skin grafts, and artificial materials [6–8]. However, these methods do not provide a perfect solution to accelerate wound healing, minimize side effects, or harmonize function, price, and efficiency [9] For example, gauze may adhere to the wound, causing secondary damage, and frequent gauze replacement may interfere with the healing process [10]. Continuous negative pressure drainage is costly and cannot be applied to infected or bleeding wounds. The limitations of existing treatment strategies have led to an urgent need to find novel treatments (Fig. 1).

Mesenchymal stem cells (MSCs) are specialized stem cell types with self-renewal ability and multi-directional differentiation potential [11–13]. MSCs participate in immune regulatory response and promote tissue regeneration by secreting active cytokines, and have become a research hotspot in regenerative medicine [14]. The therapeutic efficacy of MSCs has been well-documented in skeletal disorders [15], skin injuries [16], and wound healing. Although considerable experiments have confirmed the therapeutic utility of MSC, transferring MSC to

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https://doi.org/10.1016/j.lfs.2024.123066
Received 9 February 2024; Received in revised form 8 July 2024; Accepted 16 September 2024
Available online 19 September 2024

clinical applications is theoretically achievable. Deficiencies in immunocompatibility, stability, and heterogeneity restrain the further application of MSC [17].

Exosomes are subtypes of extracellular vesicles (EVs) with diameters ranging from 30 to 150 nm [18]. Exosomes are secreted by virtually all cell types and can be found in body fluids, such as blood [19], lymph fluid [20], urine [21], and cerebrospinal fluid [22,23]. Similar components and biomarkers in exosomes can be used for exosome identification and characterization, including proteins associated with biogenesis Alix and TSG101, flotillin, tetraspanins (CD81, CD63, and CD9), and ceramide [24,25]. Exosomes could deliver a variety of biological substances, including nucleic acids, proteins, lipids, and active cytokines, thus performing a variety of biological functions for intercellular communication [26]. As a paracrine product of MSCs, MSC-derived exos (MSC-exos) exhibit similar therapeutic utility to MSCs [27,28]. MSC-exos deliver angiogenesis and immunomodulation-related cytokines such as vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), hepatocyte growth factor (HGF), IL-6, and IL-10 [29] Bioactive substances interact with reconstruction-related cells, such as fibroblasts, keratinocytes, immune cells, and endothelial cells, thus speeding up collagen deposition and angiogenesis, hence offering better wound healing outcomes [30,31]. MSC-exos possess lower immunogenicity compared to primary stem cells, due to the absence of major histocompatibility complex (MHC) molecules on their surface, thus reducing the host immune response [32,33]. In addition, MSC-exos can be efficiently purified from cell culture medium by a standardized ultracentrifugation technique, which ensures the feasibility and controllability of the preparation process. Furthermore, MSC-exos lack nuclei and organelles, which substantially reduces their tumorigenicity and provides safety assurance for clinical applications [33]. These advantages make MSC-exos a promising candidate for cell-free therapeutic strategies in wound healing.

MSC-exos therapy is gaining momentum in wound repair research [34]. Various studies have recently been conducted to explore the mechanism of MSC-exos in wound healing and to explore better solutions for MSC-exos therapy, such as pre-treatment of MSCs, engineering exosomes, and combining MSC-exos with drugs and novel materials [35,36]. Exosomes from different tissues and stem cell sources differ in their reparative function and promotion of wound healing [37–40]. Therefore, this review focuses on recent investigations of different sources of MSC-exos related to wound healing, and summarizes the roles and mechanisms of MSC-exos in the wound healing process, hoping to provide effective treatment strategies for superior healing outcomes based on MSC-exos (Fig. 2).

2. ADSC-exos

Since their discovery, numerous studies have demonstrated the pluripotency and active paracrine activity of adipose-derived mesenchymal stem cells (ADSCs) [41,42]. ADSCs demonstrate promising therapeutic potential in areas including, but not limited to, wound healing, bone repair, cartilage reconstruction, tendon regeneration, and neuroprotection [43] ADSC-derived exosomes (ADSC-exos) exhibit similar effects to ADSCs in regenerative therapy. As a cell-free therapy, ADSC-exos are less tumorigenic and safer than ADSCs, without the risk of ethical conflicts, and therefore have attracted widespread attention [44].

ADSC-exos enhance skin cell function and regulate collagen synthesis- and angiogenesis-related cytokine expression to promote skin regeneration and improve wound healing [45]. Lee et al. demonstrated that ADSC-exos increased cell proliferation and migration of human dermal fibroblasts (HDFs) and induced upregulated expression levels of collagen, α-SMA, FGF2, and elastin [46]. Owing to these effects, ADSC-exos accelerated wound closure and re-epithelialization in vivo. Zhao et al. reported that human ADSC-exos (hADSC-exos) also inhibited apoptosis and attenuated the inflammatory response in the skin lesions, thus accelerating wound closure and epithelial regeneration in diabetic mice [47]. Besides, negative regulation of matrix metalloproteinase 1 (MMP1) and matrix metalloproteinase 3 (MMP3) enhanced collagen synthesis for wound healing by hADSC-exos.

The Wnt/β-catenin signaling pathway plays a crucial role in adult tissue homeostasis and regeneration [48,49]. ADSC-exos could promote the proliferation and migration and inhibit apoptosis of HaCaT cells via activating Wnt/β-catenin signaling pathway [50]. Li et al. found that ADSC-Exos increased COL-I, COL-III and decreased α-SMA expression in fibroblasts both in vitro and in vivo, and accelerated the healing of rat wound model by enhancing WNT/β-catenin pathway [51].

Reactive oxygen species (ROS) accumulation leads to oxidative stress, which in turn triggers cellular damage and inflammatory responses, thus delaying wound healing [52]. ADSC-exos could reduce ROS production in human umbilical vein endothelial cells (HUVECs) and improve mitochondrial function by increasing SIRT3 expression and

