

Therapeutic Applications of Mesenchymal Stem Cell Secretome in Hair Regeneration

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ABSTRACT

Hair loss is a commonly encountered condition that often causes significant distress with diverse etiologies, including androgenic, autoimmune, inflammatory, and aging-related mechanisms. Current therapeutic options, such as minoxidil and finasteride, often exhibit limited efficacy and are associated with adverse effects, necessitating the exploration of safer and more effective alternatives. This review aims to explore the therapeutic potential of mesenchymal stem cell (MSC)-derived secretome as a novel cell-free approach for hair restoration. A narrative review of recent preclinical, in vivo, and early clinical studies was conducted to evaluate the role of MSC-secretome components, including growth factors, cytokines, extracellular vesicles, and exosomes, in modulating key pathways involved in the regeneration of hair follicles. *In vitro* and *ex vivo* models demonstrate that MSC-secretome enhances the proliferation, migration, and survival of dermal papilla cells and hair follicle stem cells by activation of the Wnt/ β -catenin, IGF-1, VEGF, and PI3K/AKT signaling pathways via paracrine signaling. *In vivo* animal models of alopecia indicate accelerated anagen initiation, follicle reactivation, improved dermal papilla function, and reduced inflammatory mediators following treatment with MSC-conditioned medium or exosomes. Early clinical evidence, including topical MSC-conditioned medium application in alopecia areata, suggests improved follicular density and hair shaft thickness without significant adverse effects. In conclusion, MSC-derived secretome represents a promising, cell-free strategy for hair regeneration. Future research should prioritize optimizing production protocols, standardizing active components, validating potency assays, addressing regulatory and manufacturing challenges, and conducting well-designed clinical trials to ensure consistent therapeutic outcomes.

Keywords: Alopecia; Mesenchymal stem cells; Secretome; Hair regeneration therapy

INTRODUCTION

Hair loss, or alopecia, is a multifactorial disorder characterized by the partial or complete absence of hair in regions where it normally grows, most commonly on the scalp. It arises from diverse pathological processes, including hormonal imbalance, immune-mediated follicular injury, follicular stem cell dysfunction, aging-related

changes, inflammation, and physical damage to the hair shaft¹. Clinically, alopecia may manifest as diffuse thinning, patterned baldness, patchy loss, or total scalp involvement depending on its underlying etiology and severity. Beyond its cosmetic impact, alopecia can cause substantial psychosocial distress and remains one of the most common

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dermatological concerns across age groups and sexes.

Alopecia is generally categorized into two major types: nonscarring and scarring alopecia. Nonscarring forms constitute most cases and include telogen effluvium, androgenetic alopecia, and alopecia areata, whereas scarring alopecias, such as central centrifugal cicatricial alopecia and lichen planopilaris, involve permanent follicular damage and irreversible hair loss^{2,3}. Androgenetic alopecia is the most common form of alopecia, affecting nearly 80% of men and approximately 50% of women over the age of 70⁴. It is primarily driven by dihydrotestosterone-mediated follicular miniaturization, which shortens the anagen phase, prolongs the telogen phase, and gradually converts terminal hairs into vellus-like hairs. Alopecia areata, another important nonscarring form, is characterized by abrupt, localized hair loss and is caused by autoimmune-mediated attack on anagen hair follicles⁵. In addition to follicular-based alopecia, hair damage may also occur at the shaft level due to physical, chemical, thermal, or ultraviolet-induced injury. These insults can disrupt the structural integrity of the hair shaft, leading clinically to dry, brittle, frizzy, and breakable hair⁶.

Traditional treatments for androgenetic alopecia, such as minoxidil and finasteride, remain widely used because of their ability to increase hair density and reduce hair shedding. Minoxidil promotes hair growth by prolonging the anagen phase and increasing vascular endothelial growth factor expression, whereas finasteride inhibits the conversion of testosterone into dihydrotestosterone, the major androgen involved in follicular miniaturization^{18,19}. However, these therapies have several limitations, including variable efficacy, the need for long-term use, incomplete follicular recovery, and potential adverse effects^{18,19}. Therefore, regenerative approaches that target the follicular microenvironment and restore hair follicle activity are increasingly being explored. Among these, mesenchymal stem cell-derived secretome, particularly from adipose-derived stem cells, has emerged as a promising cell-free strategy for hair regeneration^{19,25,28}. This review aims to explore the therapeutic potential, biological mechanisms,

preclinical evidence, early clinical applications, and translational challenges of MSC-derived secretome in hair regeneration therapy.

Literature Search Strategy

A narrative literature review was conducted to evaluate the therapeutic potential of mesenchymal stem cell (MSC)-derived secretome in hair regeneration. Relevant articles were identified through searches of electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search focused on studies published in English that discussed alopecia, hair follicle regeneration, MSC-derived secretome, conditioned medium, extracellular vesicles, exosomes, growth factors, and regenerative signaling pathways. The following keywords and combinations were used: alopecia, hair regeneration, hair follicle, mesenchymal stem cell, MSC secretome, conditioned medium, exosomes, extracellular vesicles, dermal papilla cells, hair follicle stem cells, Wnt/ β -catenin, VEGF, IGF-1, and PI3K/AKT.

Studies were included if they provided relevant evidence on the biological mechanisms, preclinical effects, animal model outcomes, or clinical applications of MSC-derived secretome in hair loss or hair follicle regeneration. In vitro, ex vivo, in vivo, clinical studies, systematic reviews, and narrative reviews were considered. Articles were excluded if they were not directly related to hair regeneration, did not discuss MSC-derived products or secretome components, lacked sufficient methodological or mechanistic information, or were not available in full text. The selected literature was then reviewed and synthesized according to study type, source of MSCs, secretome components, signaling pathways involved, biological effects, and translational relevance.

