

74656_Auto_Edited.docx

Name of Journal: *World Journal of Stem Cells*

Manuscript NO: 74656

Manuscript Type: MINIREVIEWS

Mesenchymal stem cell-derived exosomes: a novel and potential remedy for cutaneous wound healing and regeneration

MSC-exosomes promote cutaneous wound healing

Jia-Chen Hu, Chen-Xi Zheng, Bing-Dong Sui, Wen-Jia Liu, Yan Jin

Abstract

Poor healing of cutaneous wounds is a common medical problem in the field of traumatology. Due to the intricate pathophysiological processes of wound healing, conventional treatment methods, such as chemical molecule drugs and traditional dressings, cannot achieve satisfactory outcomes. Within recent years, explicit evidence suggests that mesenchymal stem cells (MSCs) have great therapeutic potentials on skin wound healing and regeneration. However, the direct application of MSCs still confronts many challenges and difficulties. Intriguingly, exosomes that are cell-secreted granular vesicles with lipid bilayer membrane structure and contain specific components of the source cells, may emerge to be an excellent substitute for MSCs. Exosomes derived from MSCs (MSC-exosomes) have been demonstrated to be beneficial for cutaneous wound healing and accelerate the process through a variety of mechanisms. These mechanisms include alleviating inflammation, promoting vascularization, and promoting proliferation and migration of epithelial cells and fibroblast cells. Therefore, the application of MSC-exosomes may be a promising alternative to cell therapy in the treatment of cutaneous wounds and can promote wound healing through multiple mechanisms at the same time. This review will provide an overview of the role as well as the mechanisms of MSC-derived exosomes in cutaneous wound healing, and elaborate the potentials and future perspectives of application of MSC-exosomes in clinical practice.

Key Words: Mesenchymal stem cells; Extracellular vesicles; Exosomes; Wound healing; Skin regeneration

Hu JC, Zheng CX, Sui BD, Liu WJ, Jin Y. Mesenchymal stem cell-derived exosomes: a novel and potential remedy for cutaneous wound healing and regeneration . *World J Stem Cells* 2022; In press

Core Tip: How to better promote wound healing is an important obstacle in the treatment of trauma in clinic. Exosomes derived from mesenchymal stem cells may provide a novel remedy with advantages and prospects. We herein discuss the role as well as the mechanisms of MSC-derived exosomes in cutaneous wound healing, and elaborate the potentials and future perspectives of application of MSC-exosomes in clinical practice.

INTRODUCTION

The skin, as our body barrier to external environment, plays a crucial role in defense against surrounding challenges such as ultraviolet ray in sunlight and microbial pathogens. Additionally, the skin is significant to our mental health due to its sensory perception and aesthetic maintenance functions. However, our skin is very vulnerable to trauma or burns and is prone to form chronic wounds or ulcers under certain pathological conditions such as diabetes mellitus ^[1]. Currently, the common therapeutic strategy for wound healing is application of biologics, including growth factors and cytokines ^[2]. Nonetheless, since wound healing is a dynamic and complex process involving various cell types and crosstalk between cells and extracellular matrix (ECM), the therapeutic effects of biologics are limited and unsatisfactory ^[2, 3]. Therefore, novel curative paradigms for acute and chronic cutaneous wounds need to be explored.

Intriguingly, stem cell-based therapies emerge to show great potential for regeneration of damaged tissues in both preclinical and clinical trials ^[4-8]. Remedies based on stem cells have many advantages over conventional therapies based on growth factor or cytokine biologics, as stem cells possess higher ability of regeneration, and promote healing process and regeneration in multifactorial ways. Particularly, mesenchymal stem cells (MSCs) are the major stem cell types that have shown definite therapeutic effects on a variety of tissue injuries ^[9]. MSCs are multipotent mesenchymal stromal cells with the capabilities of self-renewal and multi-lineage differentiation. They exist extensively in the body and can be obtained from many tissues such as bone marrow, adipose tissue, dental tissue, umbilical cord, *etc.* A

