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Review

Mesenchymal stem cell therapy for wound healing: An update to 2022

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ABSTRACT

The skin is an organ that performs complex functions of both the innate and adaptive immune systems. It serves as the first physical barrier to protect the body from environmental factors. Skin also carries aesthetic value in people's desire for eternal youth. Skin lesions are often unwanted, causing open wounds that can be contagious or permit infection of the body, scars, skin aging, and loss of skin function, with long-term psychological consequences. The application of stem cell therapy based on mesenchymal stem cells (MSCs) is constantly developing in the field of skin regeneration, which is highly regarded as a therapy for patients suffering skin lesions from burns, deep wounds, cosmetic surgery, or genetic diseases. MSC therapy has shed light on groundbreaking treatments in immune, anti-inflammatory, and regenerative medicine, including for skin diseases. Additionally, the development of stem cells seems to limit skin aging. It is gradually becoming an integral technique at hospitals as a regular therapy for illness, as well as a cosmetic intervention. This review seeks to introduce the skin system and its related disorders; highlight the common characteristics and mechanisms of MSCs; and analyze updated clinical applications and experiments to date in MSC therapy for regenerative biomedicine and skin diseases.

Key words: MSC for skin, scarring, skin regeneration, skin therapies

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INTRODUCTION

During the past decade, mesenchymal stem cells (MSCs) have emerged as a promising therapy for the treatment of many pathologies. Clinical trials of MSCs to treat chronic wounds that do not heal are underway. There is also interest in their therapeutic potential to accelerate the closure of burn wounds and treat autoimmune disease damage. Many studies show the positive effects of MSC therapy. These positive results are not due to MSCs' differentiation to replace damaged skin. Their therapeutic effects derive from the secretion of soluble factors that regulate cellular responses to skin injury.

Despite the potential of MSC therapy, the field remains in its infancy, with many challenges to be addressed before it can be used effectively in clinical practice. Studies to determine the interactions between MSCs and different cell types in wounds are urgently needed. Such studies must also identify the MSC-derived factors that are responsible for regulating local cellular responses to injury and how the wound environment affects MSCs. This paper will review the current understanding of MSCs for wound healing.

SKIN AND WOUND HEALING

Skin plays an exquisite, crucial role that involves different biological functions. It is the largest organ of the human body; in adults, it has an area of approximately 1.5 – 2 m^2 and accounts for about 15% of body weight [1,2]. The skin consists of different receptors to sense temperature, moisture, pain, and texture [3]. The skin regulates body temperature, stores water, and prevents dehydration to maintain the body's internal balance and protect the body from negative conditions, such as extreme temperatures. The skin is also significant in metabolic processes, notably vitamin D synthesis and lipid storage [2,3]. One of the most important functions of the skin system is to act as a protective barrier between the external and internal environment of the body [2]. Mechanically, the skin is constantly replenished to maintain a balance between cell death and regeneration. Sweat glands, sebaceous glands, and skin flora embedded within the skin layer also contribute greatly to the overall function of this organ [4]. The skin faces challenges due to aging (chronic) and wounds (acute).

Skin aging refers to the functional and aesthetic deterioration of the skin, diminishing its capacity to protect and regulate the body. Skin aging is characterized by the accumulation of damaged macromolecules in cells, diminution of regenerative capacity, and loss of

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physiological function[5]. Some discernible features of skin undergoing early again are thickening, deep wrinkles, spotting, and roughness[6,7].

Two types of skin aging occur simultaneously: aging over time and aging due to the effects of intrinsic factors (*e.g.*, genetics, cell metabolism, hormones, *etc.*) and extrinsic factors (*e.g.*, habitat, dust, radiation, toxins, chemicals, *etc.*). Over time, the accumulation of factors leads to molecular damage, including DNA mutation, telomere shortening, epigenetic alterations, *etc.*, and cellular disorders, such as oxidative stress, cellular senescence, autophagy, proteostasis, inflammation, deficiency of the immune system, *etc.*[5,8]. Thus, molecular changes due to genetic and epigenetic aging ultimately result in the aggregation of worn-out cells and the deterioration of tissue homeostasis and healing capacity[9].