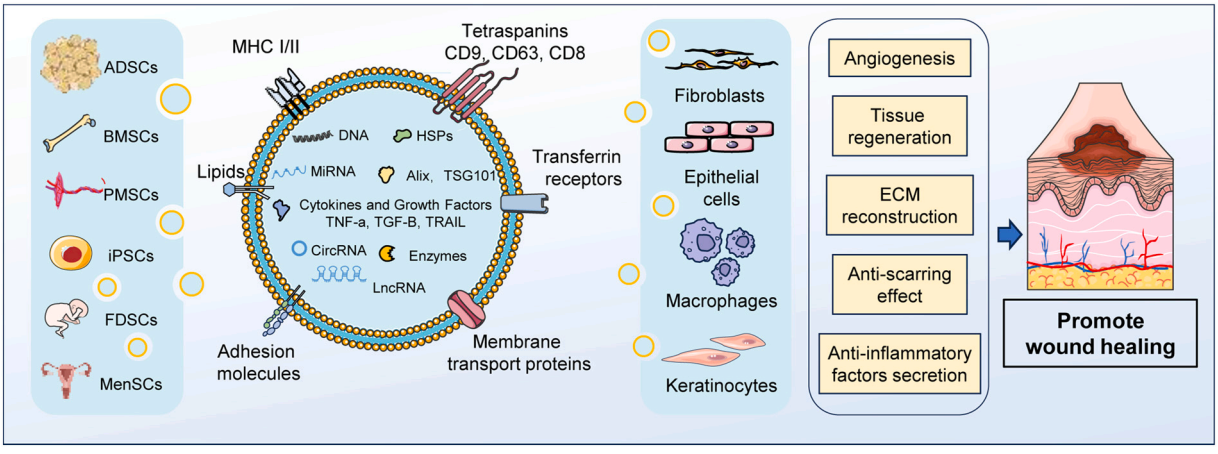

Fig. 1. Skin structure, wound types, and wound healing phases. **(A)** The skin could be divided into epidermis and dermis, connected to the deeper tissues through subcutaneous tissues. The primary cells in the epidermis are keratinocytes, which are involved in making up various layers of the epidermis. The dermis is located below the epidermis and consists mainly of dense connective tissue, with an abundance of immune cells and blood vessels. The subdermis lies beneath the dermis and is composed of loose connective tissue and adipose tissue. **(B)** Different types of wounds, including normal wound, diabetic wound, and burn wound. **(C)** The wound healing process consists of four periods: hemostasis, inflammation, proliferation, and tissue remodeling. This figure was partly generated using Servier Medical Art (https://smart.servier.com), provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license (https://creativecommons.org/licenses/by/3.0/).

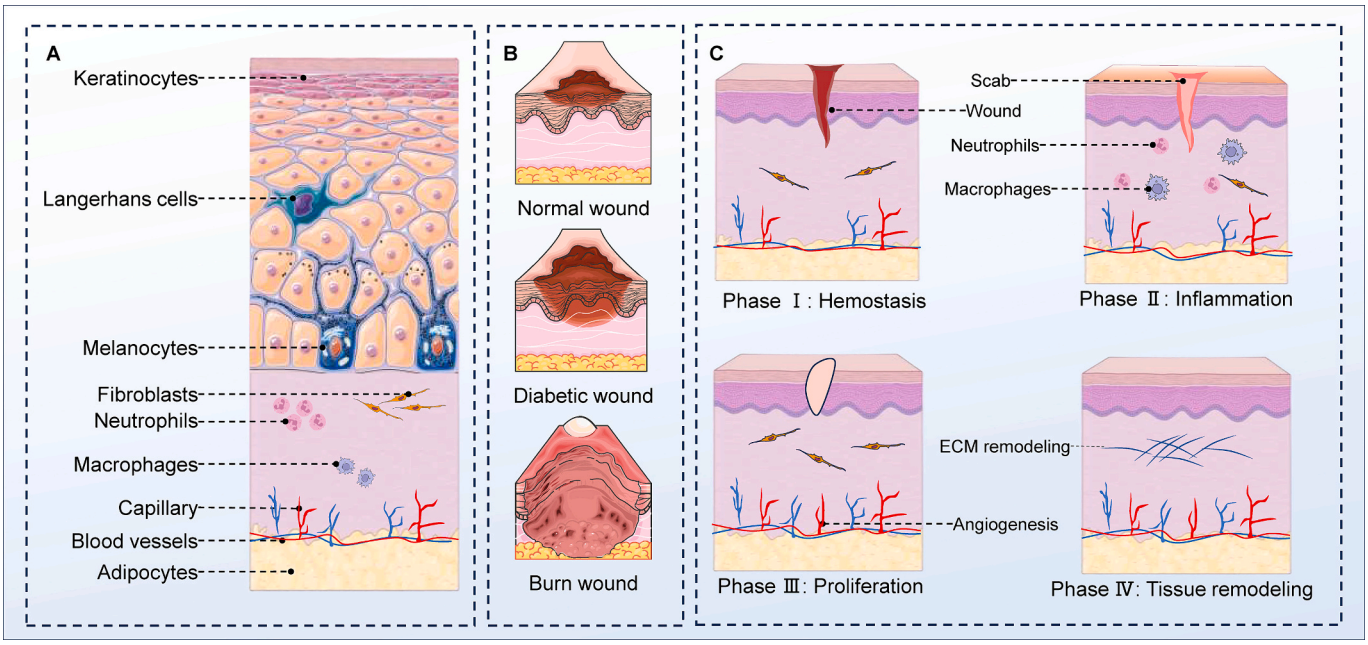

Fig. 2. The sources, features, and biological effects of MSC-exos. ADSCs, BMSCs, PMSCs, iPSCs, FDSCs, and MenSCs can secrete bioactive exosomes that facilitate the healing process of different types of wounds. Multiple macromolecules are present on the surface of exosomes, such as membrane transport proteins, transferrin receptors, tetraspanins, antigen-presenting molecules, glycoproteins, and adhesion molecules. The intracellular proteins, lipids, and nucleic acids could enter exosomes through the sorting mechanism, thus accomplishing recirculation in the body or delivering among different cells. These MSC-derived exosomes carry complex contents, acting on regeneration-associated cells and immune cells located in wounds. MSC-exos are capable of modulating cell proliferation, migration, and paracrine functions, resulting in rehabilitating inflammation equilibrium and superior wound healing. MHC, major histocompatibility complex class; HSP, heat shock protein; MiRNAs, microRNA; LncRNAs, long non-coding RNAs; CircRNAs, circular RNAs.

its downstream protein SOD2, and ameliorating vascular endothelial cell dysfunction in the high glucose (HG) microenvironment, thereby promoting angiogenesis and healing of chronic diabetic wounds [53].

2.1. NcRNAs from ADSC-exos

2.1.1. MiRNAs from ADSC-exos

MicroRNAs (miRNAs) are a series of highly conserved small non-coding RNA (ncRNA) molecules capable of affecting cellular signaling and function by inhibiting mRNA translation or promoting mRNA degradation [54,55]. However, the regulatory function of miRNAs is highly susceptible to stress, including metabolic stress [56]. Consequently, targeting miRNAs derived from ADSC-exos is a potential strategy to promote wound repair. ADSC-exos induced M2 phenotypic macrophage polarization by upregulating the expression of miR-34a-5p, miR-124-3p, and miR-146a-5p, which reduced cellular inflammation and accelerated fibroblast proliferation and migration in vitro [57]. Lv et al. produced engineered ADSC-exos loaded with miR-21-5p and demonstrated that overexpressed miR-21-5p promoted the proliferation and migration of HaCaT cells in vitro and facilitated diabetic rat wound healing by accelerating reepithelialization, collagen remodeling, angiogenesis [58]. MiR-146a-modified ADSC-exos could promote the migration and proliferation of fibroblasts and neovascularization, thereby facilitating the healing of back wounds in rats. These functions may be mediated by miRNA-146a-induced upregulation of heat shock protein 47 (SERPINH1) and phospho-extracellular signal-regulated kinase (p-ERK) [59]. Pi et al. found that miRNA-125a-3p from ADSC-exos could inhibit PTEN expression and enhance the cellular function of HUVECs, thereby promoting wound healing and angiogenesis in mice [60].