Overview of Hair Cycle and Alopecia

Hair follicles, although differing in size and shape based on the location, share common structural components. Matrix cells produce the hair shaft in the hair bulb, while melanocytes provide pigmentation. The dermal papilla, located at the follicle's base, controls matrix cell numbers and hair size⁷. Hair growth is an ongoing process with four

distinct phases: Anagen (growth): The longest phase, which last 2-8 years for scalp hair, during which the hair shaft is produced. Hair length directly correlates with anagen duration. The duration of anagen and the proportion of follicles of this phase decrease with age, resulting in weaker, thinner hair. Abnormal anagen shedding is not normal. Catagen (regression): A 2-week transitional phase where hair follicles undergo regression and detach from the dermal papilla. If the dermal papilla fails to reach the hair-follicle bulge, cycling terminates, leading to hair loss. Telogen (rest): Lasting 2-3 months, this phase sees old hair resting while new hair begins to develop. Approximately 9% of scalp hair is typically in telogen. Premature entry into this phase can cause excessive shedding (telogen effluvium). Exogen (shedding): The end of telogen and start of a new anagen phase, where new hair pushes out the old, resulting in shedding⁸.

Normal hair shedding typically amounts to about 100 strands per day. However, in the initial stages of hair loss conditions, this figure escalates considerably due to an impaired cycle of hair growth. The most critical issue is a disturbance in the anagen phase. Several types of hair loss may involve premature onset of the telogen phase or hair follicle damage, either at the bulb or the bulge region of the pilosebaceous unit².

Two primary factors typically determine the progression of hair miniaturization in its final stages, leading to hair loss. Firstly, anagen shortening occurs, leading to an abnormal hair cycle where the anagen: telogen ratio shifts from a healthy 12:1 to a problematic 5:1. This results in shorter hair shafts, premature shedding, and an increased proportion of hairs entering the telogen (rest) phase⁹. Secondly, negative impacts on hair growth can stem from the contraction of the dermal papilla or hair follicle. This leads to changes in hair diameter and morphology. Consequently, what was initially thick, pigmented hair can transform into thin, unpigmented (gray or white) hair. Scientists have also observed that as hair sheds, the scalp can contract and experience oxygen deprivation⁹. Furthermore, an excess of androgens in humans can also induce hair thinning and loss, particularly in the vertex and frontal regions, due to

their impact on hair follicles and the degradation of hair pigment. Androgens can alter the production of regulatory factors by dermal papilla cells, ultimately resulting in hair loss². Additionally, the conversion of testosterone to 5-alpha-dihydrotestosterone (DHT) via the enzyme 5-alpha-reductase can suppress hair growth. Conversely, a deficiency in the 5-alpha-reductase enzyme can lead to the growth of thick and healthy hair¹⁰.

Alopecia or hair loss can be categorized into two primary types: non-scarring (non-cicatricial) and scarring (cicatricial) alopecia. Each category is defined by distinct pathophysiological mechanisms and clinical presentations, and these differences underscore the importance of accurate diagnosis and treatment. Nonscarring alopecia includes several forms, in which hair follicles can generally return to normal function after the resolution of inflammation. The predominant types include androgenetic alopecia, telogen effluvium, alopecia areata, trichotillomania, and traction alopecia¹¹. Scarring alopecias can be classified into two categories: primary and secondary. In primary scarring alopecias, the inflammatory process directly targets the hair follicle, resulting in its loss. Meanwhile, in Secondary scarring alopecias, hair follicle damage occurs indirectly due to other diseases or disorders, for example infection of tinea capitis (scalp ringworm) or basal cell carcinomas¹¹. Androgenetic alopecia (AGA) is the predominant cause of hair loss in both men and women, followed by alopecia areata (AA)¹². Androgenetic alopecia (AGA) is mediated primarily by 5 α -Reductase and dihydrotestosterone (DHT), which induce the miniaturization of hair follicles and reduction in successive anagen cycles, resulting in progressive hair loss. AGA is an autosomal hereditary disorder condition characterized by the gradual transformation of terminal hairs into intermediate and vellus hairs. Changes in cycle of hair involve a reduction of the duration of the anagen phase and an increased duration of the telogen phase, leading to shorter hairs and ultimately baldness¹³. The intricate interplay of immune dysregulation and genetic factors underpins the development of

Alopecia Areata (AA). The pathogenesis centers on the breakdown of immune privilege within the hair follicle, which allow infiltration of cytotoxic CD8⁺ T cells and natural killer (NK) cells and damage follicular epithelium. This is accompanied by the upregulation of proinflammatory cytokines such as interleukin-15 (IL-15) and interferon- γ (IFN- γ), which further amplify immune reactivity¹⁴. Genetic predisposition plays a substantial role in AA, with strong associations reported for HLA alleles, CTLA4, and other immune-regulatory loci². Microscopically, AA is characterized by dense peribulbar lymphocytic infiltrates and aberrant expression of MHC class I and II molecules in hair bulb cells, disrupting the protective immune-sequestered environment of the follicle¹⁵. These immune reactions lead to premature catagen entry, vacuolar degeneration, and

dysregulation of keratinocyte cycling, culminating in visible hair shedding¹⁶. While AA is typically non-scarring, repeated episodes may result in chronic inflammation and secondary follicular damage. Aging further contributes to hair loss by impairing the function and viability of hair follicle stem cells (HFSCs), located in the bulge region and are crucial for initiating each new hair cycle. With age, HFSCs exhibit a decline in their regenerative potential due to niche dysfunction, reduced responsiveness to Wnt signaling, telogen retention, and inappropriate lineage differentiation. These cellular deficits are exacerbated by oxidative stress, ultraviolet radiation, chronic inflammation, and environmental pollutants, all of which promote HFSC depletion and follicular atrophy¹⁷.

