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Applications of Mesenchymal Stem Cells in Anti-Aging and Skin Regeneration

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Abstract:
Skin aging constitutes a multifaceted physiological process. With the acceleration of global aging, anti-aging and skin regeneration have become research hotspots in aesthetic medicine and regenerative medicine. This paper focuses on mesenchymal stem cells (MSCs), investigating their diverse mechanisms of action, clinical effectiveness, and future development trends in combating skin aging and promoting skin regeneration. This study employs a systematic literature review methodology to analyze the biological characteristics of mesenchymal stem cells and their anti-aging and regenerative mechanisms achieved via paracrine signaling and direct differentiation. It also examines specific application cases in photodamaged skin and difficult-to-heal wounds such as diabetic foot ulcers. Results indicate that MSCs primarily exert their effects through potent paracrine activity. By releasing multiple growth factors, cytokines, and exosomes, they synergistically confer protection against oxidative stress, exert immunomodulatory regulation, promote collagen synthesis, inhibit matrix metalloproteinase (MMP) activity, and stimulate angiogenesis. These multifaceted actions effectively delay skin aging and accelerate wound healing. Despite the broad application prospects of MSCs, further research is still needed in areas such as cell standardization protocols, safety evaluation systems, and cell-free therapeutic strategies.

Keywords: Mesenchymal stem cells, Skin anti-aging, Skin photoaging, Diabetic foot ulcers, Wound injury

1. Introduction

Skin aging is a multifaceted and irreversible physiological process. With the acceleration of global aging and the growing demand for youthful skin appearance, anti-aging and skin repair have become research hotspots in aesthetic medicine and regenerative medicine. Traditional anti-aging approaches (e.g., chemical peels, laser therapies, and dermal filler injections), while partially effective, suffer from issues like prolonged recovery periods, transient efficacy, or potential complications. In recent years, mesenchymal stem cells (MSCs) have demonstrated significant potential in skin anti-aging and damage repair due to their potent regenerative potential and immunomodulatory capabilities. MSCs are a type of multipotent stem cell with high differentiation potential, self-renewal capability, and low immunogenicity. They are readily accessible and can differentiate into multiple types of tissue-specific cells under specific conditions [1].

This paper adopts a systematic literature review approach, starting from the characteristics of MSCs, to analyze their mechanisms of action and clinical applications in combating skin aging and promoting skin regeneration, and to explore their future potential in the field of skin anti-aging and regenerative medicine.

2. Characteristics of MSCs

2.1 Sources and Classification

MSCs are a type of multipotent stem cell abundantly distributed in connective tissues and interstitia of various organs across the body. They exhibit self-renewal capacity and the potential to differentiate into various mesodermal tissue cells (such as osteoblasts, chondrocytes, and adipocytes) under specific conditions. Their main sources include bone marrow, adipose tissue, umbilical cord, and other connective tissues [1]. Among these, umbilical cord mesenchymal stem cells (hUC-MSCs), including Wharton's jelly mesenchymal stem cells (WJ-MSCs) and umbilical cord blood, exhibit robust proliferation and differentiation capabilities, extremely low immunogenicity, and no ethical controversies [1]. Adipose-derived mesenchymal stem cells, characterized by high availability and easy accessibility (via liposuction procedures), have emerged as a preferred source in cosmetic and regenerative medicine applications [2]. Due to their ability to secrete multiple cytokines (e.g., VEGF, bFGF) and promote collagen and elastin production, adipose-derived MSCs are widely used in skin repair and anti-aging therapies [3]. MSCs are suitable for cell therapy not only because they are easily isolated from primary tissues but also due to their low immunogenicity, a characteristic that enables their application in diverse therapeutic scenarios.