The phosphatidylinositol 3 kinase/Protein kinase B (PI3K/AKT) pathway plays a pivotal regulatory role in the wound healing process [61,62]. Liu et al. found that miRNA-100-5p transported by ADSC-exos promoted epidermal stem cell proliferation in vitro by activating PIP3/AKT and ERK signaling pathways through inhibiting MTMR3 expression [63]. Ma et al. demonstrated that exosomal miRNA-126-3p reduced PIK3R2 levels, thereby enhancing the cellular functions of fibroblasts and HUVECs [64]. Furthermore, exosomal miRNA-126-3p ultimately accelerated wound healing in rats with strengthened collagen production and newly formed capillaries. Hypoxic conditions resulted in altered miRNA expression in ADSC-exos, with increased expression of miR-21-3p, miR-126-5p, and miR-31-5p and decreased expression of miR-99b and miR-146-a, which are associated with wound healing [65]. Taken together, these miRNAs accelerated diabetic wound healing and suppressed inflammation through the PI3K/AKT signaling pathway.

2.1.2. LncRNAs from ADSC-exos

Long non-coding RNAs (LncRNAs) are RNA molecules with tissue-specific and diverse structures that are not involved in coding proteins and are more than 200 nucleotides long [66,67]. LncRNAs could regulate gene expression and participate in cellular physiological and pathological processes through a variety of mechanisms [68].

LncRNA H19 in ADSC-Exos downregulated miR-19b and SOX9 expression, and activated the Wnt/β-catenin pathway, thus accelerating the proliferation, migration, and invasive ability of human skin fibroblasts (HSFs). It verified the pivotal role of lncRNA H19 in ADSC-Exos in promoting cutaneous wound healing in mice [69]. Zhu et al. verified that ADSC-exos-carried lncRNA XIST restored discoidin domain receptor 2 (DDR2) expression by sponging miR-96-5p, ultimately enhancing mouse dermal fibroblasts proliferation and migration, and consequently increased collagen deposition and accelerated wound healing in rats [70]. Sun et al. reported that Early Growth Response-1 (EGR-1) in ADSC-exos could bind to the promoter of lncRNA-SENCR, thereby increasing VEGF-A expression. This study demonstrated that ADSC-exos could promote wound healing through the EGR-1/lncRNA-SENCR/DKC1/VEGF-A axis [71].

Metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) is a widely investigated lncRNA due to its role in regulating the

inflammatory response and vessel generation [72,73]. He et al. reported that lncRNA MALAT1 in ADSC-exos triggered the Wnt/β-catenin pathway, repressed miR-124, and mitigated H2O2-induced apoptosis both in HDFs and HaCaT cells [74]. In addition, exosomal lncRNA MALAT1 down-regulated miR-378a expression, promoting HSF viability and migration and skin wound healing [75].

2.1.3. CircRNAs from ADSC-exos

Circular RNAs (circRNAs) are ncRNAs with closed-loop structures and are not affected by RNA exonucleases [76,77]. CircRNAs are abundantly expressed and highly conserved among species and can sponge downstream miRNAs thereby regulating cellular activities [78,79]. Targeting circRNAs is a promising therapeutic strategy for accelerating wound healing. For example, mmu_circ_0001052-modified ADSC-exos down-regulated miR-106a-5p and activated the FGF4/p38MAPK pathway, which inhibited HG-induced apoptosis in HUVEC and promoted angiogenesis in diabetic foot ulcers (DFUs) mice [80].