large body of evidence has shown that MSCs derived from different tissues exhibit great therapeutic potentials for enhancing cutaneous wound healing and regeneration *via* regulating multiple processes, including cell migration and proliferation, angiogenesis, inflammation resolution, and extracellular matrix remodeling ^[10]. Nevertheless, the direct application of MSCs as a cellular therapy for tissue injuries still confront many restrictions and obstacles. A non-negligible restriction is the risk of teratoma occurrence and immunogenicity, of which the incidence increases with the culture expansion or cryopreservation of cells ^[1, 11]. Moreover, the extraction, transportation and expansion of MSCs as invasive or time-consuming procedures are also difficult to perform in clinic. From the cell delivery point of view, the majority of MSCs *via* systemic delivery (intravenous infusion) are entrapped in the lungs, resulting in few cells migrating through the pulmonary capillaries and reaching the target sites ^[9, 11]. Also, the survival, retention and engraftment of MSCs in local application are limited. Notably, recent studies of the MSC therapeutic mechanism have revealed that the positive effects of MSCs on cutaneous wounds are predominantly mediated *via* paracrine actions rather than differentiation ^[12-14]. Thus, the application of MSC extracts may be a more feasible and practical paradigm than direct cellular delivery treatment. Recently, with advances in MSC-based therapy research, MSC-derived extracellular vesicles (EVs), especially exosomes, have shown promising potentials in cutaneous wound healing treatment and skin regeneration. The application of exosomes has become a novel and cell-free therapeutic paradigm and been given high expectations due to their convenience in clinical use.

² In this review, we will summarize the applications of MSC-derived exosomes in cutaneous regeneration and expound the underlying cellular and molecular mechanisms. We will also explicate the future perspectives for their application in clinic and latent problems to be solved.

EXTRACELLULAR VESICLES AND EXOSOMES

EVs are a heterogeneous population of lipid bilayer particles with different sizes, biogenesis, composition and functions. They are secreted from most types of cells in the body and contain the components of the donor cells, including a variety of specific proteins, lipids, and nucleic acid molecules [15]. Thus, to a certain extent, they inherit the functional properties of the parental cells and are considered as an important player in intercellular communication, as they are loaded with signal biomolecules and shuttle from donor cells to recipient cells [16-18]. According to their diameters or biogenesis, EVs are usually divided into three main subtypes, *i.e.* exosomes, microvesicles and apoptotic bodies. Microvesicles and apoptotic bodies are vesicles derived from budding and pinching out of the surface of plasma membrane, while exosomes are vesicles derived from intracellular endosomes. Within recent years, exosomes as a special category of EVs, are more widely and deeply studied.

Exosomes are spherical lipid bilayer vesicles with distributed diameters ranging from 30-150 nm. The biogenesis of exosomes is through a series of membranetrafficking processes [19]. Firstly, invagination of the plasma membrane or budding of intracellular organelle membranes gives rise to early endosomes. Secondly, intraluminal vesicles (ILVs) are generated as early endosomes invaginate inward, generating the so-called multivesicular bodies (MVBs). ILVs within MVBs can either degrade in lysosome or undergo exocytosis when transporting with MVBs to fuse with the plasma membrane. And exosomes are generated when ILVs are secreted to the extracellular space [20]. The released exosomes can arrive at their target cells in a paracrine way or through the circulation and then be internalized by the recipient cells in the following ways: ligand-receptor interaction; surface molecule-mediated endocytosis, micropinocytosis, phagocytosis; or plasmatic membrane fusion with the recipient cells [21]. Following the release of exosome enclosed contents in the recipient cytoplasm, alterations of intracellular signaling pathways occur in recipient cells to modulate the cellular behaviors and functions. Thus, the basic biology of exosomes indicates that MSC-exosomes may contain MSC-specific components to exert specific effects on recipient cells, which somewhat equivalent to the therapeutic effects of MSCs.

