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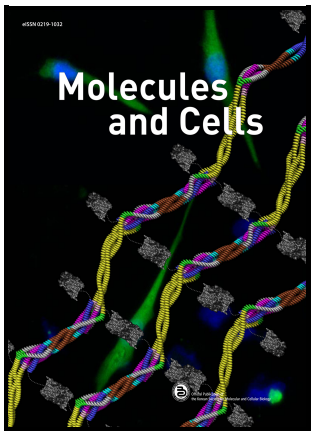

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Roles of extracellular vesicles from mesenchymal stem cells in regeneration

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Abstract

Mesenchymal stem cells (MSCs) are highly valued in regenerative medicine due to their ability to self-renew and differentiate into various cell types. Their therapeutic benefits are primarily due to their paracrine effects, in particular through extracellular vesicles (EVs), which are related to intercellular communication. Recent advances in EV production and extraction

technologies highlight the potential of MSC-derived EVs (MSC-EVs) in tissue engineering and regenerative medicine. MSC-EVs offer several advantages over traditional cell therapies, including reduced toxicity and immunogenicity compared to whole MSCs. EVs carrying functional molecules such as growth factors, cytokines and miRNAs play beneficial roles in tissue repair, fibrosis treatment and scar prevention by promoting angiogenesis, skin cell migration, proliferation, extracellular matrix remodeling and reducing inflammation. Despite the potential of MSC-EVs, there are several limitations to their use, including variability in quality, the need for standardized methods, low yield, and concerns about the composition of EVs and the potential risks. Overall, MSC-EVs are a promising alternative to cell-based therapies, and ongoing studies aim to understand their actions and optimize their use for better clinical outcomes in wound healing and skin regeneration.

Key words: Mesenchymal stromal cells, Exosomes, Paracrine factors, Skin repair, Wound healing

1. Introduction

Mesenchymal stem cells (MSCs) can be isolated from various tissues, including bone marrow, umbilical cord, placenta, adipose, and dental pulp (Figure 1)(Costela-Ruiz et al., 2022) and they possess the ability to differentiate into a number of cell types such as osteoblasts, chondrocytes, cardiomyocytes, adipocytes, and neurons (Caplan, 1991; Yang et al., 2018). In skin wound healing, MSCs promote cell migration, angiogenesis, and tissue repair, fostering a regenerative environment rather than fibrosis. Adipose-derived MSCs (AD-MSCs) have been approved to treat fistulas caused by Crohn's disease, and other studies are investigating the use of MSCs as a therapeutic strategy for burns and wrinkles. Regarding the function of MSCs in

tissue homeostasis, it has been suggested that indirect effects, such as paracrine signaling-based regulation of neovascularization, proliferation and differentiation of surrounding stem cells and immune responses, play a greater role in tissue regeneration than direct differentiation in synchrony with surrounding tissues (Hosseini et al., 2019; Rahmani et al., 2020; Xue et al., 2024).

As it has been experimentally demonstrated that these paracrine effects are mediated by extracellular vesicles (EVs), which contain a variety of intracellular bioactive molecules as well as signaling molecules secreted by mesenchymal stem cells, the application of EVs or secretomes has emerged as an alternative to reduce the risks of live cell therapies (Jeppesen et al., 2019; Kalluri and LeBleu, 2020; Liang et al., 2014). For example, an excessive and prolonged inflammatory response following trauma can impede the regeneration of skin tissue, but chemokines and cytokines contained in AD-MSC-EVs can effectively regulate the inflammatory response and promote wound healing (Wang et al., 2022). As a cell-free therapy, EVs minimize the likelihood of immune rejection and tumor formation, and are effective in promoting wound healing through angiogenesis and anti-inflammatory mechanisms (Marofi et al., 2021; Stahl and Raposo, 2019). Traditional wound care methods, including anti-inflammatory drugs and dressings, are often ineffective for chronic wounds such as diabetic foot ulcers (Jones et al., 2018). In addition, stem cell transplantation, which aims to replace lost skin, requires a large number of cells to rebuild large areas of skin tissue, which remains a major hurdle and requires the development of more effective treatments (Hynds et al., 2018). MSC-derived EVs (MSC-EVs) may surpass traditional MSC therapies in safety and efficacy, and represent a promising strategy for wound healing and trauma treatment (Deng et al., 2023; Jo et al., 2021; Moghadasi et al., 2021).