SIRT1 is a nicotinamide adenosine dinucleotide (NAD)-dependent

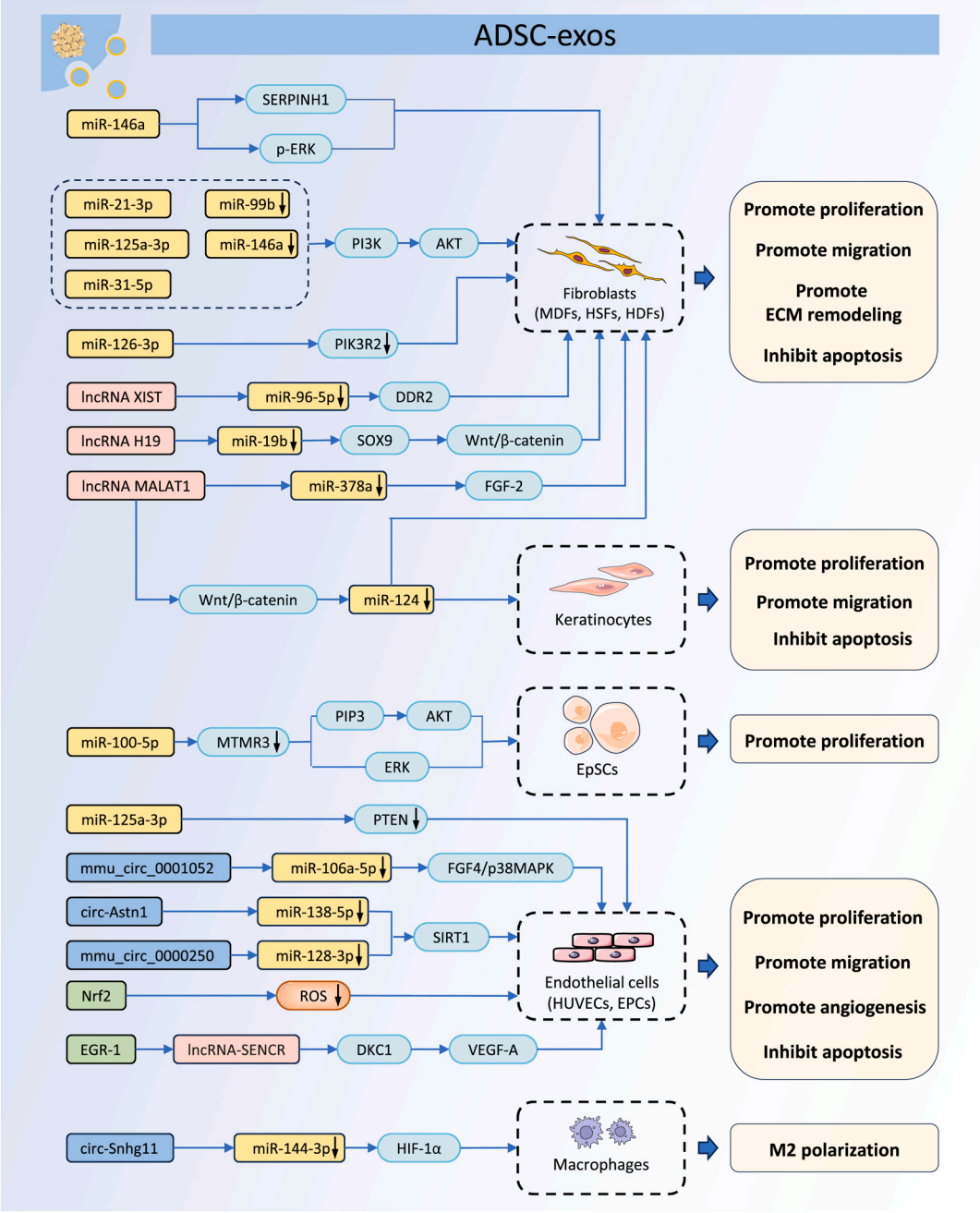

Fig. 3. Roles and mechanisms of ADSC-exos in promoting wound healing. ADSC-exos contain various biomolecules such as miRNAs, lncRNAs, circRNAs, and proteins. These biomolecules impact the cells involved in the wound healing process, including fibroblasts, KCs, ECs, EpSCs, and MΦ, by regulating their proliferation, migration, secretion, and apoptosis, thereby promoting wound healing. SERPINA1, serpin family A member 1; p-ERK, phosphorylated extracellular signal-regulated kinase; PIK3R2, phosphoinositide-3-kinase regulatory subunit 2; XIST, X-inactive specific transcript; DDR2, discoidin domain receptor; SOX9, Sex-determining region Y-box 9; MTMR3, myotubularin-related protein 3; EGR-1, early growth response 1; SENCR, Smooth muscle and endothelial cell-enriched migration/differentiation-associated lncRNA; DKC-1, dyskerin pseudouridine synthase 1; VEGF-A, vascular endothelial growth factor A; FGF4, fibroblast growth factor 4; SIRT1, Sirtuin 1; Astn1, astrotactin 1; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; HIF-1α, hypoxia-inducible factor 1-alpha.

deacetylase that regulates growth, transcription, senescence, and metabolism in different organs [81,82]. Wang et al. reported that circ-Astn1-modified ADSC-exos could promote angiogenesis through the miR-138-5p/SIRT1/FOXO1 axis [83]. Shi et al. reported that mmu_circ_0000250-modified ADSC-exos could increase angiogenesis and inhibit apoptosis by activating autophagy in endothelial progenitor cells (EPCs) [84]. In this process, mmu_circ_0000250 upregulated SIRT1 by absorbing miR-128-3p. According to another research conducted by this group, circ-Snhg11 from hypoxia-pretreated ADSC-exos sponged miR-144-3p, and promoted HIF-1α expression, thereby facilitating macrophage M2 polarization, and ultimately enhanced skin wound healing in diabetic mice [85].

2.2. Proteins from ADSC-exos

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates the expression of various anti-oxidant and anti-inflammatory genes [86,87] Li et al. reported that overexpression of Nrf2 in ADSC-exos inhibited the expression of ROS and inflammatory cytokines, thereby preventing glucose-induced EPC senescence and promoting vascularized DFU wound healing [88]. Huang et al. reported that NFIC from ADSC-exos could reverse HG-induced cell injury in HUVECs by enriching miR-204-3p expression, thereby reducing HIPK2 levels. This suggested that the NFIC-modified ADSC-exos had the potential to ameliorate DFUs [89]. HSP90 is a molecular chaperone protein involved in the folding, stabilization, and functional regulation of numerous proteins [90]. Ren et al. showed that eHSP90 derived from ADSC-exos activated the LRP1/AKT pathway, which resulted in increased skin cell function, reduced intracellular ROS levels, and accelerated wound healing in diabetic mice (Fig. 3).

3. BMSCs-exos

Bone marrow-derived mesenchymal stem cells (BMSCs), one of the most-studied MSCs, possess self-renewal, immunomodulatory, and multidirectional differentiation potential, with easy access and low immunogenicity [91,92]. BMSC-derived exosomes (BMSC-exos) and ADSC-exos exhibit similar and cross-cutting functions in the wound healing process [93]. BMSC-exos are an important active mediator of paracrine secretion by BMSCs and are involved in intercellular communication by ensuring stable cargo delivery.

BMSC-exos exhibit promisingly attractive therapeutic potential in wound healing. BMSC-exos induce multiple growth factors, such as HGF, IL-6, IGF1, and SDF1, and could stimulate important signal pathways in targeted cells, such as AKT, STAT3, and ERK, which are beneficial for wound healing [94]. Jiang et al. found that human BMSC-exos effectively induced proliferation by suppressing the TGF-β/Smad signaling pathway in both HaCaT cells and HDFs. Hence, this effect was successfully devoted to enhanced full-thickness skin wound healing [95].

Pharmacological pretreatment further enhances the ability of BMSC-exos to promote wound healing [96,97]. Melatonin (MT)-pretreated BMSC-exos increased M2 polarization by stimulating the PTEN/AKT pathway, thereby inhibiting pro-inflammatory factors IL-1β, TNF-α, and iNOS, as well as promoting the expression of the anti-inflammatory factor IL-10, which further promoted angiogenesis and collagen synthesis in STZ-induced diabetic mice [98]. Yu et al. reported that atorvastatin (ATV)-pretreated BMSC-exos improved the proliferation and migration of HUVECs in HG conditions and promoted wound healing in diabetic mice. Compared with non-pretreated BMSC-exos, ATV-exos showed better tube-forming ability, which was mediated by up-regulating miR-221-3p and activating AKT/eNOS pathway [99]. Hu et al. extracted exosomes derived from BMSCs pre-treated with empagliflozin (PGZ-exos), demonstrating their enhanced angiogenic capacity under HG conditions. Moreover, PGZ-exos accelerated wound healing in diabetic mice. The biological effects of PGZ-exos were associated with the activation of the PI3K/AKT/eNOS pathway [100].

3.1. MiRNAs from BMSC-exos

MiR-223 from BMSC-exos shifted M1 to M2 phenotype in mice model by reducing the accumulation of pknox1 protein, thus accelerating wound healing [101]. Exosomal miR-93-3p from BMSC-exos could downregulate APAF1 to promote the proliferation and migration of H2O2-injured HaCaT cells. Thus, miR-93-3p/APAF1 axis was a notable therapeutic target involved in exosomal miR-93-3p in promoting wound healing [102]. Zhang et al. discovered that exosomal miR-126, derived from miR-126-overexpressing BMSCs, increased the expression levels of VEGF and Ang-1 and promoted angiogenesis in HUVECs by targeting the PIK3R2/PI3K/AKT signaling pathway. Additionally, miRNA-126-overexpressing BMSCs markedly enhanced newly formed vessels, thereby facilitating wound healing [103]. Overexpression of miR-155 in diabetic wounds inhibited the migration of KCs, the restoration of FGF-7 levels, and the process of wound healing. Gondaliya et al. found that BMSC-exos loading with the miR-155 inhibitor, reversed these effects and accelerated wound healing in diabetic mice [104].

