

Adipose-Derived Mesenchymal Stem Cells in Facial Rejuvenation: Mechanisms, Applications, and Challenges

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Abstract. Facial aging, caused by extrinsic and intrinsic factors, have led to increasing demand for facial rejuvenation therapies. Recently, adipose-derived mesenchymal stem cells (ADMSC) have shown great regenerative potentials through paracrine signaling, extracellular matrix remodeling, and anti-inflammatory effects. Thus, this review will focus on explaining the basic mechanism of ADMSC and showcasing their clinical application in facial rejuvenation, such as nanofat techniques, cell-free therapies and injectable stem cell suspensions. Data for this review were collected from various clinical studies and systemic reviews from biomedical journals. The results of various studies show that ADMSCs can effectively provide anti-aging therapies by enhancing collagen production, suppressing oxidative stress and improving skin pigmentation. However, the lack of long-term follow up and limited sample size in current studies highlights the need for more large-scale trials and standardized protocols to ensure safety and efficacy. This review aims to provide a basic understanding of the potential role of ADMSCs in regenerative medicine and to offer guidance for future clinical innovations.

Keywords: Facial rejuvenation, stem cell therapy, adipose-derived mesenchymal stem cell, regenerative medicine, skin aging

1. Introduction

Skin aging is a complex process caused by the combined effects of various factors, including both extrinsic and intrinsic factors. Intrinsic aging can be contributed to the natural decline of cellular and molecular functions, whereas extrinsic aging results from cumulative exposures to exogenous factors such as ultraviolet (UV) radiation and air pollution. Reactive oxygen species (ROS) are major factors that leads to DNA damage, structural degradation of extracellular matrix (ECM) and cellular senescence by inducing oxidative stress (Figure 1) [1]. The dermis, which mainly consists of collagen and elastin, is particularly affected by aging. While intrinsic aging can lead to thinning of the skin, fine wrinkles, and reduced dermal elasticity, extrinsic aging is primarily characterized by deeper wrinkles, significant loss of elasticity, and dyspigmentation [2].

In recent years, the demand for non-invasive anti-aging treatments has surged. Among the various treatment methods, stem cell therapies have gained increasing attention as one of the most promising methods. According to an analysis by Data Bridge Market Research, the global facial rejuvenation market was estimated at around USD 24.62 billion in 2022 and is expected to reach approximately

USD 44.55 billion by 2030 [3]. Mesenchymal stem cells (MSCs) are a type of stem cell that offer significant advantages due to their multipotency, paracrine signaling, and immunomodulatory properties. Among MSCs, adipose-derived mesenchymal stem cells (ADMSCs) stand out due to their strong differentiation potential, powerful paracrine effects, and accessibility [3]. ADMSCs can promote angiogenesis in the dermis, secreting extracellular proteins such as collagen and elastin to stimulate the regeneration of dermal tissue, and suppress inflammation, all of which are desirable in facial anti-aging interventions [4].

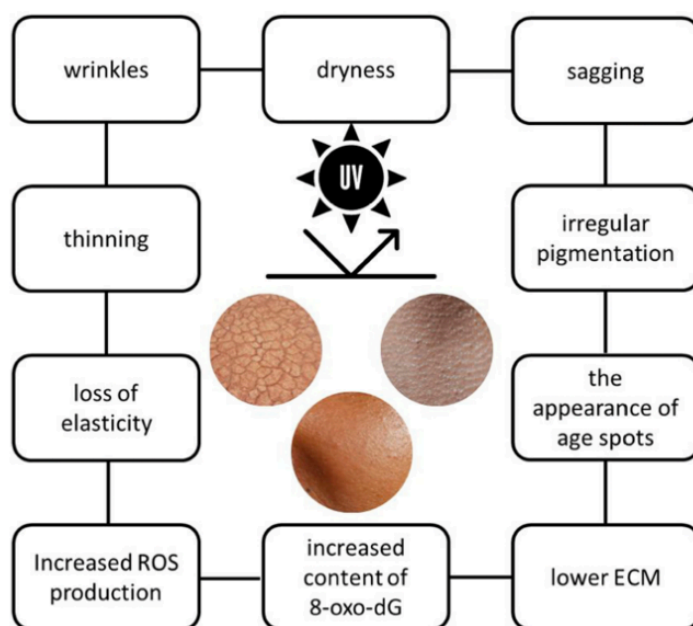


Figure 1. Characteristics of skin aging [4]