This mini-review provides an overview of the role of MSC-EVs and their mechanisms in

skin wound healing and regeneration processes. Recent research on MSC-EVs is also briefly reviewed, as well as the potential and limitations for clinical application of MSC-EVs.

2. Mesenchymal stem cells

MSCs, originally identified for their capacity to form bone and marrow when transplanted (Friedenstein et al., 1974; Friedenstein et al., 1966), were named by Caplan in 1991 (Caplan, 1991) and are also referred to as mesenchymal stromal cells due to their differentiation characteristics. The International Society for Cellular Therapy (ISCT) defines MSCs by their plasticity, specific surface markers (CD105, CD73, CD90) and ability to differentiate into osteoblasts, chondrocytes and adipocytes (Dominici et al., 2006). MSCs have shown therapeutic promise in the treatment of acute graft-versus-host disease (GVHD) (Martinez-Carrasco et al., 2019), bone defects (Levy et al., 2020) and kidney injury (Yun and Lee, 2019).

MSCs contribute to tissue repair by promoting wound healing, reducing scarring, modulating immune responses, and enhancing collagen synthesis through paracrine effects (Wu et al., 2024). For example, the factors they secrete, including transforming growth factor-beta (TGF-β), indoleamine 2,3-dioxygenase (IDO), and prostaglandin E2 (PGE2), suppress the activity of T and natural killer (NK) cells while promoting the function of regulatory T cells and inhibiting B cell activation (Gao et al., 2016). During inflammation, MSCs become activated and secrete additional factors that support immune regulation and tissue repair. They also release growth factors such as epidermal growth factor (EGF) and hepatocyte growth factor (HGF), which stimulate cell proliferation and facilitate wound healing through the HGF/cMET and EGF receptor signaling pathways (Tamama and Kerpedjieva, 2012; Yang et al., 2021). Furthermore, MSCs promote angiogenesis by secreting vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), which

support the growth and differentiation of endothelial cells (Kwon et al., 2014; Tao et al., 2016). Their anti-fibrotic effects and ability to produce extracellular matrix (ECM) components, such as collagen and fibronectin, in response to injury further enhance tissue repair (Rockel et al., 2020; Shi et al., 2010).

While clinical trials show mixed results, there have been positive outcomes in wound healing and skin regeneration. For example, adipose tissue-derived MSCs reduced matrix metalloproteinase (MMP)-1 and -2 levels and increased collagen type I in aged skin (Lee et al., 2021). Umbilical cord-derived MSCs (UC-MSCs) have been shown to accelerate wound healing and reduce erythema (Kim et al., 2020a), and in diabetic foot ulcers, both UC-MSCs and bone marrow-derived MSCs (BM-MSCs) promoted wound healing and neovascularization without complications (Qin et al., 2016; Vojtassak et al., 2006). Additionally, Wharton's jelly-derived MSCs (WJ-MSCs) seeded on acellular amniotic membranes significantly reduced wound size (Hashemi et al., 2019), and MSCs have shown promise in treating burns by reducing inflammation, enhancing neovascularization, and regulating ECM remodeling to minimize scarring (Bian et al., 2022; Burk et al., 2022).

However, despite their effectiveness and several advantages, challenges associated with MSC therapy remain, including reduced effectiveness with prolonged culture, difficulties in targeting and retaining cells at sites of injury (van Hennik et al., 1999; Zhou et al., 2021a). In addition, MSC therapy carries risks of immune rejection, tumor formation, and viral infection (Ankrum and Karp, 2010).

3. Extracellular vesicles

The recognition that the therapeutic benefits of MSCs are largely attributable to their

paracrine effects (Dittmer and Leyh, 2014), and that EVs can serve as viable substitutes for these cells, offers promising avenues for further research (Jafarinia et al., 2020). EVs are small membrane-bound particles that are naturally released from cells and found in various body fluids (Lotvall et al., 2014). EVs can be isolated using methods such as ultracentrifugation (Livshits et al., 2015), ultrafiltration (Lobb et al., 2015), and size exclusion chromatography (Foers et al., 2018), and advances in these EV extraction technology have led to a number of recent studies. As a cell-free therapy, EVs have several advantages; they are non-replicative, present minimal tumorigenic risk (Phinney and Pittenger, 2017), and can traverse protective barriers such as the blood-brain barrier (BBB) due to their biocompatibility and low immunogenicity (Milbank et al., 2021). Furthermore, EVs are stable, maintaining their contents even after multiple freeze-thaw cycles (Zhuang et al., 2021), and can be produced in large quantities by immortalized cell lines (Xunian and Kalluri, 2020).