The extracellular components in the skin encompass collagen, elastin, fibrillin, and proteases. During aging, the ratio of type III collagen to type I collagen increases due to the loss of collagen I, which involves the down-regulation of the TGF-β/Smad signaling pathway and connective tissue growth factors; consequently, the architecture of the skin is poorly reconstructed[10,11]. Moreover, the family of various matrix metalloproteinases (MMPs) exhibits a considerable impact on skin balance and anti-aging. MMPs originate from a common family of endopeptidases that decompose ECM proteins and, thus, promote the degradation of the skin[12]. This family has also been shown to increase with age, while endogenous MMP inhibitors decline correspondingly[13,14]. Furthermore, reactive oxygen species (ROS) augment MMPs with age[15]. These elements could be synthesized internally as metabolized oxidizing precursors, or derive from external ultraviolet exposure. ROS activate the mitogen-activated protein kinase family (MAPK), which then induces MMP transcription factors[16,17]. UV is associated with the NF-κB pathway, which is responsible for regulating MMP in skin fibroblasts[16,18].

Aging cells typically present a low expression of β-galactosidase, particularly those that are about to shift into senescence. Additionally, senescence-related gene expression, including CHEK1 and cyclin-dependent kinase inhibitor p16^{ink4a}, is relatively down-regulated during aging[9]. Meticulous studies have revealed the dysregulation of microRNAs (miRNAs) as aging progresses. MiRNAs (short noncoding RNAs that bind to the 3' untranslated region of target mRNA to prevent its gene expression) primarily serve as regulators for cell survival, proliferation, differentiation, and senescence[19,20]. Age-dependent defectiveness restricts repair genes[9].

The processes of skin regeneration and post-traumatic wound healing are indispensable, especially in the epidermal and dermal layers, as they help reduce the risk of infection that is associated with a high mortality rate[21]. This healing reaction occurs in three stages: the inflammatory phase, the proliferation phase, and the remodeling phase.

Skin injury triggers the inflammation response, which initiates coagulation, providing a fibrin network alongside vascular constriction to close the wound and preserve its integrity. This fibrin meshwork not only balances endogenous conditions and fights invading microorganisms, but also provides the site for cell migration and the collection of growth factors, including transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF)[22]. White blood cells are recruited into the site of injury within the first 24 hours and remain there for 2 to 5 days[23,24]. White blood cells release protease and ROS to directly destroy bacteria, digest mortified tissue, and engulf the remnants of cell debris. Meanwhile, neutrophils appear to release cytokines, including necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, to amplify the inflammatory response[25].

The proliferative phase occurs 48 after the wound occurs and can last for up to 14 days[26] after the remission of inflammation, resulting in a miniature lesion when the contraction and formation of filaments induces horn cells[26]. This phase is characterized by granulation tissue formation to replace the provisional wound matrix and vascular network recovery of the sources of cytokines and growth factors, notably transforming growth factor-beta (TGF-beta, including TGF-β1, TGF-β2, and TGF-β3), interleukin (IL), and vascular formation factors[24,27]. In response to tactile inhibition and the physical strain of endoplasmic lesions, horn cells and epithelial stem cells from hair follicles are triggered to migrate and proliferate to cover the wound margin. Furthermore, macrophages send nitric oxide[28] signals or other cell types release epidermal growth factors (EGF), keratinocyte growth factors (KGF), insulin-like growth factor 1 (IGF-1), and neural growth factor (NGF), which appear to trigger the reepithelization process[29,30]. Additionally, angiogenesis occurs to enable the transportation of nutrients and oxygen that favors wound healing. During the formation of new blood vessels, endothelial cells are activated by vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and thrombin serine protease[31]. The final step of this process is

marked by the formation of granulation tissue leading to the infiltration and proliferation of fibroblasts into the wound edge. Granulation tissue consists of loosely organized fibroblasts, macrophages, capillaries, granular leukocytes, and bundles of type III collagen [3,32].

The remodeling phase completes the healing process, beginning within 2 to 3 weeks of the injury and potentially lasting for a year [33]. The process of controlling the balance between the degeneration and synthesis of new tissue is immensely rigorous and any disruption or error results in the formation of chronic wounds [24,32]. TGF-β1 promotes fibroblast differentiation into myofibroblasts [34]. The extracellular matrix (ECM) is remodeled and synthesized to become more robust, characterized by the degeneration of type III collagen over time and its gradual replacement with type I collagen [32]. However, some skin components, such as hair follicles or sweat glands, cannot recover from severe skin damage [35]. Thus, wound healing terminates with the formation of scars, which are closely related to inflammation [34].

