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Exosomes as Emerging Therapeutics in Aesthetic and Regenerative Medicine: A Scoping Review

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Abstract

Exosomes are small extracellular vesicles secreted by various cell types that have caught significant attention in recent years for their potential roles in intercellular communication and as carriers of biomolecules such as proteins, lipids and RNA. These properties make exosomes promising candidates in the field of anti-aging research. This article explores the multifaceted roles of exosomes in aging processes and their potential applications in cosmetology for anti-aging effects. Exosomes are involved in modulating inflammation, promoting tissue regeneration and facilitating the removal of cellular waste, all of which are critical factors in aging and longevity. Furthermore, their ability to transfer bioactive molecules between cells makes them an effective tool for rejuvenating aging tissues and reversing cellular dysfunction. In this chapter, we discuss recent advancements in exosome-based therapies, including their use in stem cell-based regenerative medicine, anti-inflammatory treatments and the modulation of senescence-associated pathways.

Keywords: Exosomes; Skin Aging; Anti-Aging; Inflammation; Tissue Regeneration; Regenerative Medicine

Introduction

Aging and Cutaneous Aging

Aging is the progressive decline of physiological functions essential for survival and reproduction, leading to natural death [1]. It occurs at different rates across individuals, distinguishing chronological age from biological age, which reflects functional status influenced by environmental factors and genetic factors. These include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication [2-4]. Despite ongoing debate, defining normal aging remains complex [5]. Aging manifests as sensory decline, muscle weakness, bone loss, cognitive impairment and metabolic inefficiency [6].

Cutaneous aging occurs through intrinsic and extrinsic processes. Intrinsic aging is characterized by reduced proliferation of keratinocytes, fibroblasts and melanocytes due to cellular senescence, leading to extracellular matrix degradation (elastin, fibrillin and collagen) and decreased vascularity [7]. In contrast, extrinsic aging, mainly caused by UV radiation, disrupts epidermal keratinocyte differentiation and promotes the accumulation of abnormal elastic fibers in the dermis [8].

Facial Rejuvenation: Latest Trends

Facial rejuvenation consists of treatment techniques that facilitates restoring the skin from any damage that is caused particularly by aging or sun exposure, including the restoration of damaged skin and the enhancement or elimination of sagging tissues through surgical interventions [9]. Noninvasive procedures are widely used for skin resurfacing, tissue tightening, wrinkle reduction and volume restoration. Among these, Endodermal Radiofrequency (ER) has emerged as a promising technique. According to Rezapour, et al., ER has been shown to improve wrinkles, sagging and skin elasticity, reduce fat, tighten the face, neck and jawline, enhance pigmentation and body contouring and decrease epidermal thickness [10,11]. Additionally, minimally invasive techniques such as botulinum toxin, dermal fillers, thread lifts and platelet concentrates offer non-surgical alternatives for facial rejuvenation [12,13]. On the other hand, invasive procedures, including eyelid surgery, brow lifts, facelifts and facial implants, aim to reposition facial soft tissues for a more youthful and harmonious appearance [14]. More recently, emerging technologies such as genetic therapies, flap biology and stem cell-based treatments have attracted significant investment, with the longevity economy reaching $7.6 billion to extend healthspan and restore youth in the aging population. However, these innovations have yet to be widely adopted by plastic surgeons and dermatologists and their safety, efficacy and integration into existing skin rejuvenation workflows remain uncertain [15].

Hair Aging and Restoring

Hair undergoes noticeable changes throughout life, with the shine, volume and strength of youthful hair gradually diminishing over time. Aging often leads to thinner, duller and more brittle strands, driven by a combination of genetic and environmental factors that affect hair follicle stem cells and melanocytes. Key processes such as telomere shortening, a decline in cell numbers and shifts in transcription factors contribute to structural changes in hair fibers, reduced melanin production and an extended telogen phase in the hair growth cycle.

While these changes are a natural part of aging, several treatments including light therapy, minoxidil and finasteride have been developed to slow or counteract hair thinning and loss. Though they function through different mechanisms, their shared purpose is to preserve hair density, enhance vitality and restore a more youthful appearance [16].