TRANSLATIONAL POTENTIALS AND REGULATORY ASPECTS OF MSC-EXOSOMES

Cell therapy has made great progress in clinical practice, and a growing number clinical trials of MSC-based therapy have shown therapeutic efficacy^[22]. However, the application of exosomes as therapeutic biologics takes on many advantages over the whole MSCs ^[19, 23]. Firstly, exosomes can be stored and transported at low temperature for a longer time without significant loss in bioactivity than whole cells. Secondly, exosomes have better penetrating abilities to cross biological barriers such as blood brain barrier and avoid entrapment in filter organs or tissues. Also, their lipid bilayer membranes can protect the bioactivity of content molecules in sophisticated physiological environment. Thirdly, exosomes can be engineered to obtain specific properties and can be quantitatively administered to patients in clinic to obtain better clinical effects. Lastly, they are safer than cell transplantation therapy, with less risk of neoplastic transformation ^[24] and immune response activation ^[25].

Exosomes as natural bi-layered lipid spheres possess high skin penetration efficiency, similar to liposomal nanoparticles ^[26, 27]. This enables topical administration of exosomes, rendering wound areas more receptive to the therapeutic exosomes ^[28]. Furthermore, delivered exosomes can also be chemotactic to the inflammatory or injured site when a distance exists between the administered area and the lesion center ^[29]. Additionally, with a variety of bioactive molecules inside, exosomes can exert their curative benefits through many different therapeutic mechanisms simultaneously, which leads to better biological effects than small molecular compounds.

Nevertheless, when we consider exosomes as biological agents in clinic application, there are a series of nonnegligible challenges in the regulatory and quality control aspects of exosome manufacturing. Due to the lack of standardizations in the methodology or procedures for the collection and isolation of exosomes, exosome products often differ in safety and quality aspects. To the challenge of safety considerations, exosome manufacturing should follow clinical good manufacturing

practice (cGMP) protocols like other pharmaceutical preparations to obtain clinical-grade exosome preparations. Besides, with the successful development and use of various serum-free media, the medium that do not contain animal serum is recommended for MSC culturing to avoid mixing of exogenous exosomes derived from animal serum. Also, bioengineering technology may be applied to modify exosome phenotypes or contents, which can add or subtract specific biological molecules possessed by exosomes to increase efficacy or reduce undesirable effects during therapeutic course^[30, 31].

Homogeneity and quality control are also important considerations or challenges in regulatory aspect. Exosome homogeneity cannot be certain as chemically defined drugs, even exosomes from one cell are heterogeneous. However, exosome heterogeneity does not preclude adoption of exosome products in clinical use. A variety of experimental techniques can be used to determine the mechanism of action of exosomes in therapy. And then we can regulate the major active ingredients within exosomes related to the mechanism of action to assure quality and potency^[32]. With a better understanding of the mechanism of action, we can identify the exact active ingredients and overexpress them, through which to improve homogeneity and determine the quality control strategy of manufacturing. In addition, screening exosomes with biomarkers such as surface receptors is also a method to obtain more homogenous exosomes, and to enrich exosomes with higher efficacy^[33]. Although the lack of standardizations in the methodology for the collection, isolation, and analysis of exosomes can affect the exosome contents and potency, we can still determine the mainly active contents responsible for therapeutic efficacy by inactivation assay. And once active contents identified, we can use them to make quality control as described above and even in turn determine the best methodology for the collection, isolation and purification of exosomes^[34].

¹ The regulatory and quality control of exosome products need further development, so there is still a long way to go before they can be authentically used in clinical practice. Yet this needs to be based on in-depth exploration of the mechanism of action.

Thus, in the following part of this review, we will elaborate on the underlying mechanisms of MSC-derived exosomes in cutaneous wound healing and regeneration.