2.2 Mechanism of Action

MSCs facilitate tissue repair and regeneration through synergistic mechanisms. First, their multipotent differentiation capacity allows them to differentiate into specialized cell types like fibroblasts and endothelial cells, directly contributing to damaged tissue reconstruction. Second, MSCs release multiple growth factors via paracrine signaling. Among these, vascular endothelial growth factor (VEGF) promotes angiogenesis, fibroblast growth factor (FGF) stimulates cell proliferation, and epidermal growth factor (EGF) accelerates epithelialization, collectively enhancing collagen synthesis and tissue regeneration. Regarding immunomodulation, MSCs significantly reduce the expression of pro-inflammatory factors (e.g., TNF-α, IL-6) while inducing macrophage polarization to the anti-inflammatory M2 phenotype, effectively regulating the local inflammatory microenvironment [2]. Furthermore, MSCs exhibit potent antioxidant functions. By scavenging reactive oxygen species (ROS), MSCs strengthen the cellular antioxidant defense network, thereby protecting skin cells from oxidative stress damage and inhibiting photoaging-related apoptosis. These synergistic mechanisms collectively form the integrated network through which MSCs promote tissue repair and regeneration [2].

3. Applications of MSCs in Anti-Aging Skin Therapy

3.1 Principles of Skin Aging

Skin aging is a multifaceted and progressive physiological process fundamentally characterized by the body's impaired ability to sustain cellular homeostasis, accompanied by progressively enhanced cellular apoptosis and senescence over time. Structurally, skin aging predominantly manifests as epidermal thinning, dermal collagen depletion, and elastic fiber disruption. Functionally, it is characterized by impaired tissue repair capacity and slowed wound healing. Visible signs include wrinkles, laxity, and hyperpigmentation. Skin aging is categorized into intrinsic and extrinsic aging. Intrinsic aging denotes the body's natural aging process, predominantly genetically predetermined and inevitable. Exogenous aging, however, is caused by external environmental factors. Photoaging represents the primary form of extrinsic skin

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aging, manifesting as deep wrinkles, hyperpigmentation, and loss of skin elasticity due to prolonged ultraviolet (UV) exposure. Additional environmental precipitants of aging encompass smoking, sun exposure, wind exposure, and contact with harmful chemicals [4].

3.2 The Anti-Aging Effects of MSCs

MSCs exert their anti-aging effects on the skin primarily through several mechanisms. First, MSCs mitigate oxidative stress-induced damage by secreting antioxidant enzymes such as superoxide dismutase (SOD) to scavenge ROS triggered by ultraviolet (UV) radiation and environmental pollutants. Second, MSCs promote collagen synthesis by releasing growth factors (TGF-β1 and IGF-1) that stimulate skin cells to produce more collagen. Simultaneously, they downregulate collagen-degrading matrix metalloproteinases (MMPs)—enzymes that degrade collagen—thereby enhancing skin firmness and elasticity [5]. Furthermore, MSCs modulate the cutaneous immune microenvironment by releasing multiple growth factors and anti-inflammatory mediators to activate anti-inflammatory cells. This includes inducing macrophage polarization toward the anti-inflammatory M2 phenotype and increasing the proportion of Treg cells, thereby attenuating the levels of pro-inflammatory cytokines in the skin and mitigating chronic inflammation-induced damage. Additionally, MSCs potentiate the skin's intrinsic regenerative capacity by secreting SDF-1/CXCR4 signaling molecules, which stimulate proliferation of hair follicle stem cells (HFSCs) and epidermal basal layer stem cells, thereby facilitating repair of damaged skin tissue. Finally, VEGF and HGF secreted by MSCs promote dermal microvascular formation, enhancing cutaneous nutrient perfusion [6].

4. Application of MSCs in Wound Repair

4.1 Challenges in Skin Injury Repair

Presently, conventional skin wound repair modalities (autologous skin grafting, dressing therapy) face significant limitations. Autologous skin grafting entails harvesting skin from the patient's healthy anatomical sites, potentially leading to limited donor site availability—particularly for patients with extensive burns. Furthermore, the donor site itself may develop new wounds and scarring. While dressing therapy causes less trauma, it carries risks such as prolonged healing times and susceptibility to infection [7].

Consequently, traditional skin repair methods struggle to achieve perfect tissue regeneration, often resulting in scarring, hyperpigmentation, or functional impairment. The emergence of MSCs can partially overcome these limitations, facilitating optimal cutaneous tissue regeneration. MSCs not only differentiate into skin cells to directly participate in repair but also secrete various growth factors and cytokines to modulate the local microenvironment. They facilitate angiogenesis while attenuating inflammatory responses, thereby achieving accelerated and superior-quality skin regeneration. This stem cell-based regenerative medicine approach offers new possibilities for addressing the limitations of traditional therapies [4].