EVs can be categorized into several subtypes (Todorova et al., 2017): exosomes (30–200 nm), microvesicles (100–1000 nm), apoptotic bodies (50–5000 nm) (Doyle and Wang, 2019; Raposo and Stoorvogel, 2013), and oncosomes (1–10 μm), which are observed in cancer cells (Di Vizio et al., 2009). EVs are produced through distinct pathways: apoptotic bodies result from cell death, microvesicles arise from the budding of the cell membrane, and exosomes are formed via the endolysosomal pathway (Yang et al., 2019). Also they are enriched with a diverse array of bioactive molecules, including proteins, lipids, and nucleic acids (Pathan et al., 2019), which play crucial roles in regulating numerous physiological and pathological processes (Jeppesen et al., 2019).

3.1. Exosomes

Exosomes were first identified by Harding and Stahl during their research on iron uptake

in reticulocytes (Harding and Stahl, 1983). These disc-shaped small EVs can be isolated from various bodily fluids, including serum, saliva and urine (Colombo et al., 2014; Mi et al., 2020; Zhu et al., 2024). Exosome formation involves several steps (Figure 1): the plasma membrane invaginates to form early endosomes, which mature into late endosomes and eventually multivesicular bodies (MVBs) (Piper and Katzmann, 2007; Zhang et al., 2019). MVBs can either fuse with lysosomes for degradation or fuse with the plasma membrane to release exosomes into the extracellular space (Piper and Katzmann, 2007; Stahl and Raposo, 2019). The regulation of these processes require the participation of a number of proteins, including Rab GTPases (RAB27A, RAB11, RAB31) (Juan and Furthauer, 2018; Vanlandingham and Ceresa, 2009), endosomal sorting complex required for transport (ESCRT) complexes (Doyle and Wang, 2019; Henne et al., 2011; Juan and Furthauer, 2018), annexins, tetraspanins (CD63, CD81, and CD9) (Verweij et al., 2011), and lipids such as ceramide and cholesterol. After secretion, exosomes facilitate intercellular communication via vesicle docking, membrane fusion, and receptor-mediated endocytosis (Costa Verdera et al., 2017; Rai and Johnson, 2019). Exosomes influence target cell behavior by transferring a diverse array of biomolecules, and play a crucial role in disease diagnosis and treatment of diseases (Bian et al., 2022).

3.2. Microvesicles

Microvesicles, also referred to as microparticles, differ from exosomes in their mode of formation. They arise from the outward budding and fission of the plasma membrane, a process that occurs when a cell is either stimulated or undergoing apoptosis (Willms et al., 2018). Despite this distinction, microvesicles are characterized by high biocompatibility, low immunogenicity, and effective targeting capabilities, which render them suitable as drug carriers (Skog et al., 2008). For example, microvesicles derived from tumor cells can be utilized

to deliver chemotherapeutic agents, thereby enhancing the efficacy of cancer treatment while minimizing side effects and adverse reactions (Ma et al., 2016; Tang et al., 2012).

3.3. EVs derived from MSCs

MSC-EVs are typically circular, well-defined particles characterized by a phospholipid bilayer and a diverse array of molecular components (Bazzoni et al., 2020; Del Fattore et al., 2015). These EVs are identified by traditional markers such as CD63, CD9, and CD81, as well as mesenchymal stem cell surface markers including CD29, CD105, CD44, CD73, and CD90 (Juan and Furthauer, 2018; T et al., 2016). Additionally, they also express lysosome-associated membrane proteins (LAMP1 and LAMP2) (Zoller, 2009) and specific factors that are critical for their unique biological functions, including pro-inflammatory and anti-inflammatory cytokines, enzymes, and various other proteins (O'Brien et al., 2020), as well as miRNAs (Qiu et al., 2018; Xu et al., 2019). Currently, MSC-EVs are being evaluated in clinical trials for a range of diseases, with ongoing assessments of their safety and efficacy (Kou et al., 2022). MSCs-cell therapy has multi-faceted benefits and potential for wound healing; however, their application is often limited due to the risk of immune rejection. In contrast, MSC-EVs carry therapeutic molecules, yet lack major histocompatibility complex (MHC) class I and II antigens, thereby reducing the risk of immune rejection. (Nicolay et al., 2015). Additionally, these vesicles have the ability to cross biological barriers such as the blood-brain barrier and effectively transport therapeutic molecules due to their small size and lipid bilayer (Keshtkar et al., 2018). MSC-EVs also have the potential to replace the need for large numbers of MSC transplants and prolonged cell culture to reconstruct lost skin.