Exosomes: A Step Toward Regenerative Medicine

Exosomes are nanosized extracellular vesicles (~30 to ~200 nm) secreted by cells, carrying a diverse cargo of proteins, lipids, nucleic acids and glycoconjugates. They originate through membrane budding at both the plasma and endosomal membranes and serve as key mediators of intercellular communication. Exosomes regulate various biological processes, including tissue homeostasis, immune responses and extracellular matrix remodeling, while also playing a role in disease progression, such as cancer and neurodegenerative disorders. Additionally, viruses exploit exosomal pathways for replication and immune evasion. Due to their ability to transfer bioactive molecules, exosomes are being actively investigated for their potential as therapeutic agents in regenerative medicine and targeted drug delivery [17].

MSC-derived exosomes play a crucial role in aging and tissue regeneration by transferring bioactive molecules that influence cellular processes. They facilitate intercellular communication, exhibit anti-fibrotic effects by modulating fibrogenesis pathways and provide cellular protection through antioxidant cargo [18-21]. Exosomes also enhance mitochondrial function, regulate cellular senescence and contribute to extracellular matrix remodeling and stem cell niche maintenance [22-27].

Exosomes Injection: A Brief Review

Collagen Activation and the Role of Exosomes in Skin Rejuvenation

Skin cells gradually lose their ability to produce collagen due to both intrinsic and extrinsic aging. Human Dermal Fibroblasts (HDFs), which constitute the majority of the dermal cell population, experience a decline in proliferation and collagen synthesis. This leads to the breakdown of connective tissues and the formation of wrinkles [28].

Exosomes are influenced by their parent cells and the surrounding microenvironment. Exosomes released by senescent cells can communicate with younger cells through miRNAs, thereby accelerating aging. However, exosomes derived from healthier parent cells and an optimized microenvironment have been shown to enhance cell proliferation, migration and collagen secretion.

Exosomes derived from HDFs in three-dimensional cultures are particularly rich in miRNAs, which mediate intercellular communication and promote proliferation, collagen synthesis and DNA repair [29]. In a study conducted by Hu, et al., exosomes were injected into the skin of nude mice that had undergone UVB-induced aging. The results demonstrated a significant reduction in wrinkle formation compared to the control group, with a marked increase in pro-collagen type I production [30]. Furthermore, a study by Oh, et al., showed that human-induced pluripotent stem cell-derived exosomes promoted genotypic and phenotypic changes in photoaged HDFs, restoring collagen type I expression in senescent fibroblasts [31]. Given their critical role in regulating collagen production through intercellular communication, exosomes represent a promising therapeutic approach for skin rejuvenation and anti-aging treatments.

The Role of Exosomes in Elastin Synthesis and Skin Rejuvenation

The dermis of the skin is primarily composed of collagen fibrils, elastin and an extrafibrillar matrix consisting of proteoglycans, glycosaminoglycans and various glycoproteins. Intrinsic aging is characterized by a gradual loss of skin elasticity, largely due to the decreased ability of dermal cells to produce elastin [32].

Studies have shown that exosomes derived from human Adipose-Derived Mesenchymal Stem Cells (hAD-MSCs), when loaded with circular RNA, can promote elastin synthesis in the skin. Furthermore, clinical observations in six to ten photoaged patients demonstrated an improvement in skin appearance following treatment with these exosomes [33].

Exosomes and Their Role in Melanin Regulation and Skin Photoprotection

One of the primary lines of defense in skin photoprotection is the production of melanin. In the epidermis, the skin's outermost layer, melanin is synthesized by cells called melanocytes. Within melanocytes, melanin is produced in specialized organelles known as melanosomes, which then release the pigment as needed [34]. This process plays a crucial role in regulating skin pigmentation and protecting the skin from harmful UV radiation.

However, excessive exposure to damaging agents, particularly UV radiation, can stimulate increased melanin production and accumulation, leading to pigmentation changes such as age spots, freckles and melasma. Melanogenesis is a complex process that not only occurs in melanocytes but also involves interactions with other skin cells, such as keratinocytes, forming what is known as the epidermal melanin unit. Tyrosinase (TYR), a key enzyme in melanogenesis, mediates the initial steps of melanin synthesis. Additionally, exosomes vesicles that transport proteins and other molecules play a crucial role in regulating pigmentation. These exosomes help modulate gene expression and enzyme activity in both healthy and diseased tissues, thereby influencing the overall pigmentation process.

