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Stem Cell Secretome Therapy in Skin Photoaging: Mechanisms, Applications, and Future Directions

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Abstract. Skin photoaging, primarily driven by long-term ultraviolet (UV) exposure with features like oxidative stress, extracellular matrix degradation, and gradual loss of dermal structural integrity. These processes not only affect appearance but also demonstrate cellular aging and impaired tissue repair. Traditional anti-aging therapies, including topical retinoids and laser-based interventions, provide limited and short-term improvements, highlighting the demand for more effective and safer approaches. In the past few years, stem cell-derived secretome has proved to contain a complex mixture of growth and repair factors and extracellular vesicles like exosomes. It has emerged as an approved cell-free therapy to assist skin rejuvenation. This review discusses current evidence on the role of stem cell secretome in slowing photoaging, with a focus on its molecular mechanisms and clinical applications. Preclinical studies demonstrate that secretome components can prevent UV-induced damage by removing reactive oxygen species (ROS), controlling inflammatory processes, and blocking matrix metalloproteinase activity to protect the structure of collagen and elastin in the skin. Furthermore, secretome therapy induces dermal fibroblast production and reinforces extracellular matrix remodeling through pathways like NRF2 and TGF-β. Clinical studies report improvements in skin elasticity, hydration storage, and wrinkle reduction, particularly when combined with delivery techniques such as microneedling. This review finds that stem cell secretome therapy has great potential to overcome limitations of traditional treatments and brings safer, more effective, and more regenerative approaches for both aesthetic industry and clinical skin repair.

Keywords: Stem cell, Secretome, Anti-oxidation, Photoaging, Skin therapy

1. Introduction

Skin photoaging involves complex biological processes, primarily driven by chronic exposure to UV radiation, causing structural and functional damage to the skin. Clinically, skin photoaging is characterized by wrinkles, pigmentation, and loss of elasticity. At the molecular level, UV radiation induces the generation of ROS, which break cellular homeostasis and degrade extracellular matrix components such as collagen and elastin by oxidative damage [1, 2]. This process also amplifies the upregulation of matrix metalloproteinases (MMPs) causing loss of collagen fibers and dermal integrity, ultimately leading to visible signs of aging on skin.

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Current therapies for photoaging include topical agents like retinoids and antioxidants, incorporated with physical interventions like laser resurfacing and dermal fillers. These approaches can only provide temporary improvement in skin condition, but they often fail to solve the aging problem at a level of biological mechanisms and are associated with negative effects or limited long-term efficacy [2]. Therefore, researchers have shown growing interests in more regenerative and biologically driven therapies that can more effectively repair and restore skin structure and function.

This review analyzes current research on the role of stem cell secretome in skin photoaging, with a focus on its molecular mechanisms. The reliability of stem cell secretome therapy is validated by comparing preclinical and clinical evidence. This research contributes to the broader field of regenerative medicine by demonstrating how biological molecules and extracellular vesicles can promote tissue repair without the risks associated with direct living stem cell transplantation.

2. Stem cell secretome: Composition and mechanisms

Stem cell secretome cover diverse bioactive molecules released by stem cells into their extracellular environment. Instead of functioning independently through differentiation and tissue replacement, stem cells carry out most of their therapeutic function through paracrine signaling mediated by secretome. In the context of skin photoaging, the secretome has been discovered as a cell-free therapy that is capable of modulating multiple biological pathways involved in aging and tissue repair [3, 4].

2.1. Composition of the secretome

The stem cell secretome is a complex and dynamic mixture of soluble factors and extracellular vesicles. Its composition varies depending on the cell source and culture conditions, but it generally includes cytokines, growth factors, chemokines, lipids, nucleic acids, and extracellular vesicles like exosomes.

Secretome's key components include growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), and epidermal growth factor (EGF). They play critical roles in tissue regeneration, repairment, and cellular proliferation. Components like cytokines and chemokines within the secretome are the primary regulators of immune responses and inflammation, helping to maintain tissue homeostasis. The extracellular vesicles, particularly exosomes, serve as mediators of intercellular communication by transporting proteins, lipids, and microRNAs (miRNAs) to target cells [4]. These miRNAs can mediate gene expression in recipient cells and command processes like collagen synthesis, oxidative stress response, and cellular senescence [5].

2.2. Mechanism of anti-photoaging

Stem cell secretome's mechanism in slowing skin photoaging is mediated through several connected mechanisms that address the underlying causes of aging at the molecular level.

One of the primary mechanisms is the reduction of oxidative stress. Secretome components activate antioxidant defense systems, particularly through the NRF2 pathway. Activation of NRF2 leads to the upregulation of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, which neutralize ROS and protect cells from UV-induced damage [6].

In addition to its antioxidant effects, the secretome also performs strong anti-inflammatory activity. It downregulates pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor

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necrosis factor-alpha (TNF-α), while promoting the release of anti-inflammatory mediators. This shift in the inflammatory environment helps prevent tissue damage and supports skin repair [4].