MESENCHYMAL STEM CELLS AND THEIR BIOEFFECTS ON SKIN REGENERATION

Mesenchymal stem cells and their extracellular vesicles

MSCs have been found and isolated from various somatic locations [36]. Their biological functions have been assessed differently, as well as being isolated in different places with different methods; no distinct indication helped define the characterization of MSCs. To circumvent this problem, the International Society for Cellular Therapy suggested minimum standards to identify MSCs in humans [37]: First, MSCs must have a fibroblast shape, adhesive capacity, and maintain their shape under standard culture conditions. Second, MSCs must express CD73, CD90, and CD105 but not CD14, CD11b, or CD79α, CD19, CD34, CD45, and HLA-DR. Third, MSCs must differentiate into osteocytes, chondrocytes, and adipocytes *in vitro* [37]. Although scientists recently discovered that MSC populations do not thoroughly comply with these minimal criteria—for instance, some fail to express CD105 [38]—these rules are still ubiquitously used to compare and exchange data among MSC studies (**Figure 1**).

MSCs have been attested to work through the paracrine system via extracellular vesicles (EVs) [39,40]. MSC-EVs comprise a variety of vesicles of varying sizes and are described as miniature prototypes of the cells that secrete them [41]. EVs can be divided into three main types by origin: apoptotic bodies (1000–5000 μm), microvesicles (1000 μm), and exosomes (30 – 150 μm) [42]. EVs seem to be more stable in the living body than foreign elements [43]. Immunoregulatory factors such as IL-10, TGF-β, INF- γ, IDO, and prostaglandin E2 persist within EVs [44,45]. Their chief components include proteins, lipids, and nucleic acids. These components mediate many effects in recipient cells and are enclosed within a phospholipid bilayer. Furthermore, at least 730 different proteins have been shown to be enriched in exosomes derived from mesenchymal stem cells [46]. Additionally, 171 miRNAs have been pinpointed in EVs derived from MSCs [47] and play pivotal roles in gene expression. For example, miR-130a-3p triggers cell proliferation, angiogenesis, the inhibition of programmed death, or the regulation of immune cell survival (https://www.ncbi.nlm.nih.gov/gene/406919). Exosomes have gradually revealed their potency and paved the way for the fourth generation of stem cell therapy.

MSCs' bioeffects on skin

Immunomodulation

MSCs were first shown to regulate immunosuppressive activities in a mixture of lymphatic cells *in vitro* and persistent allograft *in-vivo* transplant rejection [48]. Since then, numerous studies have shown that MSCs mediate immunosuppression in both animal and human models. Their regulatory ability applies to both the innate and adaptive immune systems (**Figure 2**).

MSCs inhibit differentiation into type I macrophages [49–51]. IL-6 and insulin-like growth factor (IGF) prompt mononuclear cells to secrete IL-10, a strong anti-inflammatory cytokine that perpetuates osmotic balance, heals inflammatory tissue, and stimulates the transformation of macrophages into type 2 macrophages [50]. Additionally, MSC releases anti-ligands, such as interleukin 1 (IL1-RA) and PGE-2, which have similar effects [52,53].

MSC-derived IL-6 also inhibits apoptosis in neutrophils [54]. Neutrophils are the most common innate immune cells, appearing within hours in wounds. To date, the clinical associations between MSC and neutrophils are poorly understood. MSCs have been suggested to enhance neutrophil activity [55,56]. MSCs also regulate a significant reduction in intracellular hydrogen peroxide, which affects neutrophils' apoptosis process [57]. Neutrophils in environments with nutrient or serum deficiency can survive if cocultured with MSCs [58].

Critically, MSC-secreted cytokines could inhibit proinflammatory T cells and stimulate the proliferation of regulatory T cells (Tregs) [59,60]. Tregs are

