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Review Article

Unlocking the potential of the secretome in hair growth enhancement

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ABSTRACT

Hair growth and its regulation are critical in biomedical research due to the widespread issue of hair loss. Understanding the cellular and molecular mechanisms of hair follicle development, cycling, and regeneration is essential for identifying therapeutic targets for hair growth disorders. This comprehensive literature review examined research on the biological pathways of hair follicle development, the role of the secretome in hair regeneration, and the efficacy of current hair loss treatments. Databases such as PubMed, Scopus, and Web of Science were meticulously searched for relevant studies, with a particular focus on the effects of the secretome on hair growth. The review highlights the significant role of hair follicle stem cells in wound healing through re-epithelialization and neogenesis, influenced by inflammatory cells. Exosomes from hair follicle mesenchymal stem cells containing lncRNA H19 enhanced diabetic wound healing by promoting cell proliferation and inhibiting pyroptosis. Hair follicle transplantation demonstrated the activation and differentiation of stem cells, with molecular signaling pathways between epithelial and mesenchymal cells being crucial for hair follicle regeneration. PlncRNA-1 promoted hair follicle stem cell differentiation via the EZH2/ZEB1/MAPK1 axis, enhancing wound healing. Secretome-based therapies offer a promising multifaceted approach to stimulating hair follicles and promoting hair regeneration, potentially overcoming the limitations and side effects of current treatments like minoxidil and finasteride. Understanding these mechanisms provides valuable insights for future therapeutic development in hair growth disorders.

Keywords: Hair follicle regeneration, Hair growth, Hair loss treatment, Secretome, Tissue regeneration

INTRODUCTION

Hair transcends its aesthetic value by serving essential biological functions crucial for survival and well-being. The protective role of hair is most evident on the scalp, where it acts as a physical shield against ultraviolet radiation, reducing the risk of skin damage. Eyelashes and eyebrows guard the eyes against dust, sweat, and foreign particles, minimizing irritation and potential injuries. Nasal hairs further fortify the body's defences by filtering

inhaled air, trapping dust, pathogens, and other airborne contaminants to prevent respiratory infections. Beyond protection, hair is intimately linked to the body's sensory network through follicles associated with nerve endings, making it capable of detecting the slightest touch. This sensory function is particularly pronounced in specialized structures like vibrissae or whiskers in many mammals, which can sense subtle air currents and environmental vibrations, contributing to spatial awareness and navigation.¹⁻³

Hair plays a significant role in regulating body temperature. It acts as an insulator, trapping a layer of air close to the skin to reduce heat exchange with the environment, which is vital for maintaining body temperature. The piloerection response enhances this insulating property in cold conditions, while in warmer settings, sweat evaporation at the hair's surface facilitates cooling through latent heat loss. The evolution of hair density and distribution across different species reflects remarkable adaptation to diverse environmental conditions, ranging from sparse coats that facilitate heat dissipation in desert-dwelling animals to dense fur offering insulation in arctic inhabitants. This interaction between hair and physiological functions underscores its significance beyond aesthetics, highlighting hair's integral role in mammalian biology. Understanding hair's biological roles enriches our comprehension of human and animal physiology and informs medical practices in dermatology and trichology.⁴⁻⁶

Research on hair growth has shown that the secretome is a particularly intriguing area of investigation. The secretome plays a crucial role in intercellular communication, tissue regeneration, and repair. Therapies based on the secretome have the potential to promote tissue regeneration, stimulate hair follicle stem cells, and influence hair development. This represents a promising alternative to current treatment methods. This review integrates various studies to provide a cohesive analysis of the secretome's capacity to influence hair development, comparing preclinical and clinical data and incorporating insights into the molecular basis of hair follicle biology.⁷⁻⁹ This review aims to situate secretome-based treatments within the larger context of hair growth research while highlighting their potential. By bridging the knowledge gap between the basic biology of hair and the clinical search for effective treatments, this review may lead to new therapeutic approaches that could transform the treatment of hair growth disorders.