By examining the existing literature, this review aims to synthesize current findings on the biological mechanisms, applications, and future challenges of ADMSCs in facial rejuvenation. Additionally, this review intends to identify the therapeutic potential and limitations of ADMSCs and provide a foundation for future research and clinical innovation in regenerative aesthetics.

2. Mechanisms of ADMSCs in skin rejuvenation

2.1. Paracrine signaling

Paracrine signaling plays a major role in the rejuvenating mechanisms of ADMSCs. ADMSCs secrete a variety of bioactive molecules, including PDGF, VEGF, TGF- β , TIMP, and IGF-1 (shown in Table 1) [5]. For instance, VEGF can promote angiogenesis, enhance local microcirculation, and improve nutrient delivery in aged skin. Kere et al. demonstrated that VEGF-A significantly promoted skin regenerative effect of aged human skin under organ culture conditions, supporting the role of angiogenesis in reversing intrinsic aging [6]. On the other hand, TGF- β is instrumental in regulating ECM remodeling and dampening inflammatory responses [5]. IGF-1, which is mainly released by dermal fibroblasts, is crucial for supporting mesenchymal stem cell niches and regulating epidermal cell proliferation and differentiation [7]. In addition, IGF-1 signaling is essential for supporting epidermal repair by promoting keratinocyte proliferation and migration in response to UV-induced DNA damage, either by reducing cellular senescence or enhancing DNA

damage repair [8]. Through the synergistic action of these growth factors, the paracrine effects of ADMSCs lead to enhanced dermal regeneration, increased collagen and elastin synthesis, improved skin elasticity and hydration, and reduced signs of aging such as wrinkles and fine lines.

Table 1. Key growth factors [9]

Growth Factor	Cell source	Function
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, keratinocytes, fibroblasts	Involved in inflammation and granulation tissue formation; promotes reepithelialization and matrix formation; chemotactic for PNM, macrophages, fibroblasts, and smooth muscle cells; mitogenic for fibroblasts and endothelial cells; enhance the production for MMPs, fibronectin, and HA (hyaluronic acid); stimulates angiogenesis and wound closure.
Vascular endothelial growth factor (VEGF)	Keratinocytes, platelets, PMNs, macrophages, endothelial cells, smooth muscle cells, fibroblasts	Granulation tissue formation; increases vasopermeability, mitogenic for endothelial cells
Transforming growth factor β (TGF- β)	Platelets, T-lymphocytes, macrophages, endothelial cells, keratinocytes, fibroblasts.	Regulates inflammation and tissue regeneration; supports reepithelialization and matrix remodeling; act as. A chemoattractant for PNM, macrophages, lymphocytes, and fibroblasts; stimulates TIMP synthesis, keratinocyte migration, angiogenesis and fibroplasia; inhibit the production of MMPs and keratinocyte proliferation; triggers further TGF- β production.
Tissue inhibitor of metalloproteinases (TIMP)	Fibroblasts, activated hepatic stellate cells, and Kupffer cells	Regulate enzyme activities, preventing break down of collagen and hyaluronic acid.
Insulin-like growth factor (TGF-1)	Macrophages, fibroblasts	Stimulates elastin production and collagen synthesis, fibroblasts proliferation