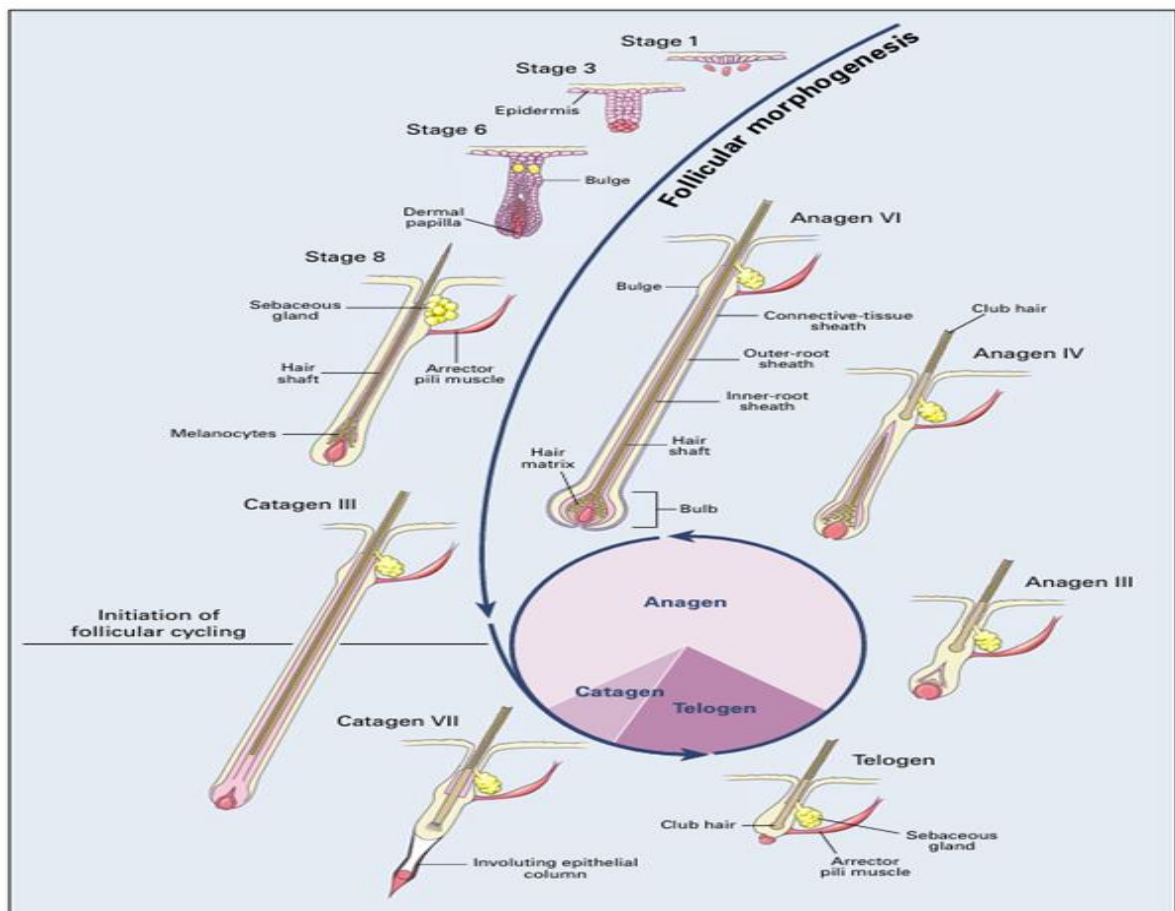


Figure 1. Hair Follicle Development and Cycling. Selected developmental stages of hair follicle morphogenesis, alongside the three phases of follicular cycling (anagen, catagen, and telogen) are depicted. The Roman numerals designate the morphological substages of anagen and catagen. The pie chart illustrates the relative duration the hair follicle spends in each stage⁷.

Current Therapies in Hair Regeneration

Hair regeneration therapy encompasses a diverse array of strategies aimed at restoring follicular density, delaying miniaturization, and promoting the reactivation of dormant hair follicles. The evolution of treatment has transitioned from single-agent pharmacologic interventions to integrative approaches that combine physical stimulation, biologic agents, and cellular technologies. The two mainstay drugs approved by FDA for androgenetic alopecia (AGA) are topical minoxidil and oral finasteride, both of which remain widely used despite their limitations. Minoxidil promotes vasodilation, prolongs the anagen phase, and increases dermal papilla vascularity by enhancing VEGF expression. Although it can increase hair count and thickness, its clinical utility is hampered by the requirement for long-term use and the high incidence of scalp irritation and compliance issues, especially among female users¹⁸. Finasteride, a selective 5- α -reductase type II inhibitor, prevents the alteration of testosterone to dihydrotestosterone (DHT), thereby inhibiting the key androgen responsible for follicular miniaturization. It has proven efficacy in halting hair loss and promoting modest regrowth, particularly in male patients. However, side effects such as erectile dysfunction, decreased libido, and mood changes, along with contraindications in women of reproductive age, have prompted the search for safer alternatives¹⁹. To address these gaps, several non-pharmacological and device-based therapies have been developed. The most investigated is low-level laser therapy (LLLT), also known as red light or cold laser therapy. LLLT uses red or near-infrared light wavelengths (typically 630–680 nm) to stimulate photobiomodulation within the hair follicle microenvironment. Mechanistically, it activates mitochondrial Cytochrome C Oxidase (Cco), increases ATP production, and modulates reactive oxygen species (ROS) and nitric oxide (NO), leading to upregulation of anti-apoptotic and proliferative pathways such as Wnt/ β -catenin signalling. Controlled trials have reported increased hair density, improved hair shaft diameter, and reduction in hair shedding, particularly when used during early AGA. Nevertheless, variability in treatment protocols

and laser parameters limits standardization²⁰. Another emerging biological intervention is platelet-rich plasma (PRP), an autologous therapy derived from centrifuged whole blood that contains concentrated platelets suspended in plasma. PRP delivers a robust mix of growth factors, including IGF-1, TGF- β , PDGF, and VEGF, which stimulate dermal papilla cell proliferation, angiogenesis, and follicular stem cell activity. Multiple randomized controlled trials have demonstrated PRP's efficacy in improving hair density, elongating the anagen phase and reducing hair fall in both male and female AGA. However, the outcomes are highly dependent on PRP preparation protocols, centrifugation speed, platelet concentration, and injection technique, underscoring the need for standardized clinical guidelines²¹.

In addition, microneedling (MN) appeared as a valuable adjunctive treatment due to its ability to trigger a controlled wound-healing cascade and enhance transdermal penetration of topical agents. Microneedling involves creating micro-channels in the skin using dermarollers or automated pens, which leads to upregulation of collagen synthesis, local cytokine release, and stem cell recruitment²². Individually, MN induces moderate improvements in hair thickness and density. However, when combined with other therapies such as minoxidil or PRP, its regenerative impact increases significantly by facilitating drug absorption and modulating the follicular niche. Clinical comparisons reveal that microneedling plus topical minoxidil outperforms minoxidil alone in terms of hair count, shaft diameter, and patient satisfaction²³. Similarly, the integration of microneedling and PRP has been shown to exert synergistic effects, optimizing follicular microcirculation and sustaining anagen growth for longer durations than monotherapies. Additional innovations explore combinations such as MN plus LLLT, which aim to merge the biological effects of light-based stimulation with the mechanical activation of stem cell pathways, though robust evidence is still emerging²⁴. Similarly, recent preclinical evidence in regenerative dermatology has shown that radiofrequency microneedling combined with polydioxanone filler can enhance dermal thickness, collagen density, and fibroblast count

under oxidative stress-mediated skin aging conditions, supporting the broader concept that minimally invasive combination-based approaches may improve tissue remodeling and regenerative outcomes⁷⁰.