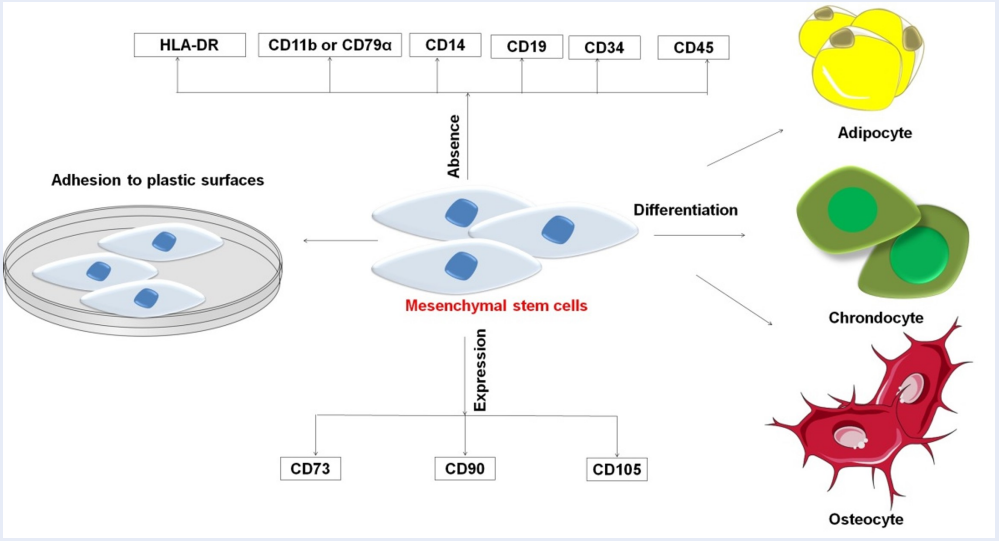

Figure 1: **The minimal criteria in defining mesenchymal stem cells**. (**1)** MSCs must have a fibroblast shape, adhesive capacity, and shape maintenance in standard culture conditions. (**2)** MSCs must express positive expression for CD73, CD90, CD105, and negative expression for CD14 or CD11b or CD79α, CD19, CD34, CD45, and HLA-DR. (**3)** MSCs must differentiate into osteocytes, chondrocytes, and adipocytes *in vitro*.

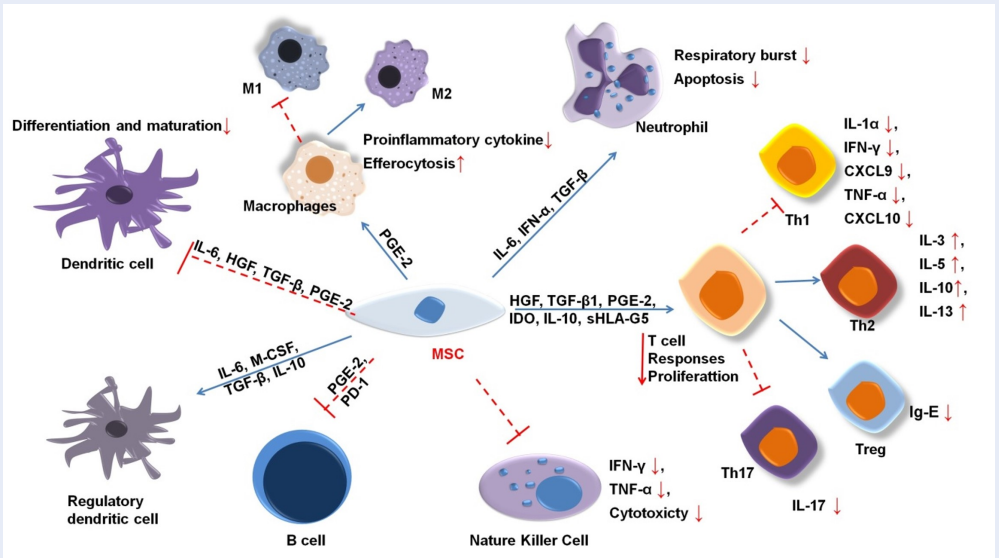

Figure 2: **The cells of the innate and adaptive immune systems are affected under the regulation of MSCs**. Arrows indicate activation or induction, T-bars indicate inhibition.

crucial for immune homeostasis because they prevent the autoimmune response. Growth factor B1 (TGFβ1), PGE2, and IL-10 innervate the increment of Tregs [7,61,62]. Although the mechanism of MSC immunomodulation remains largely unexplored, PGE2, IDO, HGF, and TGF-β1 have been strongly linked to the immunosuppression of T cells [63]. MSCs prohibit the production of IL-17, which suppresses the induction of Th17 [64], while the enhancement of IL-10 activates Tregs [65]. MSCs also secrete indoleamine 2,3-dioxygenase (IDO), an enzyme that decomposes tryptophan, which inhibits the growth of T cells by reducing tryptophan availability [10]. Several studies have suggested that a persistent decrease in tryptophan reduces the secretion of IL-4 in Th2 cells and the amount of Th1 released from IFN-gamma cells [52,66].