4. Therapeutic potential of MSC-EVs in skin injury and wound repair

4.1. Wound healing process

The process of wound healing is a complex one, involving a multitude of cell types and interactions across four distinct phases (Figure 2): hemostasis, inflammation, proliferation, and remodeling (or maturation) (Bian et al., 2022; Gantwerker and Hom, 2011). The process of hemostasis commences within minutes, initiating platelet activation and coagulation to form fibrin clots that serve as a scaffold for inflammatory cells (Hoffman, 2018; Rodrigues et al., 2019), while the subsequent inflammatory phase is initiated within 24 hours of injury and is characterized by the clearing bacteria and debris through the action of neutrophils and macrophages (Ellis et al., 2018). M1 macrophages are responsible for clearing pathogens and eventually shift to M2 macrophages that promote tissue repair and resolve inflammation (Gantwerker and Hom, 2011). During the proliferation phase, the wound is filled with new tissue and blood vessels to supply oxygen (Ben Amar and Wu, 2014). It entails fibroblast-driven collagen production and ECM formation, which are vital for fibroblast and keratinocyte migration (Cialdai et al., 2022). This is followed by the remodeling phase, which commences around the third week, can persist for years, entailing the breakdown and replacement of type III collagen with type I collagen within the ECM (Rodrigues et al., 2019). Disruptions at any stage of this process can impair healing, leading to chronic wounds or persistent ulcers (Shao et al., 2020).

4.2. MSC-EVs in skin repair

Traditional treatments for acute and chronic wounds have included debridement, dressings, anti-inflammatory drugs, skin grafts, and cytokine applications (Chen et al., 2023). However, these conventional methods have certain limitations and side effects, such as prolonged healing times, risk of infection, and bleeding. Additionally, many wounds remain

unresponsive or resistant to standard therapies. Advances in biotherapy, particularly with MSCs and their EVs, provide more effective and less invasive options for treating skin wounds and trauma by supplementing, replacing, or repairing damaged cells, tissues, and organs to address the underlying trauma.

MSC-EVs are emerging as a promising cell-free therapy for skin wound healing and tissue regeneration, with studies showing that EVs derived from sources such as bone marrow, adipose, umbilical cord and Wharton's jelly effectively enhance angiogenesis and skin re-epithelialization (Table 1). While MSCs contribute to skin repair by differentiating into resident skin cells such as dermal fibroblasts and endothelial cells (Mazini et al., 2020; Stenqvist et al., 2013), their EVs primarily facilitate intercellular communication with a variety of target cells such as macrophages, microglia and endothelial cells (Luo et al., 2022). MSC-EVs facilitate wound healing through a number of mechanisms, including homing effects (Hu et al., 2016), immunomodulation (Su et al., 2019), preventing epithelial apoptosis (Shen et al., 2022), regulating macrophage polarization and anti-inflammatory actions (He et al., 2019), and enhanced angiogenesis (Ding et al., 2023; Zhang et al., 2015b). For instance, exosomes derived from bone marrow, adipose tissue, umbilical cord are abundant in growth factors, including VEGF and platelet-derived growth factor-BB (PDGF-BB), enhancing skin cell proliferation and migration. These EVs also promote angiogenesis and nerve regeneration, reduce inflammation, and minimize fibrosis, often exhibiting greater effects than MSCs that directly differentiate into tissue-specific cells (Caplan and Dennis, 2006; Liu et al., 2020b). These effects are mediated by various bioactive molecules within EVs and their target signaling, with their composition and concentration varying according to the MSC type from which they originate. Consequently, the regulatory effects of EVs on these cellular processes may be influenced by their origin and the characteristics of the target cell (Hoang et al., 2020).