Existing studies have demonstrated that magnetic nanoparticles (MNPs) could result in improved tissue regeneration by applying a constant weak magnetic force to cells [105,106]. Therefore, Wu et al. pretreated BMSC-exos with MNPs and static magnetic field and found that miR-21-5p was upregulated in BMSC-Exos [107]. The upregulated miR-21-5p could inhibit SPRY2 and activate the PI3K/AKT and ERK1/2 signaling pathways to promote proliferation, migration, and angiogenesis in fibroblasts. There was accelerated wound closure, reduced scar width, and enhanced angiogenesis in the presence of BMSC-exo miR-21-5p. Another study conducted by Wu et al. found that miR-1260a expression in BMSC-exos was induced by MNPs and static magnetic field treatment increased the expression, and promoted osteogenesis and wound healing by inhibiting HDAC7 and COL4A2 [108].

3.2. LncRNAs from BMSC-exos

LncRNA H19 in BMSC-exos inhibited miR-152-3p and promoted PTEN expression, which enhanced fibroblast proliferation and migration and inhibited apoptosis through PI3K/AKT signaling pathway, leading to a marked acceleration of the wound healing process in DFU mice [109]. Han et al. demonstrated that exosomes from KLF3-AS1-expressing BMSCs could enhance the proliferation and migration of HUVECs and suppress apoptosis in the HG microenvironment in vitro, thereby accelerating wound healing in diabetic mice. This effect of lncRNA KLF3-AS1 was realized by sponging miR-383 and upregulating VEGF-A [110].

3.3. CircRNAs from BMSC-exos

Circ-ITCH from BMSC-exos could alleviate HUVECs ferroptosis caused by HG condition and enhance the angiogenic capacity by recruiting TAF15 protein to activate the Nrf2 signaling pathway [111]. These effects ultimately contribute to accelerated wound healing in DFUs (Fig. 4).

4. PMSC-exos

Placental mesenchymal stem cells (PMSCs), including human amniotic mesenchymal stem cells (hAMSCs) and human umbilical cord-derived mesenchymal stem cells (hucMSCs), are MSCs derived from different parts of the placenta [112]. The placenta is a highly vascularized organ that is not only easily accessible but also ethically more favorable because it provides an adequate supply of mesenchymal stem cells [113]. In addition, fetal stem cells are considered to have stronger stemness than adult stem cells [114]. PMSCs are more robust and proliferative than BMSCs and have greater long-term growth capacity.

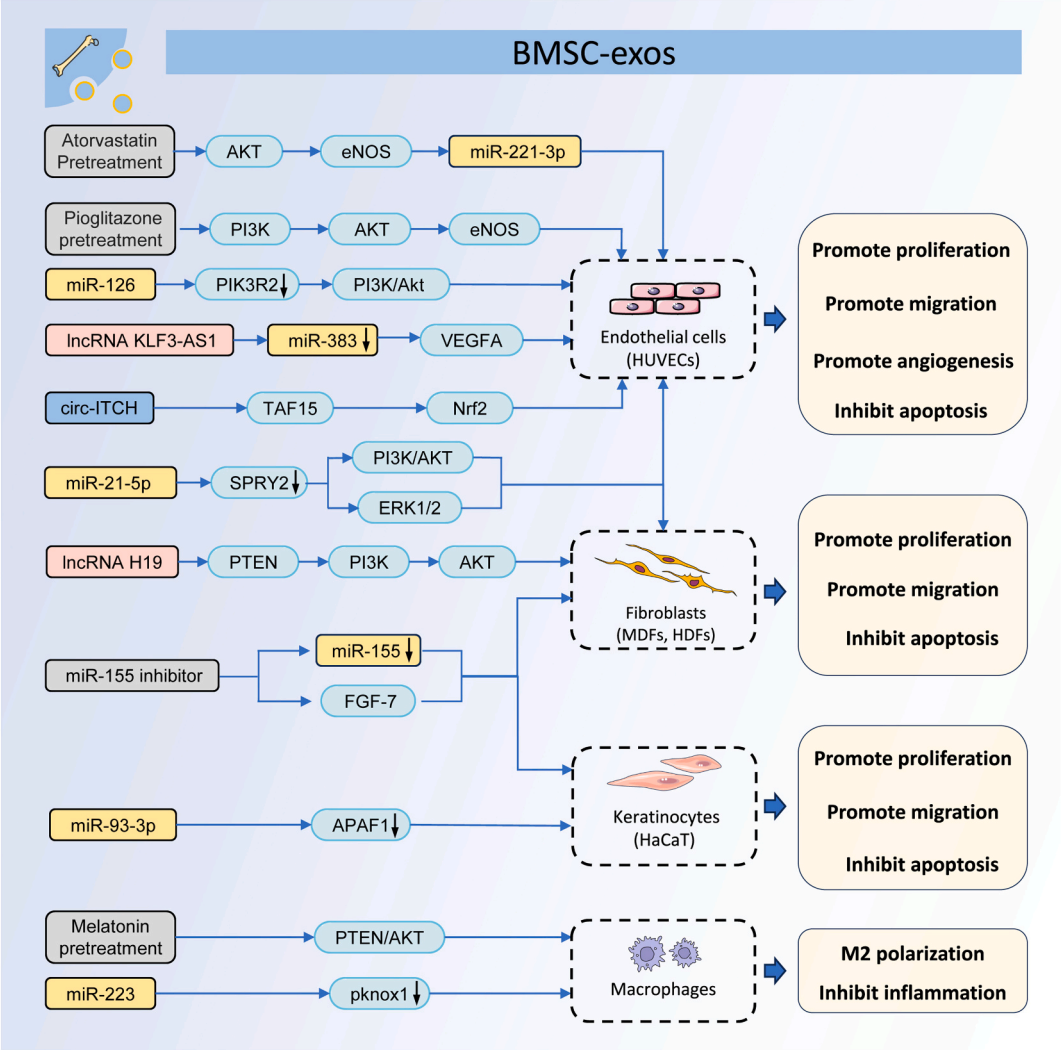

Fig. 4. Roles and mechanisms of BMSC-exos in promoting wound healing. Considering the different originations of adipose and bone marrow tissues, to some extent, BMSC-exos differs from ADSC-exos in terms of directed differentiation ability, paracrine spectrum, and degree of effect on wound healing. BMSC-delivered bioactive substances lead to behavioral alterations of cells involved in wound healing, including fibroblasts, KCs, ECs, and MΦ in vitro and in vivo, which trigger collagen deposition, angiogenesis, and re-epithelialization of the wound lesion. Moreover, the pretreatment of BMSC-exos with melatonin, atorvastatin, and engeletin, exhibits favorable results in accelerating wound healing. eNOS, endothelial nitric oxide synthase; PIK3R2, phosphoinositide-3-kinase regulatory subunit 2; VEGF-A, vascular endothelial growth factor A; KLF3-AS1, krüppel-like factor 3 antisense RNA 1; circ-ITCH, circular RNA inducer of TP53 homologous inhibitor; TAFTATA-Box-binding protein associated factor 15; Nrf2, nuclear factor erythroid 2-related factor 2; SPRY2, sprouty2; FGF7, fibroblast growth factor 7; APAF1, apoptotic protease-activating factor 1; pkonx1, PBX/knotted 1 homeobox 1.