MSCs significantly enhance the immune regulation of B cells by mediating IL-10 [67,68]. One study demonstrated that the interaction of CD3+ T cells and MSCs inhibits the proliferation of plasma B cells [69]. At high IFN-γ concentrations, MSCs could activate programmed cell death receptors through direct contact and the PD-1/PD-L1 signaling pathway to hamper the growth and maturity of B cells [70]. Additionally, MSCs inhibit the CXCR4, CXCR5, and CCR7 molecules that directly affect B cells [71].

MSCs inhibit the differentiation, maturity, and migration of DC cells [72,73]. Specifically, IL-6 and IL-10 suppress the differentiation of mononuclear cells into DC cells [74,75]. In addition, PGE2 is expected to demonstrate a similar inhibitory effect [73]. MSCs also promote the generation of regulatory DCs with immunomodulatory functions in mouse models [76].

In addition, MSCs restrict NK cell proliferation, cytokine secretion, and cytotoxicity mediated by PGE2, IDO, HLA-5, or extracellular vesicles [12,77]. This effect requires a higher ratio of MSCs to NK cells [78]. MSCs also regulate the CD73 expression of NK cells, which converts AMP to adenosine as an anti-inflammation inducer [66,79].

The effects that MSCs have on cells in the innate and adaptive immune systems are summarized in **Table 1**. MSC secretions in general and MSC-EVs, in particular, can modulate immunity and generate angiogenesis through their ability to regulate the proliferation and differentiation of cells. In the context of skin regeneration in general and chronic skin wounds, MSCs' and MSC-EVs' biological effects are apparent in infants: Early fetal skin wounds (< 3 months) heal and the skin regenerates without scarring [81]. The weak immune response found in fetal wounds reflects the low number of innate immune cells, such as neutrophils, macrophages, and mast cells, present [82]. This is characteristic of the difference between embryonic skin and adult skin.

The initial inflammatory process after the skin is wounded is very important, greatly affecting the skin composition, structure, and recovery through the subsequent processes. As **Figure 2** shows, the products of MSCs exert regulatory effects on the cells of the innate and adaptive immune systems. They activate M2 macrophages and express signal transducers and activators of transcription 3 (STAT-3) concomitant with several transcription factors. These factors promote tissue regeneration and inhibit inflammation [83,84]. In addition, MSCs increase the secretion of factors such as MCP-1, IL-6, and IL-8 to modulate inflammation [85]. Furthermore, MSCs inhibit T and B cell activation and the release of IL-10 and TGF-β—anti-inflammatory agents—and reduce IgE production [85,86].

Regeneration

The evidence suggests that MSCs and their products work to maintain skin homeostasis. In adult bodies, subcutaneous ADSCs are responsible for regulating and directing mature differentiated cells outside the epidermis, especially keratinocytes. These cells are responsible for regeneration and recovery from damage [87]. MSCs also release several factors that help modulate the expression of various pathways [6,88]. For example, several miRNAs in MSC-EVs activate the signaling pathways AKT, ERK, and STAT-3, which are involved in many cellular processes including angiogenesis, proliferation, and cell migration [89].

Keratinocytes and fibroblasts play major roles in normal proliferation and healing. Fibroblasts primarily produce ECM, cause the oral contraction of the wound, biosynthesize collagen, and regenerate tissue. Disordered or over-synthesized collagen in fibroblasts will cause scarring. MSC-EVs have been shown to influence the MAPK/ER pathway of fibroblasts, reducing scarring during the treatment of open wounds [90]. In addition, MSCs promote wound healing through the PI3K/AKT signaling pathway [91]. Fibroblast proliferation is influenced by FGF, EGF, PDGF, TGF-β, CTGF, and IGF-1 [92].

The re-epithelialization of the skin depends on the proliferation and migration of keratinocytes. These are among the most important processes in wound healing. The EGF and TGF-β of MSCs play an important role in keratinocyte migration [93]. In addition, keratinocyte proliferation is stimulated by bFGF, IGF-1, and EGF [93].

Table 1: The target cells affected by MSCs-derived cytokines [80]

Target cell	MSCs-derived cytokines
Tregs	IL-6, IL-10, TGFβ, IDO, VEGF
NK	TGFβ, Chemokines, PGE2, IDO
B	IL-6, TGFβ, IDO
Th1	IL-10, CCL-5/RANTES, VEGF
Th2	IL-6, CCL-2/MCP-1
Th17	IL-6, CCL-2/MCP-1, VEGF
DCs	IL-10, IL-6, TGFβ, IDO, VEGF, PGE2
Neutrophils	IL-10, IL-6, CCL-5/RANTES
Monocytes	IL-6, CCL-5/RANTES, IDO, PGE2

Mesenchymal stem cell transplantation: from animals to clinical trials

MSC therapy is promising as a fundamental therapy, with overwhelming advantages in regenerative capability, wound healing, and immunomodulation. Progressive effort has been made toward understanding the mechanisms by which MSCs promote skin wound healing. Studies of MSCs' impact in animal models and their effect on skin lesions are presented in **Table 2**.