2.2. Extracellular Matrix (ECM) remodeling

ADMSCs can also promote facial rejuvenation through remodeling the extracellular matrix (ECM). The ECM provides structural support for the dermis, consisting of collagen, elastin, and glycoproteins. Collagen is essential for maintaining skin integrity and tensile strength [10]. Fibroblasts in the dermis synthesize ECM components, including types I and III collagen, and are involved in granulation tissue formation [11]. As one ages, procollagen synthesis in the dermis decreases, while the degradation of ECM increases due to elevated matrix metalloproteinase (MMP) activity, leading to dermal thinning and wrinkle formation [12]. ADMSCs can counteract this process by stimulating fibroblast activity, thereby enhancing the production of type I and III collagen. Kim et al. demonstrated that ADSC injection into photo-damaged aged skin can effectively reduce wrinkles through promoting dermal thickening and increasing collagen density [13]. Additionally, ADMSCs can downregulate the expression of MMPs by regulating the expression of TIMPs, which suppress MMP activity and slow collagen breakdown [14]. Furthermore, ECM remodeling facilitated by ADMSCs creates a supportive microenvironment for cellular proliferation

and nutrient diffusion, one that is essential for sustained tissue regeneration. By restoring ECM integrity, ADMSCs not only reverse existing structural damage but also provide a protective scaffold that mitigates further age-related deterioration.

2.3. Anti-oxidative and anti-inflammatory effects

ROS cause inflammation, damaged cell membrane integrity, as well as molecular damage in DNA, RNA, and ECM proteins. ADMSCs can secrete antioxidants and cytokines that can counteract the effects of ROS. For example, Interleukin-6 (IL-6) mitigates oxidative stress by activating signaling pathways such as signal transducer and activator of transcription 3 (STAT3), nuclear factor erythroid 2-related factor 2 (Nrf2), and promoting the expression of superoxide dismutase (SOD) [15]. SOD is the major antioxidant enzyme that defends against oxidative stress by catalyzing the conversion of superoxide radicals (O_2^-) into oxygen and hydrogen peroxide. Khanh et al. show that the co-overexpression of SOD1 and SOD3 in aged ADMSCs significantly suppressed the ROS level and β -gal-positive cell density, which is indicative of cellular senescence, thereby enhancing the cellular functions [16]. Additionally, ADMSCs reduce levels of pro-inflammatory cytokines. For example, Interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α) are downregulated by ADMSCs. These two factors contribute to the chronic low-grade inflammation associated with skin degeneration and photoaging. According to Xia et al., treatment with ADMSC-Exos has been shown to elevate mitochondrial DNA copy number and ATP production, while simultaneously lowering the proportion of impaired mitochondria and reducing ROS levels [17]. Thus, ADMSCs can also protect skin cells from UV-induced mitochondrial damage by enhancing mitochondrial membrane stability and reducing apoptosis.

2.4. Modulation of melanogenesis and skin tone

Photoaging is manifested by hyperpigmentation, which occurs when accumulation of UV radiation stimulates melanogenesis (increased melanin concentration in the skin). Hyperpigmentation may lead to age spots, freckles, or melasma. The cytokines released by ADMSCs, such as interleukin and TGF- β 1 can inhibit pigmentation by suppressing tyrosinase, an enzyme necessary for melanin synthesis [15]. At the same time, antioxidants inhibit melanin formation and melanosome transfer, thereby exerting a whitening effect. The suppression of melanogenesis was verified by Fontana-Masson and HMB-45 staining in an in vivo study, where C57BL/6 mice were injected intradermally with ADSCs and followed by UVB exposure at 150 mJ/cm² [18].