MECHANISMS OF MSC-EXOSOMES IN CUTANEOUS WOUND HEALING AND REGENERATION

Cutaneous wound healing is a dynamic physiological process which is initiated ⁸ when the normal anatomical structure or integrity of the skin are destructed. It is a protection process of the skin itself to ameliorate damage, restrain infection and restore the anatomical structure and function. The typical cutaneous wound healing process can be summarized as a series of overlapping phases: hemostatic phase, inflammation phase, proliferation phase and remodeling phase [35]. During these phases, a series of orchestrated biological events sequentially occur: the damaged cutaneous tissue is activated to recruit various cell types involved in the following events; immune cells are chemoattracted to clear pathogens and damaged tissues; fibroblasts proliferate and produce ECM to support re-epithelization; the newly produced ECM is remodeled to stabilize the wound sites [36]. It has been demonstrated in multiple wound healing models that exosomes obtained from various cell types exert beneficial effects on the whole process of wound healing, particularly in inflammation, proliferation and remodeling phases (Figure 1).

During the inflammation phase, neutrophils first infiltrate into the injury site to remove microbial pathogens and then undergo apoptosis, followed by macrophages infiltration which engulf cellular debris, apoptotic neutrophils and other apoptotic cells. Of note, macrophages play a distinctive and ⁶ important role in the cutaneous regeneration process. Recent evidence has suggested that macrophages present two anti-functional phenotypes: pro-inflammatory M1 phenotype and anti-inflammatory M2 phenotype. Following injury, M1 macrophages can promote pro-inflammatory activities which are necessary for protective actions of inflammation and eliminating damaged tissue and cells, while M2 macrophages elicits anti-inflammatory activities which facilitate tissue repair and regeneration [37]. However, excessive pro-inflammation

activities as well as inadequate anti-inflammatory activities can lead to the risk for the development of chronic wounds or fibrosis. Evidence was provided that exosomes can elicit M2 polarization through transferring microRNAs (miRNAs). He *et al* [38] reported that exosomes derived from bone marrow MSCs (BMMSCs) induced macrophage polarization toward M2 phenotype. And they further showed that the polarization was regulated by miR-223 derived from exosomes of MSCs which targets pknox1. Besides, human umbilical cord MSCs (hUCMSCs)-derived exosomes can regulate inflammatory reaction of macrophages in burned rats through miR-181c [39]. The study showed that miR-181c could effectively suppress the Toll-like receptor 4 (TLR4) signaling pathway and reserve the increased levels of tumor necrosis factor α (TNF- α) and interleukin-1 β (IL-1 β) and the decreased level of IL-10 of macrophages, which indicates M2 polarization. Particularly, the polarization effects of MSC-exosomes can be enhanced under preconditioning by lipopolysaccharide (LPS). A study exploring the curative effects of exosomes derived from LPS pre-treated MSCs (LPS pre-exosomes) on wound healing inflammation has shown that LPS pre-exosomes have better immunotherapeutic potential and ability than untreated MSC-derived exosomes to promote M2 macrophage activation [40]. The enhanced effect is associated with unique expression of let-7b in LPS pre-exosomes and the let-7b/TLR4/NF- κ B/STAT3/AKT regulatory signaling pathway in macrophages. In addition, exosomes derived from adipose-derived MSCs (ADMSCs) proved to exert similar effects on macrophage polarization. In the study by Zhao *et al* [41], treatment of obese mice with ADMSC-derived exosomes demonstrated to attenuate adipose inflammation and obesity through M2 macrophage polarization. ADMSC-derived exosomes can promote M2 polarization through the transactivation of arginase-1 by exosome-carried active STAT3. Although this effect of ADMSC-derived exosomes was not demonstrated in skin wound healing model, the results still indicate a promising role of ADMSC-derived exosomes in the inflammation process of wound healing. In general, macrophages are major inflammatory mediators in cutaneous repair, whereas some observations show that T-cells also play an important role in the inflammation modulating process [42]. Evidence

suggested that MSC-exosomes can switch activated T-cells into the T-regulatory phenotype to suppress inflammatory response [43]. And recently, studies have shown that local application of exosomes can regulate the innate and adaptive immune networks as a whole, and better promote wound healing^[44]. These indicate that MSC-exosomes can exert multiple effects in inflammation phase of wound healing. Yet, more detailed mechanisms underlying exosome-mediated inflammation modulation need to be clarified by future studies.