Another critical mechanism involves the regulation of extracellular matrix remodeling. The secretome inhibits the expression of MMPs while stimulating collagen synthesis through pathways like transforming growth factor-beta (TGF-β) signaling. This double action enhances the production of collagen and elastic fibroblasts to restore skin elasticity and provide better structural support.

Additionally, the secretome promotes cellular proliferation and migration, particularly in dermal fibroblasts and keratinocytes. Growth factors within the secretome stimulate target cells to produce new ECM components and contribute to tissue regeneration. Enhanced angiogenesis, mediated by factors such as VEGF, also improves nutrient and oxygen delivery to the tissue, further supporting repair processes.

3. Evidence from preclinical studies

Preclinical studies provide insight into the potential of stem cell-derived secretome against skin photoaging. By using cell culture systems and transplantation into vivo animal models, these studies consistently demonstrated that secretome-based therapies can encounter key pathological mechanisms of photoaging, including oxidative stress, inflammation, and ECM degradation.

3.1. UV-induced photoaging models

Ultraviolet radiation is broadly divided into UVA (320–400 nm) and UVB (280–320 nm). They both contribute to skin photoaging through unique but overlapping mechanisms. UVB primarily damages the epidermis layer and is responsible for direct DNA damage by forming cyclobutane pyrimidine dimers, which lead to gene mutations and impaired cellular function. In contrast, UVA penetrates deeper to the dermis layer and indirectly damages cellular components by generating ROS [1]. ROS include superoxide anions, hydrogen peroxide, and hydroxyl radicals, which disrupt normal cellular function and enable signaling cascades associated with aging.

A large portion of preclinical research utilizes UV-induced photoaging models to replicate the molecular and structural damages in aged human skin. In these models, dermal fibroblasts or animal skin are exposed to UVA or UVB radiation to increased production of ROS and upregulation of MMPs, peering up with decreased collagen synthesis. Many studies have shown that specific treatment with mesenchymal stem cell (MSC)-derived secretome or exosomes significantly reduces these photoaging effects. For instance, the exosomes derived from adipose-derived stem cells (ADSCs) have been proved to reduce UVB-induced cellular damage by suppressing ROS generation and restoring antioxidant enzyme activity [1, 5].

3.2. Reduction of oxidative stress and inflammation

Oxidative stress plays a critical role in the pathology of skin photoaging. Under normal conditions, cells maintain a balance between ROS production and antioxidant release. When excessive UV overwhelms this system, ROS starts to accumulate damaging lipids, proteins, and DNA. Oxidative stresses activate the key transcription factors such as activator protein-1 (AP-1) and nuclear factor kappa B (NF-κB); associated pathways regulate genes that cause inflammation and matrix degradation [3]. Moreover, oxidative stresses also impair mitochondrial function and accelerate cellular senescence, further contributing to skin aging.

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One of the most observed benefits of stem cell secretome and derived exosomes in preclinical studies is its ability to reduce oxidative stress. The exosomes are components of secretome and proved to contain molecules such as microRNAs and antioxidant agents that activate protective and regenerative signaling pathways; the nuclear factor erythroid 2–related factor 2 (NRF2) pathway has been identified as a key mediator of this regulation. The activation of NRF2 enhances the expression of antioxidant agents to neutralize ROS and protect cells from oxidative damage [5]. In addition to its antioxidant features, the secretome also releases anti-inflammatory effects by downregulating pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are previously elevated by UV exposure [3].

3.3. Inhibition of matrix metalloproteinases and ECM preservation

One of the most significant consequences of oxidative stress is the degradation of the extracellular matrix (ECM) and loss of structural support for the skin. Collagen, particularly type I collagen, is the primary structural protein in the dermal layer and critical for maintaining skin strength and elasticity. UV exposure and following oxidative processes upregulate matrix metalloproteinases (MMPs) like MMP-1, MMP-3, and MMP-9, which degrade collagen and other ECM components [2]. At the same time, UV inhibits the synthesis of new collagen by shutting down the transforming growth factor-beta (TGF-β) pathway, creating a new imbalance between collagen production and degradation. This imbalance causes thinning of the dermal layer and formation of wrinkles on skin.

Preclinical evidence also highlights the role of stem cell secretome in preserving the integrity of the ECM. UV induces the expression of MMPs to degrade collagen and elastin fibers in the dermal layers. The corresponding treatments like MSC-derived secretome have been proved to significantly reduce the expression of MMP-1 and MMP-9 while promoting the regeneration of type I collagen at the same time [2]. This type of dual effect helps to restore the balance between ECM components' degradation and production. It's also critical to reform skin structure and restore its function. Additionally, the fibroblasts after being treated with secretome showed an increased proliferation rate with more migratory capacity to further supporting tissue repair and regeneration even more effectively.

3.4. Dermal remodeling and cellular regeneration

Chronic UV exposure also induces inflammation, by releasing pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These inflammatory cytokines not only amplify tissue and cellular damage but also promote the development of cellular senescence, which is a stage where cells lose their ability to proliferate but are still metabolically active. Senescent cells will secrete even more inflammatory mediators and proteolytic enzymes, and lead to a phenomenon called the senescence-associated secretory phenotype (SASP), which further accelerates ECM degradation and tissue disfunction to make cellular metabolism enter an infinite, negative loop [3].