3. Clinical applications

3.1. Nanofat techniques

One of the most established clinical applications of ADMSCs in facial rejuvenation is through nanofat techniques. In 2013, Tonnard et al. introduced nanofat, involving mechanical emulsification and filtration of harvested fat tissue into a liquid form with high stem cell content but minimal adipocytes [19]. A similar quantity of stromal vascular fraction (SVF) cells is observed in nanofat after intensive mechanical processing, while ADMSCs maintain their ability to proliferate and differentiate effectively. Nanofat, which is rich in ADMSCs containing numerous growth factors, cytokines, and biological peptides, has the potential to trigger soft tissue remodeling and result in satisfactory rejuvenative effects on aging skin. Nanofat grafting has demonstrated satisfactory clinical outcomes in reconstructive surgery. After nanofat grafting, fine facial wrinkles improved

significantly across all measured parameters (volume, depth, area, and percent area) [20]. In addition, nanofat grafting has advantages beyond facial rejuvenation, including wound healing and hair growth [21].

3.2. Injectable stem cell suspensions

Injectable stem cell suspensions involve intracutaneous or subdermal injection of a high concentration of ADMSCs suspension directly into targeted areas. By delivering viable ADMSCs to the dermis, this method takes advantage of the stem cells' regenerative properties, particularly their ability to stimulate collagen production, promote wound healing, and enhance skin elasticity. Mojallal et al. proved that autologous fat grafting not only restores volume but also significantly improves skin quality at the recipient site, such as increased dermal thickness and enhanced skin texture due to neo-collagen synthesis [22]. The injectable fat grafts enriched with ADMSCs effectively promote the formation of new collagen fibers and improve skin elasticity, contributing to a more youthful appearance. Zhao et al. show that subdermal administration of SVF-gel in regions affected by inflammatory acne alleviates lesions and contribute to overall acne improvement [23]. Furthermore, ADMSC injections offer the advantages of minimal invasiveness and reduced immunogenicity risk compared to traditional methods, making them an appealing option for patients seeking non-surgical facial rejuvenation [24].

3.3. Cell-free approaches

In addition to live-cell therapies, cell-free approaches using ADMSC-derived conditioned medium (CM) and exosomes have garnered growing interest for facial rejuvenation. CM, collected from ADMSC cultures, contains biologically active molecules like VEGF, TGF- β , IGF-1, and fibronectin, which stimulate fibroblast proliferation, collagen synthesis, and angiogenesis. Li et al. used data from their study to show that ADSC-CM demonstrated the ability to suppress UVB-induced wrinkle formation by inhibiting UVB-irradiated MMP-1 secretion and promoting procollagen type I synthesis [25]. Kim et al. reported that treating human dermal fibroblasts with ADSC-CM can counteract the UVB-irritated reduction of dermal fibroblast proliferation in a dose-dependent manner. Furthermore, cell-cycle analysis revealed that ADSC-CM decreased UVB-induced apoptosis [13]. When ADMSCs are used in vivo, there is a potential risk that malignant cell may be adjacent to the transplanted ADMSCs [26]. As a result, compared to stem cell injections, CM and exosome-based treatments offer benefits such as lower immunogenicity, reduced tumorigenic risk, and greater regulatory compliance, thus increasing their clinical appeal.

3.4. Combination therapies

The combined therapy involving ADMSCs and other regenerative techniques demonstrates a stronger efficacy in facial rejuvenation compared to a single therapy. Platelet-rich plasma (PRP) promotes tissue healing, remodeling, decreasing inflammation, and altering the local tissue environment [27]. Seyhan et al., conducted an experimental study on scalp autologous fat transplantation to investigate autologous PRP, ADMSCs, and their combinations. The study found that PRP combined with ADSCs better maintained the weight and volume of the transplanted tissue compared to PRP alone or ADMSCs alone. Tissue analysis also showed that this combination led to higher percentage of blood vessels and viable adipocytes, while inhibiting cyst and fibrosis formation [28].

Moreover, microneedling therapy (a collagen-induction therapy that has been used in dermal and transdermal drug delivery for decades) is a method that uses microneedles to create pinhole wounds on the skin, aiming to improve scars and wrinkles by stimulating wound healing [29]. In addition, microneedling can enhance the skin penetration of hESC-EPC CM, priming the skin to respond more effectively to regenerative cues [29]. Therefore, the integration of ADMSCs with established dermatologic procedures represents a powerful strategy to enhance anti-aging results in a safe and minimally invasive manner.