During the proliferation phase, mainly four regenerative episodes occur: fibroblast proliferation, production of ECM components, re-epithelization and angiogenesis. Under permitted conditions created by the prior inflammation phase, the four episodes are orchestrated to regenerate new tissues and restore the morphology and function of the skin. A substantial body of evidence has shown that exogenetic exosomes have positive therapeutic effects on these four processes. In the *in vitro* study by Shabbir *et al* ²^[45], MSC-exosomes could enhance the proliferation and migration of fibroblasts and increase tube formation by human umbilical vein endothelial cells, both in a dose-dependent manner. And the effects were proved to be triggered by activations of intracellular signaling pathway involving AKT, ERK, and STAT3, which are known to be important in wound healing. The same results of human ADMSC-derived exosomes were verified in experiments by Choi *et al* ^[46] and Zhang *et al* ^[47]. In the study by Zhang *et al*, ADMSC-derived exosomes were shown to have positive actions on fibroblasts which promote collagen deposition and expression of growth factors such as basic fibroblast growth factor (bFGF) and transforming growth factor- β 1 (TGF- β 1) both *in vitro* and *in vivo* via modulating the PI3K/AKT signaling pathway. Apart from fibroblasts, BMSC-derived exosomes could also repress apoptosis of HaCaT cells (human immortalized epidermal cells) induced by hydrogen peroxide via the miR-93-3p/APAF1 axis^[48]. Also, research demonstrated that ADMSC-derived exosomes could prompt proliferation and migration of HaCaT cells via Wnt/ β -catenin signaling^[49]. These indicate that MSC-exosomes can accelerate the process of re-epithelization in proliferation phase. In a more extensive study by Ren *et al* ^[50], the effects of ADMSC-

derived microvesicles (ADMSC-MVs) were examined on fibroblasts, keratinocytes and endothelial cells both *in vitro* and *in vivo*. Their research showed that ADMSC-MVs promoted the proliferation, migration of these cells *via* AKT and ERK signaling pathways, resulting in upregulations of growth factors, such as vascular endothelial growth factor A (VEGFA), platelet derived growth factor A (PDGFA), epidermal growth factor (EGF), fibroblast growth factor 2 (FGF2), and enhancement of re-epithelialization, collagen deposition and neovascularization. In addition, exosomes derived from other MSCs were also verified to be bioactive in the proliferation phase. Zhang *et al* [51] reported that human umbilical cord MSCs (hUCMSCs)-derived exosomes could enhance re-epithelialization and cell proliferation in rat skin burn model *via* the activation of Wnt/ β -catenin pathway. Meanwhile, heat stress-induced apoptosis was reduced by hUCMSC-derived exosomes *via* the activation of AKT pathway. Another study by Zhang *et al* [52] reported that exosomes derived from human induced pluripotent stem cell-derived MSCs (hiPSC-MSCs) had similar effects with MSC-derived exosomes on proliferation of fibroblasts and angiogenesis of endothelial cells. In a later study by Kim *et al* [53], hiPSC-MSC-derived exosomes could also promote re-epithelization by stimulating ERK1/2 pathway. Other than exosomes derived from MSCs, Zhao *et al* [54] reported that exosomes derived from human amniotic epithelial cells (hAEC-exosomes) could promote the proliferation and function of fibroblasts *via* miRNAs so as to accelerate wound healing. Although the results mentioned above highlight the therapeutic roles of exosomes derived from MSCs, what cargos in the exosomes that mediate these effects in the proliferation phase remains to be further identified.