In recent years, exosome-based therapy has gained momentum as a cell-free regenerative approach. Exosomes are nanovesicles secreted by mesenchymal stem cells (MSCs), enriched with proteins, lipids, mRNAs, and microRNAs capable of influencing cell proliferation, inflammation, and tissue remodeling. In hair regeneration, MSC-derived exosomes modulate the follicular microenvironment, suppress inflammatory responses, and activate HFSCs and dermal papilla cells via paracrine mechanisms¹⁹. Preclinical studies and early clinical data suggest that exosome application improves hair growth, density, and thickness, particularly when delivered via microneedle-assisted injection, which enhances penetration across the stratum corneum. Despite these promising findings, no exosome product has received formal approval for hair loss therapy, and further studies are warranted to validate safety, optimal dosing, and delivery protocols²⁵. The convergence of these therapeutic approaches underscores the shift toward multimodal strategies tailored to individual patient profiles and underlying pathophysiology. Combination therapies that integrate pharmacological agents, biologic stimulators, and delivery-enhancing technologies appear to yield the most sustained clinical benefits. Future developments will likely focus on refining delivery systems, optimizing treatment intervals, and establishing consensus protocols to ensure efficacy, safety, and reproducibility across diverse patient populations.

Potential of Stem Cells in Hair Regeneration Therapy

Hair loss is fundamentally a disorder of cycling, structure, or immune regulation of hair follicles; it is a promising candidate for the application of regenerative medicine. Stem cell-based therapies have emerged as biologically rational and clinically promising approaches because of their capacity to modulate multiple aspects of hair follicle physiology.

These include follicular stem cell activation, dermal papilla support, vascular remodeling, and immune privilege restoration. Among the various stem cell types under investigation, mesenchymal stem cells (MSCs) stand at the forefront of this field due to their accessibility, multipotency, and robust paracrine signaling. Preclinical studies have demonstrated that MSCs derived from sources such as adipose tissue, bone marrow, and umbilical cord tissue are capable of promoting hair regeneration. Their primary mode of action is not through direct differentiation into follicular cells, but rather through paracrine-mediated activation of native hair follicle stem cells (HFSCs) and dermal papilla cells.

A pivotal study using a mouse model of androgenetic alopecia (AGA) showed that intradermal injection of MSCs restored Wnt/ β -catenin signaling within the dermal papilla, leading to an increase of hair density and reactivation of dormant follicles. These results reinforce the idea that MSC therapy can reverse follicular miniaturization, a hallmark of AGA pathophysiology²⁶. Beyond direct cell transplantation, the MSC-derived secretome the collective term for all bioactive molecules released by MSCs, including exosomes, cytokines, growth factors, lipids, and extracellular vesicles has emerged as a potent therapeutic alternative. This secretome exerts strong regenerative influence by supporting angiogenesis, inhibiting inflammatory cytokines (e.g., TNF- α , IL-6), and improving extracellular matrix remodeling within the hair follicle niche¹⁶. One of the principal merits of secretome-based therapy is that it effectively circumvents numerous logistical and safety concerns associated with live-cell transplantation, including risks of tumorigenicity, immune rejection, and poor graft survival. Recent studies have demonstrated that preconditioning MSCs under controlled stress conditions such as hypoxia, thermal shock, or exposure to pharmacologic agents can significantly boost the regenerative content of the secretome. This strategy enhances the production of growth factors like VEGF, HGF, IGF-1, and FGF-7, which are essential in promoting dermal papilla proliferation and initiating the anagen phase of the hair cycle.

In a murine model of alopecia areata, topical application of MSC secretome resulted in the

reconstitution of follicular morphology, suppression of local inflammation, and restoration of hair growth. This was accompanied by a measurable reduction in interferon-gamma and MHC class I expression, suggesting that MSC secretome contributes to the restoration of immune privilege in the hair follicle, an essential component in treating autoimmune-mediated alopecia²⁷.

In human applications, secretome has been formulated into hydrogels, injectable serums, or microneedle-assisted topical systems, with promising results. A review on dermatological applications reported that the MSC secretome significantly improved dermal papilla cell activity and angiogenic markers in patients with diffuse alopecia and early AGA. Although long-term trials are still pending, these results validate the secretome's role as a low-risk, high-impact biological agent in the future of hair regeneration²⁸. In parallel, induced pluripotent stem cells (iPSCs) have emerged as a powerful, patient-specific source for generating hair follicle-like structures *in vitro*. Using complex differentiation protocols, iPSCs can be induced to form epithelial and mesenchymal components of the hair germ. A study demonstrated that iPSC-derived folliculoid aggregates, when transplanted into immunodeficient mice, formed *de novo* hair follicles with functional cycling ability. This approach represents a significant leap toward personalized follicular engineering. However, due to cost, tumorigenicity risk, and ethical concerns, iPSCs remain largely in the experimental phase²⁹. On the molecular level, stem cell activity within the follicle niche is governed by dynamic signaling interplay, including Wnt/ β -catenin, BMP, PI3K-AKT, and TGF- β pathways. Dysregulation of these pathways due to age, inflammation, or environmental insult, leads to HFSC dormancy and hair follicle miniaturization. It has been shown that restoring these pathways via either direct MSC delivery or secretome application can reawaken follicular growth potential. Moreover, the physical microenvironment, including extracellular matrix composition and dermal tension, also influences stem cell responsiveness to regenerative cues¹⁶. Clinically, autologous stem cell-based interventions, especially from adipose-derived sources (ADSCs), have demonstrated safety and