4.3. Mechanisms of MSC-EVs in skin repair

The role of EVs in the wound repair process is not confined to a specific phase. During the hemostatic phase, MSC-EVs promote coagulation by enhancing the expression of phosphatidylserine and tissue factor (Silachev et al., 2019). In the inflammatory phase, MSC-EVs play a crucial role in wound healing and scar reduction due to their ability to modulate immune responses. EVs contribute to the reduction of inflammation by modulating oxidative stress and decreasing levels of pro-inflammatory cytokines, including interferon-gamma (IFN-γ), interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α) (Yang et al., 2015). Simultaneously, they facilitate the expression of anti-inflammatory cytokines, such as interleukin-10 (IL-10) (Eirin et al., 2017; Guo et al., 2019) and interleukin-4 (IL-4) (Han et al., 2021; Yan et al., 2022). Zhou et al. observed that both local and intravenous application of AD-MSC-exosome accelerated wound healing by down-regulating inflammatory markers such as TNF-α and IL-6, while up-regulating factors such as VEGF and proliferation cell nuclear antigen (PCNA) (Zhou et al., 2021b).

MSC-EVs facilitate the polarization of macrophages toward the anti-inflammatory M2 phenotype, attenuate neutrophil-driven inflammation, and influence microvascular remodeling (Gregorius et al., 2021). For example, He et al. found that exosomes from BM-MSCs could induce macrophage polarization towards the M2 phenotype, thereby promoting wound repair, likely through miR-223 targeting Pknox1 (He et al., 2019). They also can accelerate wound closure and re-epithelialization by enhancing Wnt signaling and activating the AKT pathway and nerve regeneration by promoting Schwann cell activation and angiogenesis, all of which are critical for effective wound healing. MSC-EVs also regulate T cell responses by promoting a shift toward a regulatory T cell (Treg) phenotype and reduce fibrosis, highlighting their

therapeutic potential for managing chronic inflammatory conditions and accelerating wound repair (Zhang et al., 2023). MSC-EVs also have been shown to inhibit complement activation via CD59, thereby reducing interactions between neutrophils and complement components (Loh et al., 2022).

During the regenerative phases of hyperplasia and remodeling, MSC-EVs have been shown to promote several key regenerative processes, including fibroblast proliferation, ECM production, re-epithelialization, and angiogenesis (Hu et al., 2022). For instance, MSC-EVs enhance fibroblast proliferation and migration, increase the deposition of collagen types I and III through the PI3K/AKT signaling pathway, and support fibroblast differentiation to minimize scarring (Wang et al., 2017; Zhang et al., 2018). Additionally, AD-MSC-EVs and BM-MSC-EVs have been observed to promote cell proliferation, reduce apoptosis, and activate pathways such as Wnt/β-catenin and miR-93-3p/APAF1 (Ma et al., 2019; Shen et al., 2022). Research shows that Wharton's jelly MSC-conditioned medium promotes HUVEC proliferation, sebaceous gland regeneration and angiogenesis, and has shown efficacy in the treatment of radiation dermatitis and skin regeneration in rats (Sun et al., 2019).

Furthermore, MSC-EVs have demonstrated anti-aging and anti-scarring properties by reducing cellular senescence markers and modulating ECM remodeling, which in turn minimizes fibroblast differentiation into myofibroblasts and prevents excessive scarring (Oh et al., 2018). Jiang et al. found that BM-MSC-exosome improved scar formation and wound healing by affecting the TGF-β/Smad pathway, specifically by upregulating TGF-β3 and Smad7 (Jiang et al., 2020). Conditioned medium derived from UC-MSC contains growth factors such as EGF, basic fibroblast growth factor (bFGF) and rejuvenating factors such as growth differentiation factor-11 (GDF-11), which support skin rejuvenation by promoting cell migration and extracellular matrix production, and the treatment of skin inflammation by

promoting an anti-inflammatory macrophage phenotype (Kim et al., 2020b; Kim et al., 2018). In particular, UC-MSCs have higher levels of TGF-β than BM- or AD-MSCs, resulting in more pronounced effects on fibroblast-to-myofibroblast transition and anti-scarring properties.