As for the remodeling phase, the newly produced ECM is restructured and reorganized: ECM is degraded by matrix metalloproteases (MMP) and replaced by new ECM proteins; collagen III converts to collagen I; fibroblasts differentiate into myofibroblasts; and then scar tissue forms. Researches have demonstrated that exosomes play an intriguing role in optimizing this process. For example, ADMSC-derived exosomes increase the MMP-3 expression and the ratio of collagen III to

collagen I so as to promote remodeling of ECM in murine incisional wounds [55]. Moreover, ADMSC-derived exosomes can inhibit the differentiation of fibroblasts into myofibroblasts to mitigate scar formation. In addition, hUCMSC-derived exosomes were demonstrated to inhibit differentiation of fibroblasts to myofibroblasts by inhibiting the TGF- β 2/SMAD2 pathway through transfer of miRNAs (miR-21, -23a, -125b, and -145), resulting in reduced scar formation in a skin-defect mouse model⁴[56, 57]. And the same effects were observed in the study using exosomes derived from human amniotic fluid stem cells (hAFSCs), which showed that hAFSC-derived exosomes suppressed the excessive aggregation of myofibroblasts and ECM *via* inhibiting the TGF- β pathway⁴[58]. Taken together, exosomes not only promote ECM synthesis in the proliferation phase but also improve ECM remodeling in the late phase of wound healing to inhibit scar tissue formation.

Collectively, exosomes derived from a variety of MSCs, including BMMSCs, ADMSCs, hUCMSCs, hiPSC-MSCs, and hAECs, are demonstrated to have beneficial therapeutic effects on cutaneous wound healing through reducing inflammation, promoting re-epithelization and angiogenesis, promoting proliferation and migration of fibroblasts, as well as enhancing ECM formation and remodeling. The above preclinical studies of MSC-exosomes in cutaneous wound are listed in Table 1.

EFFECTS OF MSC-EXOSOMES ON CUTANEOUS REGENERATION IN AGING AND DISEASE

Skin anti-aging

Another application of MSC-derived exosome in cutaneous regeneration is skin anti-aging. hUCMSC-derived exosomes were tested on human skin tissues by Kim *et al* [59]. They discovered that the administrated exosomes were absorbed by epidermis after 18 h and increased collagen I and elastin expressions in human skin after 3 days of treatment. In another study, iPSC-derived exosomes were used to treat aged human dermal fibroblasts (HDFs) induced by UVB (315 nm) irradiation or over passage, which reduced the damages of HDFs with increased expression of collagen I and reduced

expression of natural senescence marker senescence-associated- β -galactosidase (SA- β -Gal) [60]. Additionally, exosomes derived from three-dimensional human dermal fibroblast spheroids (3D HDFs) were compared with those derived from the monolayer culture of HDFs (2D HDFs) [61]. 3D HDFs-derived exosomes were demonstrated to have better efficacy than 2D HDF-derived exosomes in inducing collagen synthesis and decreasing MMP-1 expression by up-regulating TGF- β /TNF- α ratio. Also, 3D HDFs-derived exosomes exhibited skin anti-aging properties in nude mouse photoaging model. Furthermore, at molecular level, Bae *et al* [62] made an array analysis of mouse embryonic stem cell-derived extracellular miRNAs that are enclosed in exosomes. They screened out mmu-miR-291a-3p, and proved it could inhibit cellular senescence *via* TGF- β receptor 2 signaling pathway. To sum up, these evidences show the positive effects of MSC-derived exosomes on skin rejuvenation and the potential application of MSC-derived exosomes in the cosmetics.