Engrailed-1 (EN-1) activation contributed to the formation of scars [115,116]. Zhang et al. injected PMSC-derived exosomes (PMSC-exos) into the peri-wound area of rats and demonstrated that PMSC-exos significantly accelerated wound healing rate and promoted the regeneration of skin appendages, including hair follicles and sebaceous glands. PMSC-exos inhibited EN1 activation through down-regulation of Yes-associated protein (YAP) expression, thereby inhibiting EN1 activation and improving the healing rate and quality.

4.1. HucMSC-exos

HucMSCs are typical adult stem cells with low immunogenicity and easy expansion [117,118]. HucMSC-derived exosomes (hucMSC-exos) attenuated oxidative stress injury in HUVECs in vitro and enhanced vascular remodeling to improve diabetic wounds in vivo [119]. The hucMSC-exos treatment inhibited H2O2-induced HaCaT apoptosis by suppressing the nuclear translocation of apoptosis-inducing factor (AIF). Additionally, hucMSC-exos alleviated full-thickness skin injury by enhancing epidermal re-epithelialization and dermal [120]. Moreover, hucMSC-exos recruited fibroblasts and stimulated their secretion of nerve growth factors (NGFs), which not only accelerated skin wound repair and skin regeneration but also promoted skin nerve fiber regeneration [121].

Using single-cell RNA sequencing, Liu et al. found that the hucMSC-exos intervention resulted in elevated expression of chemokines that were required for neutrophils, along with increased polarization of the macrophage M2 phenotype. Collectively, these effects led to accelerated wound healing [122]. Teng et al. found that hucMSC-exos importantly boosted the proliferation in vitro, as well as decreased wound area and inflammatory level in vivo, accompanied by M2-phenotype-shifting-induced CD206, CD31, and VEGF upregulation, and TNF-α down-regulation [123].

The concentration of eNOS presents a positive correlation with wound closure rate, wound fracture strength, and capillarogenesis in the wound healing process [124]. Using genetic engineering and opto-genetic techniques, Zhang et al. obtained hucMSC-exos enriched with

eNOS (hucMSC-exos/eNOS). They demonstrated that hucMSC-exos/eNOS could protect HUVECs from HG impairment, and promote cellular function and reduce apoptosis in HUVECs. In vivo, hucMSC-exos/eNOS boosted microvessel formation in the wound through PI3K/Akt/mTOR or FAK/ERK1/2 signaling pathways to promote wound healing.

4.1.1. NcRNAs from hucMSC-exos

MiR-21-5p and miR-125b-5p, which were highly expressed in hucMSC-exos, had critical roles in inhibiting the process of TGFBR1/2 anti-myofibroblast differentiation [125]. This confirmed the effectiveness of hucMSC-*exo*-miRNAs as novel mediators for scarless healing. Another research demonstrated that miR-125b derived from hypoxic hucMSC-exos targeted and inhibited TP53INP1, and attenuated apoptosis in HUVECs, ultimately improving wound healing outcomes in a mouse model of whole-layer skin injury [126]. After exposure to 455 nm blue light irradiation, miR-135b-5p, and miR-499a-3p expression were upregulated in hucMSC-exos, resulting in enhanced pro-angiogenic capacity in vitro and in vivo [127]. HucMSC-exos-expressed miR-181c down-regulated the TLR4 signaling pathway, thereby inhibiting LPS-induced macrophage inflammation and attenuating inflammatory responses in severely burned rat models [128].

The oncogene PTEN, as a negative regulator of the PTEN/AKT pathway, plays an important role in life activities by inhibiting cell proliferation and promoting apoptosis, and as such is often unfavorable for wound healing [129]. Liu et al. reported that miR-21 transported by hucMSC-exos inhibited PTEN expression and contributed to corneal epithelial wound healing through the PTEN/PI3K/AKT pathway [130]. Xiu et al. demonstrated that miR-150-5p-overexpressing exosomes of huc-MSC promoted skin wound healing by activating the PI3K/AKT pathway via PTEN.

Exosomal circHIPK3 from hucMSC-exos could downregulate miR-20b-5p to improve Nrf2 and VEGFA expression thus accelerating vascularization for diabetic wound healing in vivo [131]. It demonstrated the ability of the *Candida erythropolis* cell wall skeleton (Nr-CWS) to promote angiogenesis and wound repair [132]. Exosomes derived from Nr-CWS-pretreated MSCs exhibited superior pro-angiogenic effects in diabetic wound repair, presumably via regulating the circIARS1/miR-4782-5p/VEGF-A axis [133].

4.1.2. Proteins from hucMSC-exos

Wnt signaling is not only a key component of embryonic development, but is also involved in all stages of the wound healing response [134]. HucMSC-exos delivered-Wnt4 induced β-Catenin activation, which inhibited heat stress-induced apoptosis and promoted proliferation of HaCAT and DFL cells, and thus ultimately promoted cell proliferation and re-epithelialization in a rat model of deep second-degree burns [135]. The stemness of hucMSCs was enhanced by 3,3′-diindolylmethane (DIM) through activation of the Wnt/β-catenin signaling [136]. Accordingly, Wnt11 knockdown suppressed the β-catenin activation and stemness in DIM-hucMSCs and counteracted the healing effects of wound healing. Thus, DIM-pretreated hucMSC-exos showed better repair ability in a rat model of deep second-degree burns.

4.2. hAMSC-exos

AMSCs have beneficial effects on diabetic wound healing [137]. Fu et al. claimed that AMSC-exos contains multiple angiogenesis-associated lncRNAs, including PANTR1, H19, OIP5-AS1, and NR2F1-AS1. Hence, AMSC-exos promoted the proliferation, migration, and angiogenic activities of HG-conditioned HUVECs, as well as improved wound closure and angiogenesis in diabetic wounds [138]. Moreover, miR-135a was highly expressed in hAMSC-derived exosomes (hAMSC-exos), which could directly inhibit LATS2 expression. This led to the promoted migration of BJ cells of hAMSC-exos and facilitated wound healing in mice [139].

4.3. WJMSC-exos

Wharton Jelly mesenchymal stem cells (WJMSCs), which are umbilical cord-derived MSCs, exhibit superior pluripotency and proliferative capacity compared with those of BMSCs and ADSCs [140,141]. WJ-MSCs can be used to treat spinal cord and heart tissue injuries, as well as to modulate immune-related diseases. WJMSC-exos binding therapy with *Aloe vera* rhodopsin could achieve promising antileishmanial and wound healing effects in vitro [142]. In animal models, WJMSC-EVs therapy enhanced wound epithelial re-formation, extracellular matrix remodeling, and vessel formation [143].