Exosomes are formed in keratinocytes and serve as a medium for communication between melanocytes and keratinocytes. Research, such as that by Liu, et al., suggests that this communication is largely facilitated by exosomes. The content of these exosomes is influenced by the environmental conditions to which the keratinocytes have been exposed and this, in turn, helps regulate melanin production. For instance, exosomes overexpressing miR-330–5p have been shown to significantly reduce melanin production and Tyrosinase (TYR) expression in melanocytes [29].

Given their role in regulating pigmentation and facilitating pigment transfer from melanocytes to keratinocytes, exosomes are being increasingly explored as a potential therapeutic tool. They may offer new avenues for preventing abnormal pigmentation, as well as for aesthetic treatments targeting age spots and other signs of skin aging [29].

Exosome-based therapies offer a promising solution by enhancing collagen synthesis, modulating inflammatory responses and improving skin hydration. Engineered exosomes for skin rejuvenation are typically derived from MSCs or fibroblasts and are designed to deliver bioactive cargo that promotes dermal regeneration [35]. Fig. 1 the role of exosome injections in anti-aging for skin rejuvenation and hair restoration.

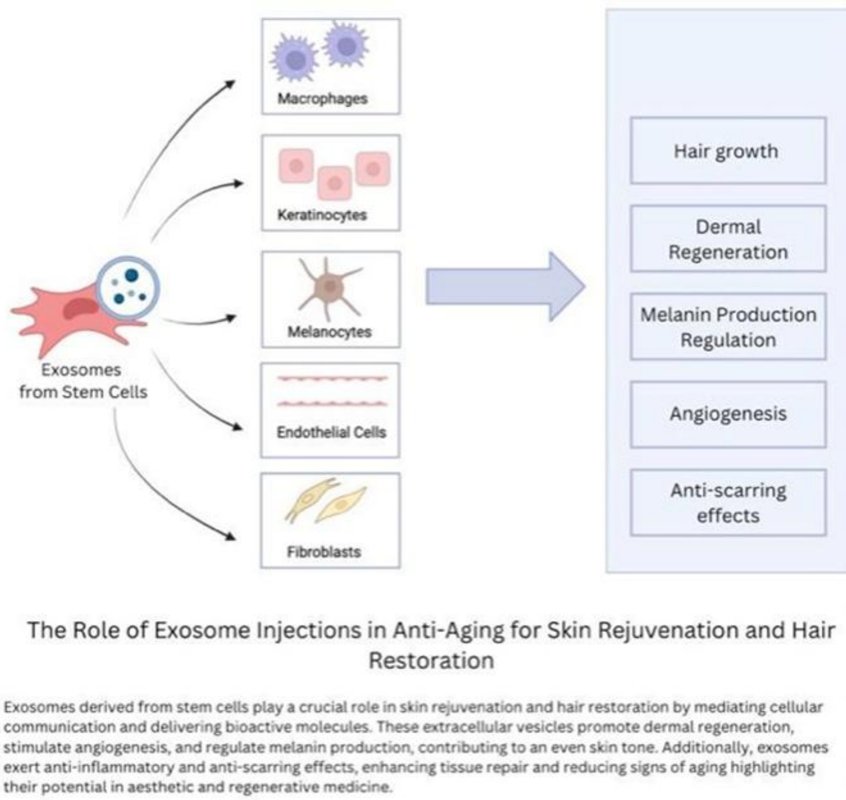

Figure 1: Exosomes derived from stem cells play a crucial role in skin rejuvenation and hair restoration by meditating cellular communication and delivering bioactive molecules. These extracellular vesicles promote dermal regeneration, stimulate angiogenesis and regulate melanin production, contributing to an even skin tone. Additionally, exosomes exert anti-inflammatory and anti-scaring effects, enhancing tissue repair and reducing signs of aging highlighting their potential in aesthetic and regenerative medicine.