efficacy in early trials. These approaches use a patient's stem cells, processed into either a cellular suspension or protein-rich extract, and are re-injected into the scalp using microneedling or mesotherapy techniques. Outcomes include improved hair count, follicular reactivation, and increased shaft thickness without significant adverse events. The autologous nature of these therapies mitigates immunologic complications and aligns well with personalized medicine principles³⁰. Finally, proteomic studies have revealed that stressed MSCs produce a distinct repertoire of regenerative proteins capable of repairing follicular units. One such study identified key bioactive factors such as SOD2, FGF-7, and thioredoxin that contribute to anti-inflammatory, pro-survival, and pro-angiogenic effects in the follicular milieu. When applied to damaged or miniaturized follicles, these proteins improved epithelial cell organization and accelerated the re-initiation into the anagen phase. This discovery suggests that protein-based therapy derived from stem cell conditioning may serve as a scalable, acellular modality for hair restoration in the future³¹. Stem cell-based strategies in hair regeneration represent a convergence of cellular biology, tissue engineering, and clinical innovation. By targeting multiple facets of follicular degeneration, including stem cell exhaustion, immune dysregulation, vascular deficiency, and extracellular remodeling, these approaches hold the potential not only to stop hair loss, but also to reestablish the biological foundation for new hair growth. As technological refinements in stem cell sourcing, secretome engineering, and delivery platforms continue to evolve, regenerative therapy is poised to become a central pillar in the management of alopecia.

MSCs and Secretome (general isolation, secretome characterization)

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can be isolated from several tissues, for example bone marrow, adipose tissue, placenta, and Wharton's jelly. While isolation protocols differ by tissue source, the general approach includes enzymatic digestion, centrifugation, and expansion on tissue culture

plastic under standard conditions. MSCs are characterized by the expression of surface markers CD73, CD90, and CD105, and their ability to differentiate into osteoblasts, chondrocytes, and adipocytes. However, recent evidence has emphasized that their therapeutic effects are largely attributed to paracrine signaling via secreted bioactive factors collectively known as the secretome³². The MSC-derived secretome comprises a diverse array of biologically active molecules, including lipids, soluble proteins, nucleic acids, and extracellular vesicles (EVs). This secretory repertoire plays a key role in processes such as immunomodulation, tissue repair, angiogenesis, and anti-apoptosis. Among its prominent components are cytokines (e.g., IL-6, IL-10, TGF- β 1), chemokines, and growth factors such as VEGF, IGF-1, and HGF, which are responsible for orchestrating regenerative responses in injured or inflamed tissues³³. A critical component of the MSC secretome is extracellular vesicles, which include exosomes and microvesicles. These nano-sized vesicles serve as cargo carriers for mRNAs, microRNAs, proteins, and lipids, mediating intercellular communication through their uptake by recipient cells. Proteomic analyses have consistently revealed the presence of functional molecules such as annexins, thioredoxin, FGF-7, galectin-1, and fibronectin in MSC-derived EVs, which modulate cellular behaviour and contribute to tissue remodeling, angiogenesis, and immune regulation³⁴. The secretome's composition and potency vary significantly depending on MSC tissue origin. For instance, Wharton's jelly- and placenta-derived MSCs tend to secrete higher levels of immunomodulatory and pro-regenerative molecules compared to bone marrow or adipose sources³⁵. These variations are attributable to the epigenetic landscape, developmental stage, and inherent metabolic state of the tissue source. Furthermore, secretome composition is affected by donor characteristics such as age, with younger donors producing secretomes enriched in anti-inflammatory and angiogenic factors³⁶. To enhance therapeutic efficacy, MSCs can be preconditioned using various stimuli such as hypoxia, inflammatory cytokines, thermal stress, or small molecules. These preconditioning strategies upregulate key genes and

signaling pathways involved in paracrine function, thereby increasing the bioactivity of the secretome³⁷. Three-dimensional (3D) culture configurations, such as spheroids or scaffold-based systems, have also been shown to increase the yield and potency of secreted factors significantly when compared to traditional monolayer cultures³⁸.

The general workflow for harvesting secretome involves culturing MSCs in xeno-free or chemically defined media, followed by the collection of the conditioned medium after a designated incubation period. This medium is then subjected to a series of processing steps, including centrifugation, filtration, and if needed ultracentrifugation or tangential flow filtration to isolate and concentrate specific fractions such as EVs or soluble proteins³⁹. Downstream processing may also involve lyophilization or formulation into delivery vehicles to enhance stability and shelf-life for clinical applications⁴⁰. Characterization of the MSC secretome relies on multi-omic approaches such as proteomics, transcriptomics, and lipidomics, with tools including ELISA, western blotting, mass spectrometry, and nanoparticle tracking analysis (NTA). These techniques are used to define the molecular fingerprint and functional identity of secretome preparations⁴¹. Functional assays that evaluate angiogenesis, wound healing, or immunosuppression are increasingly recommended as complementary potency metrics⁴². Despite recent efforts to define potency markers and improve analytical standardization, significant challenges remain in achieving regulatory consensus. Inter-batch variability, heterogeneity in isolation techniques, and lack of universally accepted quality benchmarks complicate the development of consistent, scalable secretome-based products⁴³. To overcome these limitations, harmonized production protocols and validated assays are essential, especially for translation into good manufacturing practice (GMP)-compliant environments⁴⁴. While MSCs from different tissues all release a similar mix of regenerative proteins like VEGF, PDGF, MMPs, and TIMPs, each MSC tissue source also contributes unique molecules that may be advantageous for specific therapeutic targets. Adipose-derived MSCs tend to release more extracellular matrix (ECM)

remodeling enzymes, while Wharton's jelly-derived MSCs are enriched in neurotrophic and anti-inflammatory signals⁴⁵. Ultimately, for clinical implementation, MSC-secretome production must be aligned with safety, scalability, and regulatory criteria. Secretomes generated under GMP-compatible workflows using defined, serum-free media and validated culture systems are more likely to meet translational standards. These considerations are critical for realizing the potential of secretome-based, cell-free therapies in tissue engineering and regenerative medicine⁴⁶.