5. hiPSC-MSC-exos

Induced pluripotent stem cells (iPSCs) are manufactured stem cells with multidirectional differentiation potential and self-renewal ability obtained by reprogramming mature cells [144]. iPSCs have been widely applied for cell transplantation therapies, disease modeling, and drug screening investigations [145].

Exosomes derived from human iPSC-derived MSCs (hiPSC-MSCs) could accelerate the proliferation of HaCaT cells by activating the ERK1/2 pathway in vitro [146]. Zhang et al. demonstrated that exosomes derived from hiPSC-MSCs promoted the proliferation of human fibroblasts and HUVECs [147]. In vivo experiments have shown that hiPSC-MSCs promoted granulation tissue formation and angiogenesis in rats. This suggests a therapeutic potential of hiPSC-MSCs for wound healing.

6. FDMSC-exos

Compared with adult stem cells, fetal dermal mesenchymal stem cells (FDMSCs) have the advantages of low immunogenicity, easy expansion in vitro, high proliferation potential, and differentiation ability [148,149]. FDMSCs have been shown to have therapeutic potential to promote scarless healing in several studies. FDMSC-derived exosomes (FDMSC-exos) could induce proliferation, migration, and secretion of adult dermal fibroblasts (ADFs) by activating the Notch signaling pathway, consequently accelerating wound closure in mouse full-thickness skin wound model [150].

7. MenSC-exos

MenSCs have attracted considerable attention in regenerative medicine owing to their superiority in terms of ease of extraction ease, pluripotency, proliferative capacity, and low immunogenicity [151,152]. MenSCs were proven to be able to promote axonal regeneration after nerve injury in the central and peripheral nervous system [153]. MenSC-exos could induce M2 macrophage polarization to alleviate inflammation, upregulate NF-κB p65 subunit to increase re-epithelialization, reduce scar formation, and decrease collagen I/collagen III ratio, which promoted wound healing in diabetic mice [154].

8. MSC-exos in scars

Pathological scars including hyperplastic scarring and keloid are the undesirable consequences that result from excessive repair and tissue overproliferation during the wound healing process [155,156]. MSC-exos are outstanding candidates for the treatment of pathological scarring owing to their unique immunomodulatory and paracrine functions.

MiRNAs are indispensable for the inhibition of scar formation by MSC-exos. MiR-138-5p in MSC-exos significantly downregulated SIRT1 and reduced the expression of HSF-derived inflammatory and profibrotic proteins, including NF-κB, α-SMA, and TGF-β1, resulting in the attenuation of pathological scars [157]. MiR-7846-3p in ADSC-exos inhibited NRP2 expression in keloid fibroblasts (KFs), leading to the deactivation of the Hedgehog pathway, thereby reducing KF viability,

proliferation, and apoptosis resistance, offering new hope for cell-free therapy to inhibit keloid formation [158]. Yuan et al. reported that ADSC-exos-derived miR-29a suppressed fibrosis and scar proliferation in HSF after scald injury in mice by targeting the TGF-β2/Smad3 signaling pathway [159]. MiR-192-5p in ADSC-exos inhibited HSF proliferation and migration, as well as accelerated wound healing and reduced collagen deposition in a mouse model [160]. Such biological effects were achieved by decreasing IL-17RA expression and thus suppressing the activity of the Smad signaling pathway by miR-192-5p. Fang et al. also discovered that hucMSC-exos enriched with specific miRNAs, including miR-21, -23a, -125b, and -145, inhibited the activation of the TGF-β/SMAD2 pathway, which led to the inhibition of TGF-β-induced myofibroblast formation in vitro, and suppressed myofibroblast aggregation and scarring in full-thickness skin defect mouse model [161]. Tumor necrosis factor stimulated gene 6 (TSG-6) is the protein that performs a regulatory role in inflammation and tissue remodeling processes. TSG-6 modified BMSC-exos attenuated scar formation, repaired cellular damage, and restored cell polarity by reducing the secretion of inflammatory molecules and inhibiting collagen deposition in a mouse model [162].

9. Discussion

Wound healing is a complicated physiological process involving multiple cellular events [163,164]. Numerous studies have demonstrated the favorable effects of MSC-exos in different stages of wound healing. Multiple sources of MSC-exos have been found to affect wound healing-associated cellular functions, with excellent therapeutic potential demonstrated in diabetic wounds, burn wounds, and scarring. Although the results of the in vitro and animal experiments have illustrated that MSC-exos-based therapy is feasible and effective, there are still significant limitations and challenges to be encountered.

Firstly, obtaining MSC-exos is highly complicated, including MSC culture, exosome amplification, isolation, and purification [165–167]. The production of MSC-exos is tightly related to the source of MSCs, the cellular activities, and the culture conditions, which leads to potential fluctuations in the efficiency of MSC-exo amplification [22]. Moreover, there is still a lack of fully harmonized separation criteria that can completely separate exosomes from lipoproteins with similar biophysical properties and extracellular vesicles originating from non-endosomal pathways. The current commonly used isolation techniques include ultracentrifugation, density gradient centrifugation, and polymer precipitation, but all of them have more or less drawbacks such as time-consuming, high cost, structural damage, and polymerization into clusters. The combined use of multiple exosome isolation methods is a worth considering strategy. For example, the combination of ultracentrifugation and density gradient centrifugation can improve the purity of exosomes. Taken together, there are many variables in the acquisition of MSC-exos that contribute to the high degree of MSC-exos heterogeneity [168]. Even the same stem cell-derived exosomes may present vastly different biological effects depending on the method of isolation and extraction [169]. Therefore, comprehensive quality control of MSC-exos for yield, purity, integrity, and function is mandatory [170]. The main existing preservation techniques for MSC-exos are freezing, freeze-drying, and spray-drying, and the best-integrated storage method is frozen storage at -80 °C [165]. The long-term stability of MSC-exos storage remains to be further verified. Storage methods that balance long-term stability and affordability are still worth pursuing. Taken together, exploring standardized procedures of isolation, identification, and conservation of exosomes is a necessary prerequisite for advancing clinical application and commercialization.

Secondly, many questions remain to be pondered about the mechanism by which MSC-exos promotes the wound healing process. The biological functions and the bioactive substances of exosomes are firmly relevant to their original cells [24]. Exosomes derived from other stem cells also have a positive impact on the treatment of wound healing. For example, epidermal stem cell-derived exosomes (EPSC-exos) could accelerate diabetic wound healing by inducing M2 macrophage polarization, inhibiting inflammation, promoting angiogenesis, and facilitating cell proliferation in vivo [171]. Human ureogenic stem cells (USCs) have similar biological characteristics to MSCs, making the therapeutic potential of USC-exos of equal interest in diabetic wound healing [172]. Therefore, exosomes derived from other somatic stem cells or skin stem cells are equally potential candidates for the treatment of wound healing.