Most studies of MSCs' relationship to skin wounds on different model types report positive effects. This dynamic supports the application of MSCs to human skin lesions. To date, more than 400 clinical studies affirm the positive effects of MSCs on skin lesions (clinicaltrials.gov). These studies use mesenchymal stem cells from a variety of sources; MSC products, such as EVs, proteins, or miRNAs; and these agents together, along with a biomatrix (tissue engineering) to treat skin wounds. Some of the most up-to-date clinical trials are presented in **Table 3**.

In addition to the use of MSCs to heal ailments related to skin damage, MSCs and MSC products have been used for anti-aging cosmetic purposes. Research on animal models showed that exosomes from young mice could transfer miR-126b-5p to the tissues of old mice and reverse the expression of aging-related molecules such as p16, mTOR, and IGF-1R. They also affect the expression of telomerase-related genes, including Mre11a, Tep1, Terf2, Men1, Tert, and Tnks, in old mice [105]. If this effect occurs in humans, MSCs in general and MSCs originating from umbilical cords or placentas, in particular, will be a potential source of cosmetic pharmaceuticals, eliminating other cosmetics that currently dominate the market.

The market for exosome-related cosmetics is flourishing. Some MSCs and MSC products used in cosmetics are presented in **Table 4**.

PERSPECTIVES

Because MSCs and MSC exosomes manifest hypoimmunogenic properties, they are hopeful choices for treating chronic wounds, injuries, and plastic surgery incisions. This has huge potential in the field of tissue remodeling and engineering. Since the Physiology Nobel prize in 2013 was awarded to the three Laureates who presented insights into exosomes, studies of MSC exosomes have increased at a dizzying rate. According to Mordor Intelligence, the exosome market was reportedly worth 174.04 million USD in 2020 and is predicted to increase by 27.89% in this year (https://www.mordorintelligence.com/). The growing demand for anti-aging therapies drives much of the market. Furthermore, the availability of various methods for exosomal isolation and purification helps fuel further studies of exosome treatments.

Most research now focuses on proving the utility of MSC exosomes as a single treatment. Clinically, MSC exosomes should be used in combination with other therapies, such as laser, topical medication, surgery, etc. Consequently, more studies are needed to demonstrate the synergistic or inhibitory effects of MSC exosomes in combination with conventional treatments. Researchers are optimistic about the development of MSC therapy. Similarly, exosomes as a drug delivery system are a bright research path. For almost a decade, there has been tremendous progress in our understanding of all aspects of exosomes. Further improvements in drug-loading strategies and the optimization of these therapies are promising for future clinicians.

Table 2: Studies on MSCs' effects on skin wounds in animal models

Number	Sources	Model	Result	References
1	Adipose-derived stem cells	Burned skin, Wistar rats	+	[94]
2	Adipose-derived stem cells	3rd-degree burns, BALB/c mice	+	[95]
3	Human amniotic mesenchymal stem cells	Burned skin, C57BL/6 mice	+	[96]
4	Human umbilical cord mesenchymal stem cells	Burned skin, C57BL/6 Mice	+	[97]
5	Adipose-derived stem cells	Surgical wound, Balb/c mice	+	[36]
6	Wharton's jelly-derived mesenchymal stem cells	Radiation-induced skin wounds, rats	+	[98]
7	Human umbilical cord blood-derived mesenchymal stem cells	Imiquimod-induced psoriasis-like skin inflammation, C57/BL6 mice	+	[99]
8	Human umbilical cord-derived mesenchymal stem cells	Diabetic rats	+	[100]
9	Bone marrow mesenchymal stem cells	Wounds, Sprague-Dawley rats	+	[101]
10	Human umbilical cord Wharton's jelly MSCs	Full-thickness skin defects, Balb/C mice	+	[102]
11	Umbilical cord and umbilical cord blood-derived mesenchymal stem cells	SKH-1 hairless mice	+	[103]
12	Human bone marrow and jaw bone marrow-derived mesenchymal stem cells	Full-thickness skin defects, C57BL/6J mice	+	[104]