Except for protective effects, stem cell secretome also actively promotes dermal remodeling and regeneration. Vitro studies demonstrate that secretome enhances fibroblast activity, which will increase the deposition of collagen and other ECM components to restore structural density. In animal models, topical and injected secretome therapies have been shown to improve skin thickness, elasticity, and overall aesthetical appearance. These regenerative effects are primarily driven by the presence of growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β); they both promote angiogenesis and collagen [3, 4].

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4. Clinical and dermatological applications

The transition of stem cell secretome from experimental research to clinical practice has gained interest in dermatology, especially for the treatment of skin photoaging. Early clinical studies suggest that secretome-based therapies can improve skin condition from various aspects, including wrinkles, elasticity, hydration, and texture. These applications are largely related to the secretome's ability to induce dermal layer regeneration and modulate key pathways involved in aging [2, 3].

4.1. Clinical evidence in skin rejuvenation

Several clinical studies have tested the efficiency of stem cell secretome, specifically those derived from adipose-derived stem cells (ADSCs) and mesenchymal stem cells (MSCs), in skin rejuvenation. In tested human trials, a topical or injectable form of secretome cooperates with various delivery strategies to improve skin condition. The human trial results shown reduced fine lines and wrinkles, increased dermal layer thickness with enhanced elasticity. For instance, secretome-based treatments applied in human trials in combination with microneedling delivery have demonstrated significant improvements in dermal structure by improving the penetration and bioavailability of active factors within the ADSCs. [2, 6, 7]. Patients who received these treatments often show increased collagen density and improved skin texture, revealing effective dermal layer remodeling.

4.2. Delivery methods and treatment modalities

Topical application involves creams or serums that contain secretome are applied directly to the skin. Although they are non-invasive and convenient, this method may be limited by the skin's barrier function and penetration of large biomolecules is restricted.

Microneedling delivery uses microneedle devices that create microchannels in the skin, allowing deeper and easier penetration of secretome components. This method became popular due to its synergistic effects because small wounds after treatment provide extra physical stimulation of collagen production, combining with biochemical regeneration.

Injection delivery involves direct intradermal injection of secretome or exosomes into skin tissue. The method provides very precise delivery which may yield more pronounced and rapid results, but is also more invasive and requires longer clinical recovery.

Combination therapies refer to combining secretome therapy with dermatological treatments like laser resurfacing or radiofrequency to enhance outcomes. These combination approaches are considered and involve both physical and biological mechanisms of skin rejuvenation.

4.3. Comparison with traditional treatments

Preclinical studies consistently demonstrate its ability to reduce UV-induced damage, enhance fibroblast activity, and speed up collagen synthesis, while early clinical evidence shows relative improvements in skin texture, elasticity, and wrinkle reduction [8, 9].

Compared to traditional, physical anti-skin aging treatments, stem cell secretome therapies offer several unique advantages. The conventional therapies researched have been used before like retinoids and laser treatments, and only target basic-level symptoms or induce a sort of controlled, small-scale damage to stimulate skin regeneration. In contrast, secretome therapy works at a molecular and more biological level, solving the skin aging problem from the source of photoaging

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such as oxidative stress, inflammation, and ECM degradation. These results are also proved to be more structural and potentially longer-lasting improvements in skin health [3].

Additionally, secretome treatments are well-tolerated, with fewer reported side effects compared to more invasive traditional procedures. The cell-free pattern of the therapy also reduced the risk of tumor formation to the lowest, even zero. It also has benefits like higher transplanation rate and shorter recovery period compared to traditional MSCs treatment which involves living cells, more invasive procedure, and lower quality control [6, 7, 10].

5. Conclusion

Skin photoaging is a complex process driven primarily by chronic UV exposure, causing oxidative stress, inflammation, and degradation of the ECM. These biological mechanisms result in the structural and functional dysfuntion of the skin tissues, leading to wrinkles, loss of skin elasticity, and visible pigmentation. While traditional treatments like retinoids, antioxidants, and physical procedures can temporarily reduce visible signs of aging, they often fail to solve the underlying biological processes behind aging.

Stem cell secretome has emerged as a cell-free therapy that targets multiple pathways involved in skin photoaging. By releasing its components like growth factors, cytokines, and vesicles, particularly exosomes, the secretome reduces oxidative stress, suppresses inflammatory signaling, and promotes ECM remodeling.

Despite these significant findings, there are still limitations and challenges that remain, including variability and quality control in secretome and vesicle composition, lack of standardized manufacturing and dosing plans, and limited amount of long-term clinical data and results. Considering and improving these limitations will be important for translating secretome-based therapies into more reliable, safer, and widely accepted treatments.

Overall, stem cell secretome therapy represents a thriving field in regenerative medicine with huge potential for the treatment of skin photoaging. Continuing research, particularly large-scale clinical trials and studies, will be critical in establishing its safety, efficiency, and specific clinical applications in an age of medicine 3.0.

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