Synthesize or Customized Exosome

Advances in Hair Restoration: Techniques and Emerging Therapies

Hair loss impacts millions of people globally and can significantly affect a person's psychological and emotional health. Advances in hair restoration technologies, including robotics and both manual and motorized follicular unit extraction, have led to outstanding clinical outcomes for patients. Additionally, supplementary treatments like platelet-rich plasma injections, laser therapy and stem cells can improve the survival rate and appearance of hair transplants [36].

There are two main types of hair restoration procedures. With follicular unit extraction, individual hair follicles are removed from the back of the scalp and then inserted into the recipient site. In the follicular unit transplant method, a strip of skin with hair follicles is removed from the back of the scalp. The hair follicles are then removed from the strip of skin and placed into the recipient site. Follicular unit extraction is the newer, more common method for hair restoration. Although the more traditional follicular unit transplant is still performed and has its own benefits, follicular unit extraction is typically seen as less invasive, resulting in quicker recovery and reduced scarring.

Modern hair transplantation is based on the use of naturally occurring hair groupings referred to as Follicular Units (FUs). These FUs may be acquired with the use of strip harvesting or the extraction of the FUs with a small punch, generally 0.8 mm to 1.2 mm in diameter [36].

The decision as to how the grafts should be obtained will vary with each individual patient and their needs at the time of surgery. Each technique has advantages and disadvantages. The process of hair restoration continues to be refined in an effort to create better cosmetic results, growth of hair and preservation of existing hair [36].

The advances that we are witnessing in hair restoration are occurring in several areas. These include technological advances in recovering grafts and placing grafts, bio-enhancements with storage media and intraoperative manipulation and adjunctive treatments [37].

First, non-surgical therapeutic modalities play a central role not only as an adjunct to surgical interventions, but also an important primary means of therapy in the early phases of hair loss. Medical treatment modalities that act through differing underlying mechanisms may have a summative or synergistic effect particularly in the early stages of hair loss, prior to significant loss of hair density. In cases of more severe hair loss, surgical intervention is likely to yield more esthetically pleasing outcomes [38].

Minoxidil plays a key role in promoting hair growth by stimulating hair follicles and improving blood circulation to the scalp. It is believed to work by widening blood vessels, which enhances the delivery of oxygen and nutrients to hair follicles, encouraging them to enter the growth phase: anagen. Minoxidil is commonly used to treat androgenic alopecia in both men and women. It helps to slow hair loss, promote hair regrowth and increase the thickness of existing hair. Although the exact mechanism of action is not fully understood, it is thought to involve the opening of potassium channels in the hair follicles, leading to follicle stimulation and hair regrowth [39].

In addition, 5-alpha reductase plays a key role in hair restoration, especially in the context of male and female pattern baldness (androgenetic alopecia). This enzyme is responsible for converting testosterone into dihydrotestosterone, a potent androgen that is primarily implicated in hair loss in genetically predisposed individuals [38].

Also, Low-Level Laser Therapy (LLLT) mediated combs for the treatment of hair loss has been approved by the FDA. Studies comparing these devices to placebo or sham devices have shown a statistically significant increase in hair count. Finally, Platelet-Rich Plasma (PRP) has gained significant popularity in recent years due to the discovery of Platelet-Derived Growth Factor (PDGF) and its role in promoting wound healing. PRP involves injecting concentrated autologous platelets into the patient's scalp, where, upon activation, they release growth factors such as PDGF, vascular endothelial growth factor, insulin-like growth factor and interleukin-1. Early studies suggest that PRP may help accelerate the healing process after hair transplantation. However, evidence supporting its direct stimulation of hair growth remains limited [38].

On the other hand, several surgical techniques are available to treat the balding scalp depending on different factors including patient age, degree of hair loss, donor site density and elasticity, hair texture and caliber. The most common procedure include Follicular Unit Transplantation (FUT) which involves the microscopic dissection of donor hair from the back and sides of the scalp using a long, narrow strip of tissue. This tissue is then carefully divided into individual follicular units under a stereomicroscope and implanted into the recipient area. The second technique is Follicular Unit extraction which is a graft harvest method involving the usage of different punches to extract individual follicular units from donor area. Benefits of this technique include avoiding the creation of a noticeable linear scar at the donor site and promoting a faster postoperative recovery. Additionally, FUE allows for the correction of "pluggy" or poorly positioned hairlines from previous hair restoration procedures [38]. Engineered exosomes can be designed to deliver key regenerative factors that promote follicle activation and prolong the anagen phase of hair growth [40].