The ncRNAs and proteins delivered by MSC-exos are key factors in the therapeutic effects of MSC-exos. These active molecules are taken up and internalized by the target cells, thus regulating the wound healing process. Exosomes are carriers with complicated components, and previous studies have tended to investigate or enhance the function of only one of the uploaded components, while the effects of other substances are unknown. There are still a large number of ncRNAs, proteins, lipids, and biomolecules with untapped functions in MSC-exos. Thus despite the lack of proliferative capacity of MSC-exos, the bioactive compounds may indirectly affect tumor progression by modulating the tumor microenvironment or promoting angiogenesis. For example, in the context of multiple myeloma (MM), the miRNAs within the BMSC-exos are pivotal in modulating the growth dynamics of MM cells.

Furthermore, since wound healing is the consequence of the combined contribution of a multitude of cells and active biomolecules, it remains a mystery exactly what kind of functional cells and the corresponding exosomes occupy the dominant position. The precise mechanisms of MSC-exos in promoting wound healing need further investigation. Immune cells and inflammatory responses are involved in the process of wound healing [155]. The interaction of MSC-exos with immune cells is critical in promoting wound healing outcomes. MSC-exos transfer bioactive molecules to immune cells, stimulate anti-inflammatory pathways, leading to a balanced immune environment conducive to healing. Numerous studies have demonstrated that MSC-exos interact with immune cells such as T-cells, natural killer cells, B-cells, dendritic cells, and macrophages, influencing their activation, proliferation, and differentiation, through the delivery of immunomodulatory factors. In the main text, we found that multiple sources of MSC-exos could attenuate the wound inflammatory response by inducing M2 macrophage polarization, thus facilitating a boost wound healing process. However, macrophage polarization presents a double-edged role during scar formation. Excessive M2 polarization may also lead to hyperfibrosis and scar contraction. Therefore, it is crucial to target specific signaling pathways to precisely regulate the functions of MSC-exosomes in the wound healing process. Given the presence of numerous bioactive molecules such as non-coding RNAs, proteins, and lipids within exosomes, whose biological functions are not yet fully understood, continuous sequencing and validation are essential for enhancing safety and therapeutic efficacy.

Thirdly, MSC-exos are capable of delivering bioactive molecules to specific target cells or tissues with precision. However, the potential for exosomes to interact with off-target cells or tissues could attenuate therapeutic efficacy and augment the risk of adverse reactions. Optimizing the surface modification of exosomes and precisely controlling the molecular cargo within them are promising strategies to enhance their targeting specificity [4,173]. Overexpression of specific miRNAs of MSC-exos enhances the wound healing efficacy of MSC-exos. MNP pretreatment has also been reported to reinforce the efficacy of treatment with BMSC-exos. The composition of exosomes is a complex combination of a large number of ncRNAs, proteins, lipids, and biomolecules. In addition, delivering the drug of interest in a specific and controlled manner is a critical step to increase therapeutic benefit and minimize off-target effects. Loading MSC-exos onto materials such as hydrogels also fully combines the bioactivity of MSC-exos and the physicochemical properties of hydrogels, resulting in composites with more significant targeting and wound healing properties.

Lastly, most studies involved in wound healing have focused on the

cellular and animal levels, but not on the clinical trial stage. Animal wound models have obvious limitations, and the reparative environment for wound healing still differs from that of the human body in many ways.

Although MSC-exos have a positive effect on wound healing, their therapeutic dose, frequency of administration, mode of administration, and possible side effects still need to be further investigated. Long-term follow-up studies with large samples and multiple centers to monitor potential chronic effects are indispensable. Currently, MSC-exos is still more frequently applied in basic research only as an independent exploratory mode. Once MSC-exos can break through the bottleneck of clinical application, their combination and application modes and scenarios with traditional therapeutic modalities is a matter worth exploring.

10. Conclusion

In general, exosomes derived from ADSCs, BMSCs, hUC-MSCs, WJ-MSCs, hiPSC-MSCs, and MenSCs showed effective therapeutic capabilities in promoting the healing of ordinary wounds, diabetic wounds, burn wounds, and reducing the formation of scar tissues by influencing the activities of fibroblasts, KCs, immune cells, and ECs. Exosomal ncRNAs and proteins are key components for the biological function of MSC-exos. Strategies based on active functional enhancement such as engineering and pre-treating MSC-exos are powerful facilitators for improving the capabilities of MSC-exos in wound healing. MSC-exos is expected to be a novel cell-free therapeutic tool for wound healing and skin regeneration.

Abbreviations

mesenchymal stem cells MSCs
extracellular vesicles EVs
vascular endothelial growth factor VEGF
transforming growth factor-β1 TGF-β1
hepatocyte growth factor HGF
adipose-derived mesenchymal stem cells ADSCs
human dermal fibroblasts HDFs
high glucose HG
phosphatidylinositol 3 kinase/protein kinase B PI3K/AKT
matrix metalloproteinase 1 MMP1
matrix metalloproteinase 3 MMP3
reactive oxygen species ROS
metastasis-associated lung adenocarcinoma transcript-1 MALAT1
diabetic foot ulcers DFUs
heat shock protein 47 SERPINH1
phospho-extracellular signal-regulated kinase p-ERK
dinucleotide NAD
discoidin domain receptor 2 DDR2
early growth response-1 EGR-1
nuclear factor erythroid 2-related factor 2 Nrf2
bone marrow-derived mesenchymal stem cells BMSCs
melatonin MT
atorvastatin ATV
magnetic nanoparticles MNPs
placental mesenchymal stem cells PMSCs
human amniotic mesenchymal stem cells hAMSCs
human umbilical cord-derived mesenchymal stem cells hucMSCs
engrailed-1 EN-1
Yes-associated protein YAP
apoptosis-inducing factor AIF
nerve growth factors NGFs
Candida erythropolis cell wall skeleton Nr-CWS
Wharton Jelly mesenchymal stem cells WJMSCs
induced pluripotent stem cells iPSCs
fetal dermal mesenchymal stem cells FDMSCs
menstrual blood-derived MSCs MenSCs
keloid fibroblasts KFs
tumor necrosis factor-α-stimulated gene 6 TSG-6
human ureogenic stem cells USCs

Funding

This study was supported by Natural Science Foundation of Hubei Province (2022CFB298), China University Industry-University-Research Innovation Fund (2021ITA03006), Natural Science Foundation of Hubei Province (2023AFB717), Wuhan University Education and Development Foundation (NO.2002330) .

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Sicheng Li: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Yichuan Li:** Writing – original draft, Visualization, Investigation. **Keyu Zhu:** Writing – review & editing, Writing – original draft, Visualization. **Wenlin He:** Investigation, Data curation. **Xingjun Guo:** Validation, Resources, Funding acquisition. **Ting Wang:** Writing – review & editing. **Song Gong:** Writing – review & editing, Supervision, Project administration. **Zhanyong Zhu:** Writing – review & editing, Resources, Funding acquisition.

Declaration of competing interest

All the authors declare that there is no conflict of interest.

Data availability

No data was used for the research described in the article.

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