LITERATURE RESEARCH

To ascertain the impact of the secretome on hair growth, a thorough literature search was imperative, aimed at gathering all relevant studies within the scope of this research. The methodology commenced with the development of a comprehensive search strategy, designed to navigate through extensive biomedical databases effectively. Renowned databases including PubMed, Scopus, Web of Science, and Google Scholar were selected for their wide-ranging collection of biomedical research, ensuring a broad spectrum of literature was considered. The search strategy was refined using a set of carefully chosen keywords and phrases, tailored to cover the diverse aspects of secretome research and its relevance to hair growth. Terms such as “secretome”, “hair growth”, “hair follicle regeneration”, “extracellular vesicles”, and “growth factors in hair” were utilized in various combinations, employing Boolean operators to maximize the search's breadth and depth. Inclusion criteria were precisely defined to focus on original research articles that

delve into the secretome's effects on hair growth, encompassing both preclinical and clinical studies. This approach ensured a rich collection of data, ranging from fundamental biological mechanisms to potential therapeutic interventions. Studies were expected to provide detailed methodologies and report outcomes directly related to hair growth, such as hair density, hair shaft thickness, and anagen to telogen ratio, to ensure the findings' relevance and applicability. Conversely, exclusion criteria were set to discard studies not specifically addressing the secretome's role in hair growth, such as those focusing on general tissue regeneration without direct implications for hair follicles. Reviews, opinion pieces, and studies devoid of empirical data were also excluded to maintain the review's empirical foundation.

The literature selection process was carried out in two stages, beginning with an initial screening of titles and abstracts against the inclusion and exclusion criteria. This step efficiently eliminated irrelevant studies and identified articles for in-depth evaluation. Following this, a detailed full-text review was conducted on the shortlisted articles to assess their eligibility thoroughly, ensuring the inclusion of only the most relevant and methodologically sound studies. Quality assessment of the included studies was rigorously performed based on established criteria, evaluating the methodological rigor, the validity of the findings, and the strength of the conclusions. This assessment considered the study design, with a preference for randomized controlled trials and well-structured experimental studies, to ensure a high level of evidence. The clarity of reporting, statistical analysis adequacy, and management of potential confounders were also examined to verify the results' reliability. Additionally, the relevance of the study populations, the specificity of the interventions, and the outcome measures' pertinence to hair growth were scrutinized to confirm the findings' applicability to secretome research in hair regeneration.

HAIR FOLLICLE

Hair follicle exhibits a complex anatomy characterized by its bulb, dermal papilla, hair matrix, and associated stem cell niches. These components collaborate intricately to facilitate the cyclical nature of hair growth, which is segmented into three principal phases: anagen (growth phase), catagen (regression phase), and telogen (resting phase).^{10,11} During the anagen phase, the hair follicle is in its most active state, with cells in the matrix proliferating rapidly to produce the hair shaft, driven by signals from the dermal papilla and surrounding microenvironment. This growth phase is succeeded by the catagen phase, where the follicle undergoes involution, leading to a cessation of hair production and a detachment of the hair shaft from the dermal papilla. The telogen phase then ensues, marking a period of quiescence before the follicle is reactivated to re-enter the anagen phase, signifying the start of a new hair growth cycle.^{12,13} Within this biological framework, the secretome emerges as a pivotal factor

influencing hair follicle behavior and regeneration. The secretome encompasses a diverse array of secreted molecules, including growth factors, cytokines, chemokines, extracellular vesicles, and other bioactive compounds, collectively orchestrating a myriad of cellular processes. In the context of hair follicle biology, the secretome's components are recognized for their roles in modulating cell proliferation, differentiation, and migration, as well as in fostering angiogenesis and extracellular matrix remodeling. These actions are particularly salient during the transition phases of the hair growth cycle, where the secretome can influence the reactivation of hair follicles from the telogen to the anagen phase, thereby promoting hair growth.^{8,14}

The mechanisms through which the secretome exerts its effects on hair follicle regeneration are multifaceted and involve intricate interactions with hair follicle cells and their microenvironment. Growth factors within the secretome, such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), and insulin-like growth factor (IGF), bind to their respective receptors on hair follicle cells, initiating signalling cascades that promote cellular proliferation and differentiation. Similarly, cytokines and chemokines in the secretome modulate immune cell recruitment and inflammation, processes that are crucial for hair follicle regeneration and cycling. Extracellular vesicles, another component of the secretome, serve as vehicles for the transfer of nucleic acids, proteins, and lipids between cells, facilitating intercellular communication and the transfer of regenerative signals. The interplay between the secretome and the hair follicle is further underscored by the spatial and temporal dynamics of secretome release. Secretome components are not uniformly distributed; rather, their release and activity are tightly regulated by cellular and environmental cues, ensuring that their regenerative effects are exerted precisely where and when needed. This regulatory complexity is exemplified in the hair follicle, where the secretome's influence varies across different hair growth phases and anatomical regions of the follicle, reflecting the nuanced control required to modulate hair growth and regeneration effectively.¹⁵