IV Exosomes: A Possible Alternative?

Recent advancements in translational and nanomedicine have accelerated the development of targeted drug delivery systems among researchers worldwide. Alongside these innovations, exosomes have emerged as a promising means for cell-free drug delivery, as they retain the inherent properties of their parent cells [41]. Advances in regenerative medicine have enabled researchers to isolate exosomes from Mesenchymal Stem Cells (MSCs), which possess exceptional regenerative potential for targeting diseases. The cargo within exosomes plays a crucial role in both diagnosing and treating diseases, as well as regulating disease processes. Numerous *in-vitro* studies have demonstrated the safety, effectiveness and therapeutic potential of exosomes in treating various cancers, neurodegenerative disorders, cardiovascular diseases and orthopedic conditions [41].

In addition, exosomes therapies are investigated as another option to reverse the fragility of aging. The Chinese clinical trial database (chictr.org.cn/searchprojen.aspx) includes a study on MSC-derived exosomes for photoaging. Interestingly, the exosomes were modified with circular RNA, a genetic alteration method that may enhance the therapeutic outcome. The administration of exosomes containing Nicotinamide Phosphoribosyl Transferase (NAMPT) notably improved wheel-running activity and extended the lifespan of aged mice [42]. Exosomes and extracellular vesicles have diverse effects on skin aging: Exosomes derived from bovine milk (MK-Exo) have shown anti-aging benefits by affecting keratinocytes and fibroblasts, leading to a reduction in wrinkles and improved skin hydration. Aging is typically associated with the breakdown of the extracellular matrix, a process regulated by a group of zinc-containing enzymes called Matrix Metalloproteinases (MMPs), specifically MMP-1 and MMP-3. The expression of these MMPs increases as we age. Exosomes derived from human induced Pluripotent Stem Cells (iPSCs) also show significant effects on photoaging by inhibiting these MMPs. Studies on iPSC-derived exosomes and Human Dermal Fibroblasts (HDFs) have shown that these exosomes promote the proliferation and migration of HDFs under normal conditions [42].

In conclusion, exosomes have gained considerable attention in the realm of anti-aging treatments due to their capacity to affect cellular processes that contribute to aging. These extracellular vesicles, which contain proteins, lipids, RNA and other bioactive molecules, have the potential to regulate various biological functions and possibly reverse or slow down aging-related changes in the skin and other tissues. As a cutting-edge approach to anti-aging, exosomes leverage their natural ability to influence cellular mechanisms and promote regeneration. By enhancing skin rejuvenation, reducing inflammation and aiding tissue repair, exosome-based therapies hold significant promise for counteracting or slowing both the visible and systemic effects of aging. With ongoing research, exosome therapies may become a fundamental part of anti-aging medicine, offering innovative solutions to preserve youthfulness and overall health [42].

Conclusion

Despite the promising potential of engineered exosomes for hair regrowth and skin rejuvenation, several challenges remain. One of the primary concerns is the scalability and standardization of exosome production, as large-scale manufacturing requires stringent quality control measures. Additionally, exosome stability and storage conditions need to be optimized to preserve their bioactivity. The regulatory landscape for exosome-based therapies is also evolving, with ongoing discussions regarding their classification as biologics or Advanced Therapy Medicinal Products (ATMPs). Engineered exosomes are emerging as a promising tool in regenerative aesthetics, offering innovative solutions for hair regrowth and skin rejuvenation. These nano-sized extracellular vesicles play a key role in intercellular communication, delivering bioactive cargo to target the root causes of skin aging and tissue degeneration. While still in the early stages of clinical application, advancements in exosome synthesis, purification and targeted delivery are driving their potential as a mainstream therapeutic option. However, challenges such as standardization, storage and scalability remain. This review explores the current and evolving role of exosomes in aesthetic medicine, highlighting their potential impact on skin health and hair restoration.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions
All authors contributed equally to this paper.

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