Regulatory and Manufacturing Barriers of MSC-Secretome Therapy

Although MSC-derived secretome offers several advantages as a cell-free regenerative product, its clinical translation remains limited by regulatory and manufacturing challenges. Unlike conventional small-molecule drugs, MSC-secretome preparations consist of complex and heterogeneous mixtures of soluble proteins, cytokines, growth factors, lipids, nucleic acids, and extracellular vesicles. This biological complexity makes it difficult to define specific active ingredients, establish potency markers, and determine consistent quality-control parameters^{32,39,40,41}. Differences in MSC tissue source, donor characteristics, passage number, culture medium, oxygen concentration, preconditioning strategy, harvesting time, and downstream processing may result in substantial batch-to-batch variability^{32,38,43}.

From a manufacturing perspective, large-scale production requires standardized and reproducible protocols that comply with good manufacturing practice (GMP). The use of serum-free or xeno-free media, validated isolation methods, sterile filtration, extracellular vesicle purification, lyophilization, storage conditions, and stability testing must be optimized before secretome-based products can be widely used in clinical settings^{32,39,40,44}. In addition, regulatory classification remains challenging because MSC-secretome products may be considered biological products, advanced therapy medicinal products, or cell-derived acellular therapeutics depending on national regulatory frameworks⁴⁶. Therefore, future development

should prioritize harmonized manufacturing protocols, validated potency assays, clear release criteria, long-term safety assessment, and regulatory guidelines to ensure product consistency, safety, and clinical efficacy^{32,40,41,46}.

***In Vitro* and *Ex Vivo* Studies of MSC-Derived Secretome for Hair Regeneration**

In vitro and *ex vivo* studies have advanced the understanding of how mesenchymal stem cell (MSC)-derived secretome promotes hair follicle (HF) regeneration. The secretome, particularly in the form of extracellular vesicles (EVs) and exosomes, has been shown to influence the proliferation, migration, and signaling activity of dermal papilla cells (DPCs), outer root sheath (ORS) keratinocytes, and HFSCs⁴⁷⁻⁴⁹. Exosomes from human umbilical cord MSCs (hUC-MSCs) are known to enhance DPC proliferation via Wnt/ β -catenin signaling pathway activation and upregulation of hair-inducing genes such as versican and LEF1⁴⁷. These exosomes also increased alkaline phosphatase activity, a functional marker of DPCs, while elevating anti-apoptotic Bcl-2 expression and reducing pro-apoptotic Bax levels⁴⁹. Moreover, secretome derived from 3D-cultured hUC-MSCs contained higher levels of HGF and VEGF compared to conventional 2D culture, significantly promoting hair shaft elongation in human HF organ culture⁴⁸. The secretome from adipose-derived stem cells (ADSCs) also demonstrated effectiveness in *ex vivo* HF models. Conditioned medium (CM) from ADSCs prolonged the anagen phase and enhanced the proliferation of matrix keratinocytes, partly through paracrine upregulation of IGF-1 and PDGF-AA^{50,52}. Pharmacological preconditioning of ADSCs with ATP or rapamycin further enhanced the regenerative potential of their secretome, reflected in elevated levels of exosomal miR-218-5p and miR-21, which specifically target inhibitors of Wnt and PI3K/AKT signaling pathways, respectively^{52,53}. Additionally, *ex vivo* models using full-thickness skin and isolated follicles confirmed that MSC-derived exosomes stimulate HFSC proliferation and promote transition to the anagen phase. In cultured human HFs, exosomal application upregulated Ki67 and PCNA expression in the bulge and matrix regions⁵⁴. Additionally, exosomes from DPCs facilitated HFSC

proliferation by transferring regenerative proteins such as Wnt3a and FGF10⁵⁵. These findings highlight the direct molecular transfer of pro-regenerative signals through EVs. *In vitro* co-culture systems have shown that secretome from DPCs and MSCs can modulate the hair-inductive microenvironment by regulating extracellular matrix (ECM) components and inflammatory mediators. Treatment with secretome resulted in upregulation of collagen IV and laminin-511, both essential for niche signaling, while reducing IL-6 and TNF- α in stressed keratinocytes, supporting anti-inflammatory benefits relevant to alopecia pathology⁵⁶⁻⁵⁸. Overall, *in vitro* and *ex vivo* studies demonstrate that MSC-derived secretome, particularly extracellular vesicles and exosomes, promotes hair follicle regeneration by enhancing the proliferation, migration, and signaling activity of key follicular cells, upregulating hair-inducing genes, and modulating the hair-inductive microenvironment.

***In Vivo* Evidence of MSC-Secretome Application in Animal Models of Hair Loss**

In vivo investigations across distinct mouse models of alopecia autoimmune, toxic, hormonal, and physiological have validated the regenerative capacity of mesenchymal stem cell (MSC)-derived secretome. These studies demonstrate that MSC-conditioned medium (CM) and extracellular vesicles (EVs), including exosomes, stimulate hair regrowth by suppressing inflammation, activating key follicular signaling pathways, and improving the dermal microenvironment. In autoimmune-mediated alopecia areata (AA), induced by interferon-gamma (IFN- γ), repeated intradermal injections of bone marrow-derived MSCs significantly restored hair coverage compared to saline-treated controls. Treated mice showed reduced infiltration of CD4+CD8+ T cells and normalized follicular morphology. Molecular profiling revealed downregulation of STAT1, STAT3, JAK1, JAK2, IFN- γ R, IL-1 β , IL-6, IL-17 α , and IL-18, indicating immunosuppressive action. Simultaneously, expression of Wnt/ β -catenin pathway targets such as LEF1 and β -catenin increased, along with fibroblast growth factors FGF2 and FGF7, suggesting follicular reactivation⁵⁹. In contrast, a chemically