5. Limitations, challenges and strategies for MSC-EV-based therapies

Before MSC-EVs can be widely implemented in clinical settings, several challenges must be addressed. These include the variability in EV quality from different MSC sources and batches, which complicates quality control and increases the risk of inconsistent therapeutic outcomes (Yin et al., 2019). Structure, composition, and effects of EVs can vary depending on cellular sources, isolation methods, and culture conditions. Standardizing production methods and implementing robust quality assurance protocols are crucial for overcoming these challenges (Meng et al., 2020). A deeper understanding of EV's heterogeneity is also crucial for optimizing clinical applications (Kalluri and LeBleu, 2020).

Additionally, MSCs derived from adult tissues have a limited capacity for proliferation, which restricts the large-scale production of EVs. The efficacy of EVs can be enhanced through pretreatments such as hypoxia, cytokine exposure, or biochemical treatments (Domenis et al., 2018; Wang et al., 2021), but achieving production consistency remains challenging. Utilizing MSCs derived from pluripotent stem cells (PSCs) presents a viable solution, as they exhibit higher proliferation rates and the ability to produce substantial quantities of EVs (Li et al., 2014; Lian et al., 2010). Despite the advantages of iPSC-derived MSC-EVs, there are still obstacles to overcome, including the need for standardized protocols for EV generation, isolation and characterization.

Safety concerns, including potential carcinogenic effects and variability in in vivo responses, remain unresolved. A comprehensive understanding of the pharmacokinetics,

pharmacodynamics, and biodistribution of EVs is essential for determining optimal dosages and administration routes, as well as for developing Good Manufacturing Practice (GMP)-compliant protocols and standardized Standard Operating Procedures (SOPs) for EV isolation and donor selection (Roefs et al., 2020). Establishing these guidelines will ensure consistent therapeutic outcomes and mitigate potential side effects, thereby making MSC-EVs a viable therapeutic option in regenerative medicine.

Current strategies to improve therapeutic efficacy and reduce limitations include the development of modified EVs with alterations to their surface, membrane, and internal composition, or combining them with biological scaffolds. EVs can be enhanced through external and internal modifications, or by developing EV-mimetic nanovesicles (NVs) (Park et al., 2019), which can be designed to carry biomolecules such as mRNA and non-coding RNAs and improve targeting (Golchin et al., 2022; Yao et al., 2023). For example, miRNA-126-loaded EVs have been shown to activate the PI3K/Akt signaling pathway and promote vascular remodeling (Zhang et al., 2021). Additionally, integrating EVs with biomaterials such as hydrogels and 3D-printed scaffolds is emerging strategy aimed at enhancing their clinical applications in wound healing and regenerative medicine (Cao et al., 2020b; Lee et al., 2024; Qazi et al., 2017).

6. Conclusion

MSC-EVs show significant potential for wound healing due to their immunomodulatory and regenerative properties, as well as their ability to promote angiogenesis, reduce inflammation, and facilitate tissue remodeling. However, several barriers hinder their clinical application, including variability in EV quality, limited scalability, and challenges in characterization and sustained therapeutic release (Ding et al., 2023). A more profound

comprehension of MSC-EVs and overcoming of current issues, such as the establishment of standardized EV production protocols, will be crucial for the translation of MSC-EVs into effective clinical treatments for acute and chronic wounds. Combining EVs with advanced bioengineering technologies could also further enhance their use as a viable alternative to cell-based therapies in medicalapplications for treating various wounds.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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Figure legends