4. Challenges and future directions

4.1. Challenges

One major challenge for ADMSCs therapies is biological heterogeneity. Stem cell potency and regenerative efficacy can vary from donor to donor, depending on genetic information, health condition, age, and so on [24]. Elderly individuals, a population most interested in facial rejuvenation, may have reduced stem cell potency and diminished paracrine activity [30]. Consequently, this inconsistency in cell stemness makes it difficult for studies to compare results and validate the value of their methods. Although numerous studies have been done on ADMSCs therapies, long-term data remain limited. There are concerns regarding fibrosis and uncontrolled proliferation, especially when stem cells are administered in high concentrations or combined with growth factors. For example, injection of ADMSCs around the ocular region have been associated with the formation of ectopic bone in eyelid tissue [31]. In addition, MSCs can induce innate and humoral immune response, which hamper clinical efficacy. Furthermore, the unpredicted pathogenesis of localized skin diseases should be carefully considered before these procedures [24]. The systematic review by Toyserkani et al. shows that thromboembolic complications were rare in patients undergoing ADMSC-based cell therapies; however, between 19% and 34% of patients were found to develop specific antibodies against donor cells, indicating that there is indeed an immune response to allogeneic ADMSC treatments [32]. Moreover, while some countries like the United States have classified stem cell therapies as investigational drugs requiring FDA approval, many clinics are still underregulated. In addition, patients often lack oversight from regulatory bodies. That is why many insufficiently tested procedures may be offered commercially without clinical validation, which will lead to safety problems [33]. Finally, recent ADMSC therapies lack standardized protocols for isolation, characterization, and quantification to ensure consistency in quality and efficacy [34]. Existing therapies lack consensus on dosage, indicating limited reproducibility.

4.2. Future directions

Despite the promising potential of ADMSCs therapies in facial rejuvenation, numerous questions remain unanswered. Thus, it is important to conduct large-scale randomized clinical trials with long-term monitoring to achieve robust clinical approval and eliminate long-term side effects. In addition, protocols standardization for ADMSCs therapies is essential for commercialization. One promising direction is the development of personalized stem cell therapies tailored to individual molecular profiles. By incorporating genomic, proteomic, and metabolomic data, clinicians may be able to predict which patients will respond best to ADMSCs treatments and optimize treatment protocols accordingly.

5. Conclusion

ADMSC therapies have emerged as a compelling frontier in facial rejuvenation, offering regenerative capabilities through paracrine signaling, ECM remodeling, antioxidative effects, and melanogenesis modulation. For clinical applications, ADMSCs have shown promising prospects in biotechnologies such as nanofat grafting, injectable therapies, and cell-free approaches. In addition, integrating ADMSCs with other regenerative techniques (e.g., PRP or microneedling) further enhances treatment efficacy and anti-aging outcomes. However, while there are some advantages, development of ADMSC therapies still faces many challenges, including biological heterogeneity, long-term safety concerns, regulatory uncertainty, and lack of standardized protocols for ADMSC isolation and application. Looking toward the future, personalized regenerative therapies tailored to an individual's biological profile may become the norm, but before that, robust and randomized clinical trials with long-term follow-ups and consistent protocols are needed.

Finally, this review has several limitations. While providing a brief overview of the mechanisms and clinical applications of ADMSCs in facial rejuvenation, it lacks in-depth explanation and comparison of clinical trials. In addition, the review is based on a limited selection of literature, constrained to studies conducted in certain geographical areas. Future work will involve market research and patient surveys to obtain more supporting data and refine evaluation accuracy. Moreover, as further studies in biomedicine or related fields are planned, laboratory experiments will be designed and conducted to more directly explore the therapeutic potential of ADMSCs.

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