induced model of alopecia using fluconazole toxicity demonstrated that hypoxia-preconditioned MSC secretome (SH-MSC) downregulated IL-1 β and upregulated PDGF expression in dorsal skin, improving hair retention. These findings highlight the anti-inflammatory and pro-angiogenic properties of the secretome in non-autoimmune alopecia⁶⁰. Beyond immune-related hair loss, studies have also explored the role of MSC-derived EVs in natural follicular cycling. In C57BL/6 mice synchronized in the telogen phase, intradermal injection of MSC-EVs induced early anagen transition, increased follicle counts, and enhanced hair shaft thickness. These effects correlated with upregulation of Wnt3a, IGF-1, VEGF, and versican in dermal tissues, reflecting stimulation of papilla cell function and folliculogenesis⁶¹. Hormone-dependent alopecia was modeled using testosterone-induced androgenetic alopecia (AGA). In this model, subcutaneous administration of EVs secreted from hyaluronic acid-stimulated induced MSCs (HA-iMSC-EVs) significantly accelerated hair regrowth. The treatment suppressed androgen receptor (AR) expression, activated β -catenin and phospho-GSK3 β signaling, and promoted anagen entry. Additionally, elevated levels of IGF-1, VEGF, and FGF7 were observed in scalp tissue, indicating dual activation of proliferative and angiogenic pathways. Notably, the regenerative outcome was comparable to that of finasteride, a standard anti-androgenic treatment⁶². Despite their diverse etiologies, these *in vivo* models consistently show that MSC-secretome therapies enhance hair follicle regeneration by reactivating growth phase transitions, modulating inflammatory responses, and improving vascular and epithelial signaling. These results support the translational potential of MSC-derived secretome as a cell-free therapeutic option for alopecia.

Clinical Applications and Therapeutic Potential of MSC-Secretome in Human Hair Loss

The clinical application of mesenchymal stem cell (MSC)-derived secretome for treatment of human hair loss has gained increasing interest due to its regenerative efficacy, safety profile, and cell-free nature. While traditional approaches such as minoxidil and corticosteroids have limited success

and frequent relapse, MSC-secretome offers a novel biologically active formulation that targets the underlying immune, inflammatory, and follicular regeneration mechanisms involved in alopecia. One clinical case study demonstrated significant hair regeneration in a patient with alopecia areata following topical application of MSC-conditioned media (MSC-CM) over a 3-month period. The treatment resulted in increased follicular density and hair shaft thickness, with no adverse effects or signs of irritation. This case supports the translational potential of secretome therapy in autoimmune-mediated hair loss conditions and highlights its tolerability in human skin application⁶³. In a broader review of dermatologic applications, MSC-secretome has been shown to influence various aspects of skin and hair regeneration. Secretome harvested from adipose- or umbilical-derived MSCs contains bioactive factors such as VEGF, IGF-1, and TGF- β which play roles in angiogenesis, immune modulation, and follicular cycling. Topical or microneedle-facilitated delivery of MSC-CM in clinical dermatology settings has led to improved outcomes in both alopecia and wound healing, with early clinical data indicating enhanced dermal thickness, follicular neogenesis, and anagen phase restoration³⁶. Stress-induced alopecia, particularly alopecia areata, has also been explored in narrative reviews where MSC-secretome is proposed as a means of restoring immune privilege and follicular quiescence. Paracrine mediators within the secretome particularly interleukin-10, hepatocyte growth factor, and prostaglandin E2 have been shown to suppress perifollicular inflammation and stimulate dormant stem cells within the bulge region of hair follicles. These mechanisms are essential in halting the autoimmune cycle and promoting sustained hair regrowth²⁷. To enhance clinical efficacy and ensure reproducibility, recent strategies have focused on pre-conditioning MSCs during *in vitro* culture. Hypoxia, cytokine exposure, or mechanical stimuli can optimize the content of growth factors and extracellular vesicles in the secretome. This modulation increases the consistency and potency of the therapeutic product, addressing a major barrier to clinical translation batch variability. Furthermore, cell-free secretome

eliminates risks associated with whole-cell transplantation, including immune rejection and tumorigenesis, making it a safer candidate for repeated topical or intradermal administration in cosmetic dermatology⁶⁴.

Despite these promising findings, current clinical evidence on MSC-derived secretome therapy for human hair loss remains limited. Most available studies are still based on case reports, small-scale observations, or early clinical applications rather than large randomized controlled trials^{19,25,36,63}. In addition, variations in MSC source, secretome preparation, dosage, delivery method, treatment interval, and outcome assessment make it difficult to compare results across studies^{32,39,40,64}. Long-term safety data, including the durability of hair regrowth and the effects of repeated administration, are also insufficient. Therefore, larger randomized controlled trials with standardized protocols, objective outcome measures, and longer follow-up periods are required before MSC-secretome therapy can be recommended as a routine clinical treatment for alopecia. Collectively, these clinical and preclinical findings support the feasibility of MSC-secretome as a therapeutic approach for alopecia and other hair loss conditions. Future directions include randomized clinical trials, optimization of delivery systems, and establishment of GMP-grade protocols to standardize formulation and dosing.