The role of hair follicles in wound healing has been extensively researched, with particular attention to the mechanisms involving stem cells and their interactions within the inflammatory environment. Hair follicle stem cells are crucial in wound healing, significantly contributing to re-epithelialization and hair follicle neogenesis, processes heavily influenced by immune cells and inflammatory conditions. According to Morgun and Vorotelyak, hair follicle stem cells are activated by immune cells such as macrophages, $\gamma\delta$ T cells, and Tregs, promoting re-epithelialization and hair follicle neogenesis through inflammation-induced pathways. Yang et al highlights the potential of exosomes from hair follicle mesenchymal stem cells, particularly those containing lncRNA H19, in enhancing diabetic wound healing. These exosomes inhibit pyroptosis and promote cell proliferation

and migration, demonstrating significant improvements in wound closure in diabetic mouse models.^{16,17}

Nuutila discusses the practical application of hair follicle transplantation in wound repair, revealing that epidermal stem cells from hair follicles can migrate to wound sites and differentiate into epidermal cells, thus facilitating re-epithelialization. This method has shown promise in clinical settings for treating partial-thickness burns and abrasions, where hair follicles serve as a valuable source of stem cells. Mao et al explore the complex interactions between epithelial and mesenchymal cells in hair follicle regeneration and wound healing, emphasizing the importance of signalling molecules and extracellular components in regulating these interactions and enhancing our understanding of the molecular pathways involved. Jin et al identify the role of PlncRNA-1 in promoting hair follicle stem cell differentiation via the EZH2/ZEB1/MAPK1 axis, a molecular mechanism that significantly enhances the proliferation and differentiation of hair follicle stem cells, thereby contributing to wound healing processes.¹⁸

FACTORS OF HAIR GROWTH

The intricate interplay of genetic, hormonal, nutritional, and environmental factors play a pivotal role in influencing hair growth and health, each contributing uniquely to the complex tapestry of processes that govern hair physiology. Genetic predispositions are fundamental in determining hair characteristics such as color, texture, density, and the predisposition towards hair thinning and loss.^{19,20} Hair color is influenced by variations in melanin production, governed by specific genes, while texture and density are determined by genetic codes that regulate follicle shape and hair growth cycles. Furthermore, genetic factors can predispose individuals to various forms of alopecia, with androgenetic alopecia being a prime example where hereditary patterns of hair loss are observed, highlighting the genetic underpinnings in the susceptibility to hair thinning.^{20,21}

Hormonal influences, particularly androgens, play a significant role in modulating hair growth patterns. Androgens, including testosterone and dihydrotestosterone (DHT), are known to affect the hair growth cycle, especially in androgen-sensitive areas such as the scalp, where they can lead to the miniaturization of hair follicles.^{22,23}

This hormonal interaction is a key element in the pathophysiology of androgenetic alopecia, where genetically predisposed individuals exhibit sensitivity to androgenic effects, leading to progressive hair thinning and loss. Beyond androgens, other hormonal factors such as thyroid hormones, growth hormone, and cortisol levels can also influence hair growth, with imbalances potentially leading to hair disorders, further emphasizing the critical role of hormonal homeostasis in hair health.^{24,25}

Nutritional status exerts a profound influence on hair growth and integrity, underscoring the adage that 'beauty comes from within'. Adequate nutrition is crucial for the provision of essential vitamins, minerals, and proteins necessary for the synthesis of keratin, the primary structural component of hair.²⁶ Deficiencies in key nutrients such as iron, zinc, vitamins A, C, D, and E, biotin, and essential fatty acids can manifest as weakened hair shafts, reduced hair density, and an increased propensity for hair loss. The hair growth cycle itself is energy-intensive, relying on a steady supply of nutrients to support the proliferative activity within the hair follicle. Thus, nutritional deficiencies or imbalances can disrupt the hair growth cycle, leading to conditions such as telogen effluvium, where a significant proportion of hair transitions prematurely into the resting phase, culminating in diffuse hair shedding.^{27,28}