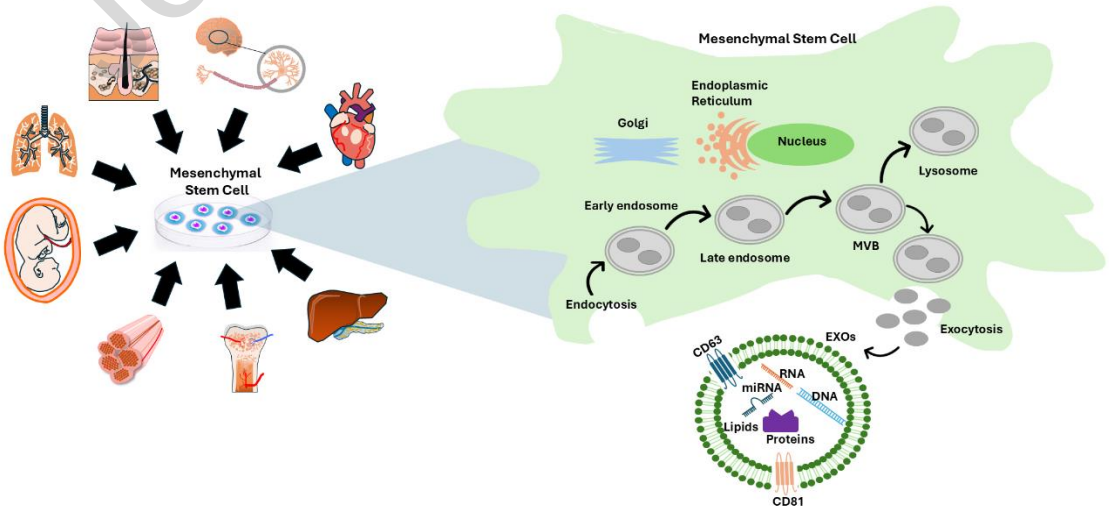

Figure 1. A schematic diagram illustrating the sources of MSCs and the biogenesis of exosomes.

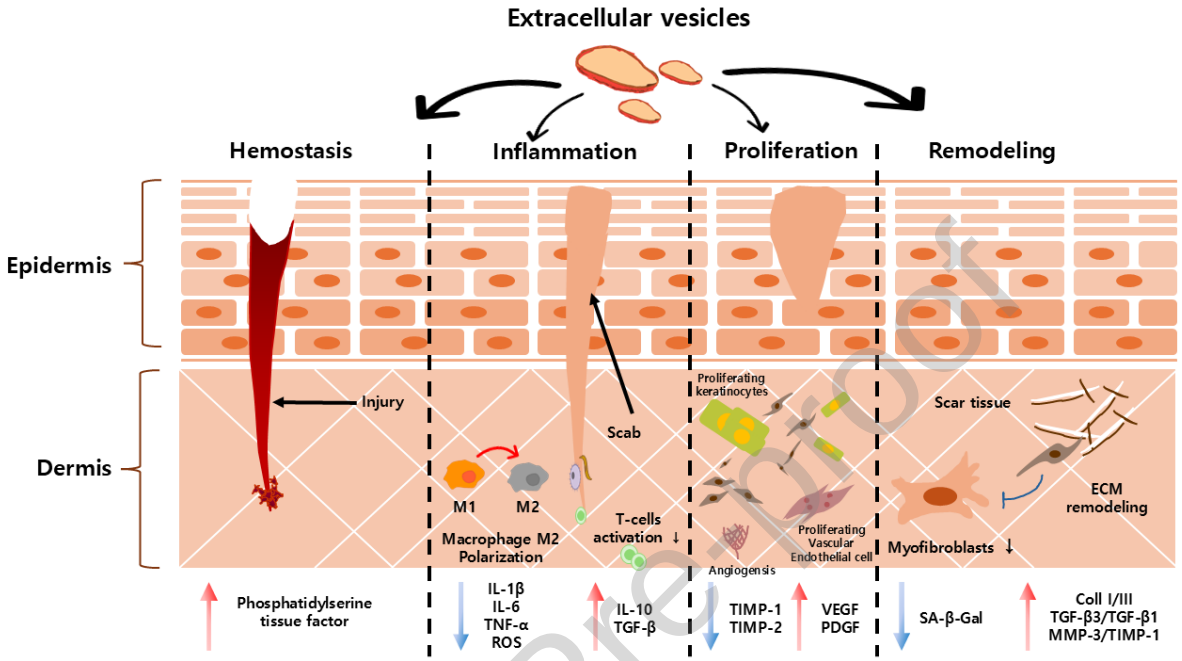

Figure 2. A schematic diagram of the skin repair process and the potential roles of EVs.

Table 1. Summary of studies on MSC-EVs involved in *in vivo* wound healing (Cao et al., 2020a; Cheng et al., 2020; Fang et al., 2016; Franco da Cunha et al., 2020; Haertinger et al., 2020; He et al., 2019; Heo and Kim, 2022; Hoang et al., 2020; Jiang et al., 2020; Li et al., 2022; Li et al., 2021; Liu et al., 2020a; Ren et al., 2019; Sun et al., 2019; Wang et al., 2019; Wu et al., 2020; Xie et al., 2022; Yan et al., 2022; Zhang et al., 2015a; Zhang et al., 2018; Zhao et al., 2020; Zhao et al., 2023; Zhou et al., 2021b; Zhu et al., 2022).