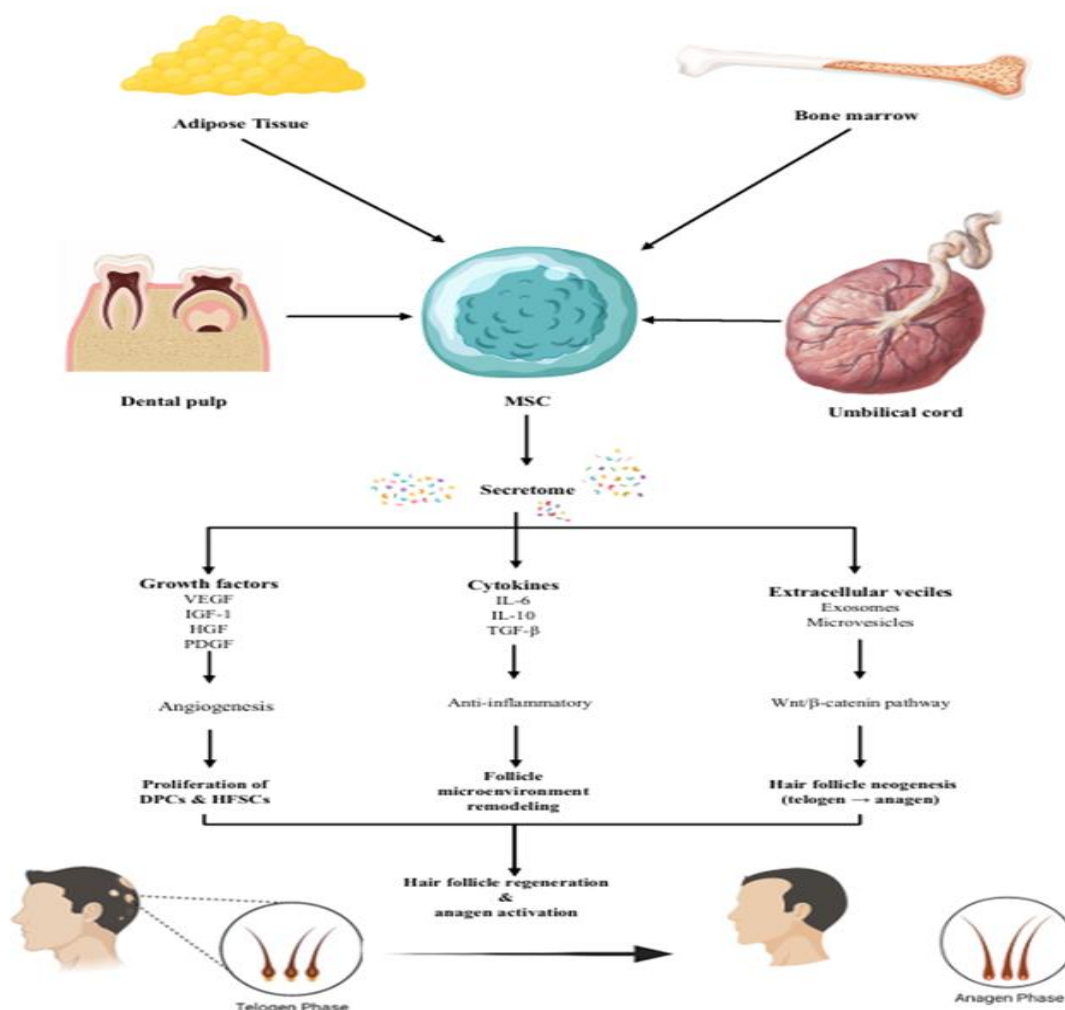


Figure 2. The Potential of Mesenchymal Stem Cells (MSCs) in Hair Follicle Regeneration

Mesenchymal stem cells can be isolated from several tissue sources, including bone marrow, adipose tissue, dental pulp, and umbilical cord. These cells secrete a bioactive secretome composed of cytokines (e.g., IL-6, IL-10, TGF- β), growth factors (e.g., VEGF, IGF-1, HGF, PDGF), and extracellular vesicles (e.g., exosomes and microvesicles). Each component plays a distinct role in follicular repair: growth factors stimulate angiogenesis and cellular proliferation; cytokines modulate inflammation and support microenvironment remodeling; and extracellular vesicles deliver molecular signals that activate the Wnt/ β -catenin pathway. These actions lead to the proliferation of dermal papilla cells (DPCs) and hair follicle stem cells (HFSCs), the remodeling of the follicular niche, and the neogenesis of hair follicles—ultimately promoting the regeneration of hair and reactivation of the anagen phase.

Table 1: Key Evidence on MSC Secretome Applications in Hair Regeneration

Source and Kind of Secretome	Testing	Signaling and Bioactive Molecules Involved	Effects	Reference
Adipose-Derived MSC Secretome (ADSC-CM)	<i>In vitro</i> & Clinical	VEGF, HGF, KGF, PDGF	Promotes hair growth, improves hair density and thickness	Advances in Stem Cell-Based Therapy for Hair Loss ⁶⁵ .
ADSC-derived Exosomes	<i>In vivo</i> (mouse AGA model)	Wnt/ β -catenin, CDC42	Stimulates anagen phase, increases DPC proliferation	Mesenchymal stem cell exosomes enhance the development of hair follicle ⁶⁶ .
MSC Secretome (multiple sources: UC, BM, adipose)	<i>In vitro</i> & <i>In vivo</i>	VEGF, TGF- β , IL-6, Exosomes	Regenerates skin tissue, enhances hair follicle cycling	Mesenchymal Stem Cell Secretome for Dermatology Application ³⁶ .
Wharton's Jelly MSC-derived Exosomes	<i>In vitro</i>	miRNAs, cytokines, proteins	Activates HFSC, supports follicle regeneration	Exploring the Potential of MSC-Derived Exosomes for Alopecia ⁶⁷ .
Adipose-Derived Stem Cell Exosomes	<i>In vitro</i> (immune cell model)	Anti-inflammatory cytokines	Restores hair in immune-mediated alopecia via immunomodulation	Exosomes Secreted from ADSCs for Immune-Mediated Alopecia ⁶⁸ .
Umbilical Cord MSC-derived Secretome	<i>In vitro</i> (keratinocytes, DPCs)	Growth factors, Exosomes	Stimulates follicle stem cell niche, enhances hair growth markers	Advancing Regenerative Cellular Therapies in Non-Scarring Alopecia ⁶⁹ .

CONCLUSION

Mesenchymal stem cell-derived secretome has emerged as a promising cell-free therapeutic strategy for hair regeneration because of its ability to modulate inflammation, stimulate angiogenesis, activate follicular stem cells, and support dermal papilla function. Unlike traditional pharmacologic agents or direct stem cell transplantation, secretome-based therapy offers a biologically active alternative that relies on paracrine mechanisms to restore the hair follicle microenvironment, reverse follicular miniaturization, and promote re-entry into the anagen phase. Preclinical studies have consistently demonstrated the capacity of MSC-secretome, particularly its extracellular vesicles, growth factors, cytokines, and exosomes, to enhance dermal papilla activity, induce anagen transition, and suppress immune-mediated follicular damage. *In vivo* animal models further support its regenerative efficacy across different alopecia mechanisms, while early clinical applications suggest favorable outcomes with no major adverse effects reported to date. However, current human clinical evidence remains limited by small sample sizes, short follow-up periods, variable outcome measures, and heterogeneity in MSC source, secretome

preparation, dosage, and delivery methods. In addition, regulatory and manufacturing challenges, including batch-to-batch variability, lack of standardized potency assays, product stability, and GMP-compliant production, must be addressed before MSC-secretome therapy can be translated into routine clinical use. Future studies should prioritize well-designed randomized controlled trials, standardized production and characterization protocols, validated quality-control criteria, optimized delivery systems, and long-term safety evaluation to ensure consistent, scalable, and clinically approved therapeutic outcomes.

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