Environmental factors further compound the influences on hair growth and health, with exposure to extreme conditions, pollutants, and harsh hair care practices introducing external stresses that can damage hair and impede its growth. UV radiation, environmental pollutants, and toxic chemicals can induce oxidative stress within hair follicles, damaging cellular structures and DNA, which can compromise hair growth and lead to increased hair fragility and loss.²⁹ Mechanical stress from harsh hair care practices such as excessive heat styling, chemical treatments, and tight hairstyles can inflict physical damage to the hair shaft and alter the hair growth cycle, potentially leading to conditions such as traction alopecia. Furthermore, the scalp's microenvironment, influenced by external factors such as hygiene practices and exposure to irritants, plays a critical role in maintaining follicular health and, by extension, healthy hair growth.^{29,30}

EFFICACY OF SECRETOME IN HAIR GROWTH

The investigation into the secretome's capacity to stimulate hair growth represents a dynamic and expanding field of research that has captured the attention of the scientific community, driven by the secretome's potential to pave new therapeutic pathways for hair regeneration amid the widespread and psychologically impactful nature of hair loss conditions. This line of inquiry encompasses a broad range of studies, extending from pre-clinical *in vitro* experiments and animal model investigations to rigorously conducted clinical trials involving human participants. Animal model studies, particularly those utilizing murine models, have been instrumental in elucidating the secretome's impact on hair growth within a living organism.^{8,27} These investigations typically entail the application or injection of secretome-based formulations onto areas of shaved skin, followed by careful observation of hair regrowth dynamics, follicular density, and the hair cycle's progression. The findings from such animal model studies have been encouraging, consistently demonstrating notable improvements in hair regrowth, an increase in follicular density, and a hastened entry of hair follicles into

the anagen phase post-treatment with secretome components. These results not only reinforce the observations from *in vitro* studies but also highlight the secretome's translational potential for hair regeneration therapies.^{31,32}

Progressing to clinical investigations, the secretome's role in promoting hair growth has been examined through several clinical trials. These studies are meticulously structured to assess the safety and therapeutic effectiveness of secretome-based interventions in individuals afflicted by hair loss. Clinical trial protocols typically involve administering secretome-derived products through various means, such as topical applications, injections, or incorporation within tissue engineering constructs, over predetermined periods to evaluate their impact on hair growth metrics.^{26,33} The insights garnered from these clinical endeavors have been encouraging, demonstrating the safety and efficacy of secretome-based treatments in enhancing hair growth. Notable outcomes include statistically significant improvements in hair density, thickness, and an increased ratio of hair follicles in the anagen phase, along with positive subjective assessments from patients regarding hair quality and coverage. These clinical outcomes, supported by rigorous statistical analysis, furnish robust evidence for secretome's viability as a therapeutic option for hair regeneration, marking a significant advancement in treating hair loss conditions.^{34,35}

COMPARATIVE ANALYSIS

The pursuit of efficacious therapies for hair growth has been a critical focus within dermatology, underscored by the significant psychological effects of hair loss. Conventional treatments like minoxidil and finasteride have been central to therapeutic efforts, providing relief albeit with certain constraints. Minoxidil, initially a hypertension medication, fortuitously revealed hair growth properties, though its precise action mechanism remains partially elucidated, believed to involve potassium channel activation and improved follicular blood flow.³⁶ Finasteride targets hormonal pathways, inhibiting 5-alpha-reductase to reduce DHT levels, a principal factor in androgenetic alopecia. While effective, these treatments are not devoid of limitations; minoxidil necessitates ongoing use and may cause scalp irritation and unintended hair growth nearby, whereas finasteride is linked to potential sexual side effects and is not suitable for women of reproductive age due to teratogenic risks. Hair transplantation offers a lasting remedy through surgical follicle transfer but is constrained by donor hair availability, cost, and surgical risks such as infection and scarring.^{37,38}