4.2 Mechanisms of MSC-Mediated Wound Healing

Wound healing proceeds through four sequential yet overlapping phases: hemostasis, inflammation, proliferation, and maturation. MSCs modulate repair cascades across all phases through diverse signaling pathways. During the inflammatory phase, MSCs release diverse immunomodulatory factors through paracrine mechanisms, promoting the phenotypic shift of macrophages from pro-inflammatory M1 to anti-inflammatory M2 types. This suppresses excessive inflammation and facilitates immune regulation. During the proliferation phase, MSC-secreted VEGF and FGF promote angiogenesis, stimulate granulation tissue proliferation, and enhance cell migration, proliferation, and vascularization [8]. In the maturation phase, MSCs reduce scarring and matrix remodeling by suppressing the TGF-β/Smad signaling pathway.

5. Clinical Application Case

5.1 hUC-MSCs for Diabetic Foot Ulcers

Diabetic foot ulcers (DFUs) constitute a devastating complication of diabetes mellitus (DM). Conventional therapeutic modalities encompass debridement, negative pressure wound therapy, and growth factor therapy. Nevertheless, these approaches are hindered by limitations including suboptimal cure rates (roughly 40%-50%), high recurrence rates, and increased susceptibility to infection.

For refractory ulcers, autologous skin grafting faces donor site limitations, while bio-dressings struggle to promote deep tissue regeneration, resulting in limited efficacy of conventional approaches. According to Zhang et al., local delivery of hUC-MSCs markedly enhances DFU healing outcomes. By modulating inflammation, promoting re-epithelialization, and enhancing microcirculation, hUC-MSCs attain an 80% complete wound closure rate within 1.5 months while shortening healing time. Long-term follow-up revealed no amputations and favorable survival rates within 3 years, though poor glycemic control and prior amputation history may impact prognosis. Furthermore, hUC-MSCs significantly enhance DFU healing rates through multiple mechanisms with good safety profiles, offering a novel therapeutic option for refractory diabetic foot ulcers. Subsequent investigations ought to optimize cell delivery strategies and evaluate long-term efficacy [9].

5.2 Treatment of Skin Photoaging

The etiological factors of skin photoaging comprise UV-induced oxidative stress, inflammatory responses, DNA damage, and disruption of the extracellular matrix (ECM). Traditional approaches to combat photoaging predominantly involve topical antioxidants (such as vitamin C and vitamin E), chemical exfoliation, laser therapy, and injectable fillers. While these methods can enhance cutaneous appearance to some extent, they often address only superficial symptoms, offering transient alleviation without fundamentally repairing deep tissue damage [10]. Adipose-derived mesenchymal stem cells (ADSCs), owing to their pluripotency, self-renewal capacity, and immunomodulatory functions, have emerged as a novel strategy against photoaging. By secreting growth factors and exosomes, ADSCs inhibit matrix metalloproteinases (MMPs), promote collagen synthesis, and facilitate DNA repair, thereby ameliorating photoaging through multiple pathways. Advantages of this approach include minimally invasive harvesting (e.g., adipose tissue), high proliferative capacity, and low immunogenicity. Furthermore, ADSC-derived exosomes (ADSC-Exos) serve as a cell-free therapy, circumventing transplantation-associated risks while enhancing efficacy through delivery approaches such as microneedling or laser-assisted delivery [4].

6. Conclusion

In summary, mesenchymal stem cells (MSCs) exhibit substantial translational potential in combating skin aging and promoting skin regeneration. Capitalizing on their multilineage differentiation capacity, potent paracrine effects, immunomodulatory functions, and antioxidant properties, they mediate multifaceted therapeutic effects through integrated mechanisms. These include promoting collagen synthesis, inhibiting matrix metalloproteinases, improving local microcirculation, and regulating inflammatory responses. Clinical studies confirm that MSCs achieve highly efficient and high-quality tissue repair and regeneration with notable efficacy and favorable safety profiles, whether used to treat recalcitrant diabetic foot ulcers or improve photoaging skin damage. However, future research must focus on standardizing cell isolation sources, preparation workflows, and delivery regimens while thoroughly evaluating long-term safety. Concurrently, developing cell-free therapies like exosome-based approaches and enhancing MSC functionality through gene editing technologies will be pivotal directions for propelling this field toward clinical implementation.

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