EV Source	Key Findings/Mechanism/Pathway	Target Cells	Reference
Human adipose mesenchymal stem	Downregulation of inflammatory markers (TNF-α, IL-6) Upregulation of VEGF and PCNA	Wound healing cells	Zhou et al., 2021b

cell (hADSC)	miR-19b expression Regulation of TGF-β pathway via CCL1 targeting	Fibroblasts, immune cells	Cao et al., 2020a
	Improvement of scar healing and reduction of fibrosis Downregulation of IL-17RA and P-SMad2/P-SMad3	Hypertrophic scar fibroblasts	Li et al., 2021
	Promotion of angiogenesis through upregulation of pro-angiogenic molecules	Endothelial cells, nerve cells	Heo and Kim, 2022
	Reduction of apoptosis and promotion of SC proliferation	Schwann cells	Liu et al., 2020a
	Axonal regeneration Schwann cell proliferation Neurotrophic factors and miRNAs	Neurons, Schwann cells	Haertinger et al., 2020
	Upregulation of growth factors (VEGFA, PDGF, EGF, FGF2) Activation of AKT, ERK, and STAT3 pathways	Fibroblasts, keratinocytes, endothelial cells	Ren et al., 2019
	Activation of PI3K/AKT pathway Collagen production	Fibroblasts	Zhang et al., 2018
Mouse adipose tissue mesenchymal stem cell (mADSC)	Modulation of CD4(+) T Lymphocytes via the TGF-β pathway	T cells	Franco da Cunha et al., 2020
Human bone marrow mesenchymal stem cell (hBMSC) or nanoparticle-treated	Improved scar formation and wound healing by regulating TGF-β/Smad pathway	Skin fibroblasts	Jiang et al., 2020
	Induction of macrophage polarization towards the M2 phenotype miR-223 targeting of Pknox1	Macrophages	He et al., 2019

Mag-BMSC exosomes	Stimulation of primary dermal fibroblasts and anti-scarring effects	Dermal fibroblasts	Hoang et al., 2020
	Acceleration of wound closure and re-epithelialization Enhancement of Wnt signaling and activation of the AKT pathway	Epithelial cells, skin cells	Zhang et al., 2015
	Inflammation modulation via M2 macrophage polarization NF-kappaB signaling pathway	Macrophages	Li et al., 2022
	Promotion of peripheral nerve regeneration	Neurons, vascular cells	Zhao et al., 2020
	Promotion of angiogenesis and accelerated healing Activation of the PI3K/AKT and ERK1/2 pathways	Endothelial cells, skin cells	Wu et al., 2020
Human umbilical cord mesenchymal stem cell (hUCMSC) or Wharton's jelly mesenchymal stem cell (WJMSC)	Facilitation of wound healing	Skin cells	Cheng et al., 2020
	Treatment of cutaneous nerve damage and promotion of wound healing	Neurons	Zhu et al., 2022
	Acceleration of diabetic wound healing through angiogenesis	Vascular endothelial cells	Yan et al., 2022
	Modulation of TLR4 signaling through miR-181c Reduction of inflammation in burn-induced macrophages	Macrophages	Li et al., 2016b
	Enrichment of miRNAs (miR-21, -23A, -125b, -145) Inhibition of the TGF-β2/SMAD2 pathways	Fibroblasts	Fang et al., 2016
	Promotion of angiogenesis and HUVEC proliferation, minimal scarring	Endothelial cells, skin cells	Sun et al., 2019
	Promotion of angiogenesis	Fibroblasts and vascular endothelial cells	Zhao et al., 2023

	Enhancement of wound closure rate		
Human exfoliated deciduous teeth (SHED)-derived MSC	Stimulation of macrophage autophagy Reduction of itching	Macrophages	Xie et al., 2022
Fetal dermal mesenchymal stem cell (FDMSC)	Promotion of fibroblast proliferation and migration Activation of the Notch signaling pathway	Fibroblasts	Wang et al., 2019

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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