Against this backdrop, the secretome emerges as an innovative therapeutic contender, signalling a potential shift in hair growth treatment paradigms. Encompassing an array of growth factors, cytokines, and extracellular vesicles, the secretome adopts a comprehensive approach

to hair regeneration, impacting various facets of hair follicle biology. Preliminary pre-clinical and clinical research indicates its capability to stimulate hair growth, increase follicular density, and facilitate anagen phase entry, with a minimal adverse effect profile observed to date. This favourable safety aspect, combined with the non-invasive nature of secretome-based interventions, renders it an appealing alternative or complement to traditional modalities.^{8,31}

The secretome's action mechanisms offer substantial benefits over existing therapies. Contrary to the relatively specific actions of minoxidil and finasteride, the secretome engages a wide array of pathways, fostering angiogenesis, cellular proliferation, and modulating the follicular microenvironment to activate stem cells and promote regeneration. This comprehensive approach may underlie the secretome-based treatments' noted effectiveness, offering a holistic solution to hair growth by addressing various follicular aspects.^{15,39} Moreover, the secretome's adaptability facilitates personalized treatment approaches, allowing the customization of secretome formulations to meet individual hair loss conditions, a contrast to the universal application of minoxidil and finasteride. This nuanced approach holds promise for more precise and effective treatment outcomes.

FUTURE DIRECTIONS

The rigorous investigation into the secretome's impact on hair growth has unveiled compelling evidence, affirming the secretome's viability as an innovative therapeutic approach in the dermatological arena. Through a meticulous aggregation and scrutiny of a diverse array of studies, encompassing in vitro research to human clinical trials, a coherent narrative has emerged, underscoring the secretome's positive influence on hair follicle function and hair regeneration. The principal findings from this comprehensive review underscore the secretome's ability to augment hair density, activate the anagen growth phase, and ameliorate hair quality, corroborating the initial proposition of the secretome as a potent facilitator of hair growth. This evidence not only validates the preliminary hypothesis but also broadens the understanding of the secretome's comprehensive involvement in hair follicle physiology. The secretome, characterized by its rich composition of growth factors, cytokines, and extracellular vesicles, interacts with a plethora of cellular pathways, illustrating its capability to exceed the performance and mechanistic actions of conventional hair growth therapies, signifying a shift in the therapeutic landscape for hair loss treatment.^{15,39}

For clinical practice, the ramifications of these insights are substantial. Given its commendable safety profile and non-invasive administration, the secretome stands as a compelling treatment alternative for patients seeking options beyond traditional therapies. Furthermore, the adaptability of secretome-based treatments to meet individual patient conditions heralds a new era of

personalized dermatological treatments, potentially improving therapeutic effectiveness and patient contentment. Future research endeavors should focus on defining the optimal secretome formulations and administration strategies to enhance therapeutic impact. Comprehensive long-term clinical studies are crucial to ascertain the enduring safety and efficacy of secretome treatments in promoting hair growth. Investigating how secretome therapies might be integrated with existing hair loss treatments could also reveal additive or synergistic effects, proposing a multifaceted approach to managing hair loss.^{31,40}

CONCLUSION

The intricate biology of hair follicles and their growth cycles provides a rich context for the diverse actions of the secretome. Comprising components like growth factors, cytokines, and extracellular vesicles, the secretome exerts a significant influence on hair follicle biology by promoting hair growth, increasing hair density, and enhancing hair quality. Compared to existing hair growth treatments such as minoxidil, finasteride, and hair transplantation, the secretome emerges as a superior alternative or supplementary therapy. Traditional treatments often have limited mechanisms of action and potential side effects. In contrast, the secretome offers a comprehensive, multifunctional approach that targets various aspects of hair follicle biology with minimal adverse effects, making it a potentially safer and more effective choice for individuals seeking hair growth solutions. Furthermore, the secretome's efficacy and safety profile, along with its mechanistic benefits over conventional therapies, underscore its potential for clinical application. Tailoring secretome-based therapies to individual patient needs could transform hair loss treatment, leading to more personalized and effective strategies. Recent research highlights the role of hair follicle stem cells in wound healing, the enhancement of diabetic wound healing through mesenchymal stem cell exosomes, and the practical application of hair follicle transplantation in wound repair, further supporting the secretome's benefits.

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