THE LIMITATIONS OF MSC-EV USE

The extracellular secretions of MSCs, especially the exosomes, are being intensively studied for their notable features. MSCs' impact via exosomes is significant in tissue repair. MSC therapy is gaining popularity and is known as fourth-generation stem cell therapy—the new cell-free therapy [106]. MSCs not only play an essential role in the treatment of wounds, skin regeneration, and anti-aging but also contribute to the treatment of immune-related diseases, tumors, and neurological disorders and are the standard by which to diagnose and prevent disease. In addition, exosomes from MSCs can be used for drug delivery, encasing pharmaceuticals in a phospholipid bilayer that confers outstanding physiological advantages [107].

In contrast, the considerations for using MSC exosomes include:

It is challenging to determine the composition of exosomes, such as their proteins, lipids, and, especially, miRNAs. All of these components derive from the cell culture process and are variable and heterogeneous. Qualitative studies generally seek to confirm whether an agent of interest persists within exosomes. The half-life of exosomes is also unknown. This is an important evaluation criterion to use exosomes for drug transport [107]. Drug efficacy is highly dependent on delivery time, so this is a major limitation of knowledge regarding the potential use of exosomes for transport.

Another important consideration is the exosome productivity of mesenchymal stem cells. The exosomes for this new cell-free therapy are usually obtained from MSC cultures. This means that cell therapy and exosome therapy are linked. A study has determined that producing sufficient exosomes to have the same effect as cell therapy requires 10 – 25 times the normal quantity of MSCs [108]. Significant development is needed before exosome therapy can be routinely applied. More research on a suitable culture medium to

Table 3: Clinical trials on the MSC and MSC products effects are registered (Clinicaltrial.gov), updated 2021

Number	Type	Phase	Nation	Ref
1	Corlicyte® umbilical cord lining mesenchymal stem cells	Phase 1	Usa	NCT04104451
2	Placental mesenchymal stem cells	Phase 1	China	NCT04464213
3	Umbilical Cord Lining Stem Cells	Phase 1	USA	NCT04723303
4	Adipose-derived mesenchymal stem cells	Phase 2	China	NCT04785027
5	Adipose-derived stromal/stem cells	Phase 2	France	NCT04356755
6	Umbilical Cord Mesenchymal Stem Cells	Early phase 1	China	NCT03765957
7	Mesenchymal stem cells -derived Exosome	Phase 2	USA	NCT04173650
8	Adipose-derived mesenchymal stem cells	Phase 2	Korea	NCT04137562
9	Umbilical Cord Mesenchymal Stem Cells	Pha 2	China	NCT03745417
10	Hematopoietic stem cells	Phase 3	Belgium, Croatia	NCT03754465
11	Adipose-derived mesenchymal stem cells	Phase 2	USA	NCT03754465
12	Human bone marrow-derived mesenchymal stem cells	Phase 2	Korea	NCT04179760

produce more extracellular vesicles is needed to address this limitation. The current cell culture abandonment medium does not meet the conditions required to develop a routine therapy.

There is also substantial concern about cell properties. Exosomes reflect the properties of their parent cells. Research shows that exosomes from young cells can reverse the aging of aging cells [105]. Therefore, more in-depth studies are needed on the relationship between MSC age and the exosomes they release. This greatly affects the potential of mesenchymal stem cells from different sites. If the assertions in [105] are true, mesenchymal stem cells obtained from umbilical cords and placentas will be preferred.

Another problem in the production of exosomes is purity. MSCs do not express HLA-DR, so they should not induce an adverse immune response. However, an immune response has been observed when MSCs enter the body. This is associated with impurities in the injections. Ultracentrifugation is a standard method for exosome isolation and purification. It uses a density gradient, which may permit other agents or types of vesicles with the same density as the target components to remain. Developing an environment to eliminate, limit, or replace undesirable elements is one solution. However, the optimization of the culture and acquisition process is the ideal way to eliminate this problem.

Despite these limitations, the enormous potential of MSC exosomes is apparent. Exosomes have many advantages over mesenchymal stem cell therapy: They can be stored as proteins for short-term use without the concern of cell survival and using them after thawing is much easier. They are much smaller than MSCs and do not become trapped in small capillaries like cells do. One report shows that this is a serious limitation of cell therapy, as when intravenous administration results in pulmonary embolism [109]. However, exosome therapy cannot completely replace mesenchymal stem cell therapy because of their interrelationships.