Diabetic wound healing

Due to the high glucose environment and chronic inflammation condition, patients with diabetes are often confronted with impaired wound healing, resulting in limb loss and disability. Considering their anti-inflammation and pro-proliferation properties, the application of MSC-derived exosomes in diabetic wound healing is a promising therapeutic strategy. It is reported that the delayed healing of diabetic foot ulcers (DFU) partly results from impaired function of endothelial progenitor cells (EPCs) in diabetic condition. Yet ADMSC-derived exosomes could promote proliferation and angiogenesis of EPCs in a high glucose environment *in vitro*, and reduce ulcerated area in DFU rats *via* increasing angiogenesis and growth factor expression as well as reducing inflammation [63]. Geiger *et al* [64] reported that exosomes derived from human circulating fibrocytes could induce the proliferation and migration of keratinocytes and fibroblasts in diabetic mice, and accelerate diabetic wound closure *in vivo*. In the study by Dalirfardouei *et al* [65], exosomes derived from menstrual blood-derived MSCs (MenSCs) were applied to full thickness excisional wound in diabetic mouse model,

which reduced inflammation *via* promoting M2 macrophage polarization, strengthened angiogenesis through upregulating VEGF-A expression, enhanced re-epithelialization *via* activating NF- κ B signaling pathway, and reduced scar formation *via* decreasing Collagen I: Collagen III ratio. And recently, Han *et al* reported that BMSC-derived exosomes contained lncRNA KLF3-AS1, which could induce angiogenesis to promote wound healing in diabetic condition^[66]. Above all, based on the beneficial effects of MSC-derived exosomes on wound healing, MSC-derived exosomes hold great potentials in diabetic wound therapy.

Ischemic wound healing

Chronic ischemic wounds are another challenging problem in trauma clinic with delayed wound healing and therapeutic difficulties. Due to ischemia and hypoxia, the healing process of ischemic wounds is inhibited, resulting in imperfect curative effect of conventional treatments. Thus, exosome-based therapies, with multiple therapeutic benefits, have been tentatively applied in this disease area. In the study by Shi *et al* ^[67], exosomes loaded with TGF- β have been proved to promote ischemic wound healing, which suggesting a promising regenerative therapy. And another study by Cooper *et al* ^[68] showed that human ADMSC-derived exosomes (hADMSC-exosomes) could stimulate human dermal fibroblasts migration and enhance ischemic cutaneous wound healing. All these results provide prospects and theoretical basis for clinical trials of exosomes in ischemic wounds.

To sum up, evidence shows that MSC-derived exosomes not only promote healing of cutaneous wounds in normal condition, but also promote healing of wounds in diabetic and ischemic conditions, as well as skin regeneration in aging condition. To make MSC-derived exosomes more effective in treating cutaneous wounds in special conditions, exosomes isolated from pretreated MSCs were studied. For instance, exosomes isolated from pioglitazone-pretreated BMMSCs and hypoxia ADMSCs were both confirmed to induce high-quality healing of diabetic wound^[69, 70]. These experiments expand the

available scope of application of exosomes in cutaneous wounds, and suggest better sources of MSC-exosomes.

PERSPECTIVES FOR APPLICATION OF EXOSOMES IN CUTANEOUS WOUND HEALING AND REGENERATION

Notwithstanding a large body of evidence in the preceding sections that MSC-exosomes have positive effects on cutaneous wound healing in animal studies and preclinical trials, the data of exosomes in cutaneous wound healing from clinical studies is inadequate. Exhilaratingly, a lot of meta-analyses demonstrate MSC-exosomes to be potential and promising remedy for many acute and chronic diseases including cutaneous wounds in pre-clinical studies^[71-73], revealing the therapeutic effect of MSC-exosomes on inflammation and injury. And these make successful clinical translation of MSC-exosomes more hopeful in cutaneous wound healing. Moreover, a randomized double-blind controlled clinical trial by Kwon *et al* demonstrated acne scars treated with human ADMSC-exosomes and fractional CO₂ laser exhibited better improvement than the control treated group, which gave a broad hint that ADMSC-exosomes provide synergistic therapeutic effects on atrophic acne scar clinical treatments^[74]. Therefore, there are positive prospects of MSC-exosomes for a promising future in clinical translation.

Once MSC-exosomes are translated into clinical practice, improving their therapeutic efficacy is an issue to be prospected. One of the methods is combining exosomes and biomaterials to exert synergistic functions. Recently, Wang and colleagues^[75] reported the application of exosome-loaded biocompatible natural-based methylcellulose-chitosan hydrogels in severe wound models under diabetic conditions. The hydrogels acted as three-dimensional porous scaffolds to provide a favorable environment for cell proliferation and ECM remodeling. In specific, based on the hydrogels, exosomes could be sustainably released for a long period of time and exert lasting curative functions for better effects. The transformation of biomaterials provides a more flexible form for the application of exosomes. For instance, antibacterial

exosomes hydrogels^[76] and adhesive ultraviolet shielding exosome-releasing dressings^[77] were applied on diabetic wound models and proved to exert better therapeutic effects on wound healing and skin reconstruction. Another method is bioengineering the properties of exosomes, such as their cargos or surface molecular functions. The selected molecules with therapeutic value (such as miRNAs or drugs) can be loaded in exosomes to endow exosomes with exogenous efficacy^[78]. Also, the surface of exosome can be modified with some functional molecules such as aptamers to enable the transfer of engineered exosomes to target sites when administered systematically or locally, which can improve therapeutic efficiency. All of these above strategies will enhance the therapeutic efficacy of exosomes in cutaneous wound healing and regeneration.

Despite many exciting prospects, we also need to recognize that actually the clinical use of exosomes is still hampered by many safety concerns and consistent regulatory issues. The clinical translation process of MSC-exosomes is still in a long way and far from the foreseeable prospect. Thus the use of exosomes in clinic is still far from being applied, until these problems are better solved and perfected.

CONCLUSION

Taken together, MSC-derived exosomes, as a cell-free therapeutic paradigm, provides a novel promising option for cutaneous regeneration. Yet, more researches are needed so as to further excavate the curative potentials of exosomes and make them more suitable for clinical use.

4%

SIMILARITY INDEX

PRIMARY SOURCES

- 1

www.ncbi.nlm.nih.gov
Internet

32 words — 1%
- 2

Peipei Wu, Bin Zhang, Hui Shi, Hui Qian, Wenrong Xu. "MSC-exosome: A novel cell-free therapy for cutaneous regeneration", Cytotherapy, 2018
Crossref

31 words — 1%
- 3

www.science.gov
Internet

30 words — 1%
- 4

Bi Chen, Qing Li, Bizeng Zhao, Yang Wang. "Stem Cell-Derived Extracellular Vesicles as a Novel Potential Therapeutic Tool for Tissue Repair", STEM CELLS Translational Medicine, 2017
Crossref

14 words — < 1%
- 5

Yueyuan Zhou, Nobuyoshi Kosaka, Zhongdang Xiao, Takahiro Ochiya. "MSC-exosomes in regenerative medicine", Elsevier BV, 2020
Crossref

14 words — < 1%
- 6

academic.oup.com
Internet

13 words — < 1%
- 7

Donghui Bian, Yan Wu, Guodong Song, Ramyar Azizi, Amir Zamani. "The application of mesenchymal stromal cells (MSCs) and their derivative

12 words — < 1%

exosome in skin wound healing: a comprehensive review",
Stem Cell Research & Therapy, 2022

Crossref

8

He Qiu, Shuo Liu, Kelun Wu, Rui Zhao, Lideng Cao, Hang Wang. "Prospective application of exosomes derived from adipose - derived stem cells in skin wound healing: A review", Journal of Cosmetic Dermatology, 2019

12 words — < 1%

Crossref

9

www.dovepress.com

12 words — < 1%

Internet