ABBREVIATIONS

AMP: Adenosine monophosphate, **bFGF**: Basic fibroblast growth factor, C**CL-2/ MCP1**: Chemokine (C-C motif) ligand 2/ onocyte chemoattractant protein 1, **CCL-5/ RANTES**: Chemokine (C-C motif) ligand 5/ regulated on activation, normal T cell expressed and secreted, **CXCR4 C-X-C**: chemokine receptor type 4, **CXCR5 C-X-C**: chemokine receptor type 5, **DCs**: Dendritic cells, **ECM**: Extracellular matrix, **EGF**: Epidermal growth factor, **EVs**: Extracellular vesicles, **HGF**: Hepatocyte growth factor, **HLA-5**: Human Leukocyte Antigen - 5, **HLA-DR**: Human Leukocyte Antigen – DR isotype, **IDO**: Enzyme Indoleamine 2,3-dioxygenase, **IGF-1**: Insulin-like growth factor 1, **IL**: Interleukin, **KGF**: Keratinocyte

Table 4: Some products related to MSC and MSC-products in cosmetics on the current market

Number	Name	Sources	Nation	Ref
1	XoGlo	Mesenchymal stem cell (MSC)-derived Exosome	USA	https://www.refineusa-exosomes.com/
2	HematoPAC™-HSC-CB	Umbilical cord blood stem cells	USA	https://www.businesswire.com/news/home/20210311005075
3	Venus Skin™	Bone Marrow Stem Cell	USA	https://www.venustreatments.com/en-us/sct-serum.htm
4	AnteAGE Serum	Bone Marrow Stem Cell	USA	https://anteage.com/products/anteage-pro-serum-30ml
5	Exo skin simple	Adipose Stromal Cell-derived Exosome	USA	https://exoskinsimple.com/collections/products
6	ASCE+ skin	Adipose Stromal Cell-derived Exosome	KOREA	http://www.asceplus.co.kr/
7	REBELLAXO	Umbilical cord blood-derived Exosome	USA	https://rebellabiologic.com/product/rebellaxo/
8	InfiniVive Exosome Serum	Umbilical cord blood-derived Exosome	USA	https://infinivivemd.com/products/infinivive-exosome-serum
9	CELL PERFORMANCE SERUM	Bone Marrow Stem Cell	KOREA	https://ndclist.com/ndc/60949-080
10	U Autologous™	Stem cells derived from their	USA	https://www.leadingsalons.com/en/article/50/u-skincare
11	Dermaheal Stem C'rum	Adipose stem cell	KOREA	https://caregennordic.se/product/stem-crum/
12	Cutisera™	Bone marrow mesenchymal stem cell	INDIA	https://www.stempeutics.com/stempeucare.html
13	Adipose Stem Cell Growth Factor Anti-Aging Serum	Adipose Stem Cell	USA	https://www.amazon.com/Adipose-Hyaluronic-Matrixyl-Advanced-Anti-Aging/dp/B07SCPTSGN
14	Beautigenix Hydrating Mask	Adult Human Stem Cell	USA	https://incidecoder.com/products/beautygenix-hydrating-mask
15	ProPlus Eye Firming Complex	Peptides from Non-Embryonic Human Stem Cells	USA	https://lifelineskincare.com/products/proplus-eye-firming-complex

Growth Factor, **MAPK**: Mitogen-activated protein kinase, **MMP**: Matrix metalloproteinase, **MSC**: Mesenchymal stem cell, **NK cells**: Natural killer cells, **NGF**: Nerve growth factor, **PDGF**: Platelet-derived growth factor, **PGE-2**: Prostaglandin E 2, **ROS**: Reactive oxygen species, **TGF-β**: Transforming growth factor beta, **TGF-β1**: Transforming growth factor beta 1, **TGF-β2**: Transforming growth factor beta 2, **TGF-β3**: Transforming growth factor beta 3, **TNF**: Tumor necrosis factor, **Th1 cells**: T helper cells, **Th2 cells**: T helper cells, **Tregs**: Regulatory T cells, **VEGF**: Vascular endothelial growth factor, **IFN-γ**: Interferons γ

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Phat Duc Huynh was responsible for the layout and content of the manuscript. Quynh Xuan Tran, Vy Quang Nguyen, and Sao Thi Nguyen equally contributed to this work. Ngoc Bich Vu conceptualized,

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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