Research Progress on the Application of Stem Cells in Hair Regeneration

Xinyu Mu*

Experimental School of Guangzhou Institute of Science and Technology, Guangzhou, China

*Corresponding author: hudeh@ldy.edu.rs

Abstract. Hair follicle stem cells (HFSCs) exhibit significant potential in hair regeneration research due to their self-renewal and multi-directional differentiation abilities. Hair loss is a common dermatological issue, and current treatment methods have limited efficacy; however, the investigation of HFSCs offers new avenues for developing novel therapies. HFSCs are relatively easy to isolate and culture from hair follicles, making them ideal candidates for laboratory and clinical applications. In addition to their role in hair regeneration, HFSCs contribute to the regeneration of skin, bone, cardiovascular, and neural tissues. Nonetheless, challenges remain regarding the effective expansion of HFSCs, their survival rates, and functional recovery in vivo. Furthermore, further research is needed to elucidate the specific mechanisms by which HFSCs operate in various types of hair loss. Overall, stem cells hold significant promise in the field of hair regeneration, and with a deeper understanding of HFSC biology and advancements in related technologies, more effective hair loss treatment strategies are anticipated in the future.

Keywords: Hair follicle stem cells; hair regeneration; tissue engineering; stem cell therapy.

1. Introduction

Stem cells are a subgroup of cells with self-renewal and differentiation potential. Due to their low immunogenicity, strong differentiation capacity, paracrine effects, and regenerative ability, they have been applied in the treatment of various diseases and have become a focus of biomedical research. Studies have shown that stem cells and their derivatives can promote hair follicle regeneration, improve the microenvironment of damaged follicles, and potentially reverse hair loss. The fast pace of modern life, combined with high stress levels, frequent late nights, smoking, and other factors, has led to an increasing number of people suffering from pathological hair loss. Pathological hair loss is a common dermatological condition characterized by a reduction in hair density. Several factors, including genetics, hormonal imbalances (such as thyroid disorders and insulin resistance), autoimmune diseases (such as alopecia areata and systemic lupus erythematosus), nutritional deficiencies, environmental influences (such as medications and UV radiation), psychological stress, and aging, can trigger hair loss. These destructive factors disrupt the hair growth cycle and reduce stem cell activity and the regenerative capacity of hair follicles. Hair loss can severely impact an individual’s psychological well-being and quality of life, particularly in women, where the aesthetic consequences of hair loss can cause significant emotional distress [1]. Therefore, this paper reviews the latest research on stem cell-based approaches for treating hair loss.

2. Characteristics and Functions of Hair Follicle Stem Cells (HFSCs)

2.1. Definition and Characteristics of HFSCs

HFSCs are the most extensively studied in the field of hair follicle (HF) regeneration. HFSCs are multipotent stem cells that express nestin and reside in the bulge area of the HF. They have self-renewal capabilities, a relatively slow cell cycle, strong proliferative capacity, and the ability to maintain the stability of local tissues over the long term [2]. Some HFSCs express the stem cell marker CD34 (+) and K15 (-), indicating they are in a relatively undifferentiated state and may represent the most primitive stem cells in the skin or serve as a source for other skin stem cells. Each HF contains at least two HFSC reservoirs located in the upper and lower parts, which fuse during the catagen and telogen phases and separate again in early anagen. HFSCs themselves form a complete niche immediately upon assembly [3]. HFSCs exhibit high plasticity and differentiation potential, contributing to wound healing by differentiating into the skin epidermis [4]. They can also differentiate into osteoblasts, keratinocytes, smooth muscle cells, and adipocytes, suggesting a promising role for HFSCs in regenerative medicine.

2.2. Role of HFSCs in Hair Growth

HFSCs play a crucial role in hair growth. Located at the base of the hair follicle, these stem cells are key players in maintaining and regenerating hair follicle structure and function throughout the hair growth cycle. HFSCs influence hair growth by regulating the different phases of the hair cycle, which consists of anagen (growth phase), catagen (regression phase), and telogen (resting phase). HFSCs are particularly active during anagen, helping to sustain the health of the follicle and promote new hair growth. Their activity is regulated by a variety of signaling molecules and growth factors. However, the proliferation and survival of HFSCs can be inhibited by factors such as the overexpression of DUSP6, which suppresses HFSC proliferation by inducing cell cycle arrest in the G1 phase and promoting apoptosis. This suggests that DUSP6 may play a critical role in modulating HFSC activity and maintaining hair follicle health. The essential role of HFSCs in hair growth, along with the influence of both intrinsic and extrinsic factors, highlights the importance of further research into their regulatory mechanisms. Such studies could pave the way for more effective treatments for hair-related conditions, including hair loss.

2.3. Regulatory Mechanisms of HFSCs

The growth of hair follicles is primarily determined by the interaction between HFSCs and the dermal papilla (DP). DP, connected to the epithelial sheath, forms the epithelial component of mature HF. During the regenerative phase, after the DP sends growth-inducing signals, HFSCs are activated in two stages: first, the hair germ cells rapidly proliferate, providing the energy required for the initial phase of hair growth. As HF enters the anagen phase, stem cells migrate downward to the lower part of the bulge, forming a new pool of progenitor cells known as secondary hair germ cells. These secondary germ cells migrate to the hair matrix, proliferating and differentiating into transient amplifying cells, which further proliferate and differentiate into new hair shafts, outer root sheaths (ORS), and skin-derived precursors (SKPs). During telogen, HFSCs undergo a second round of activation in the bulge area to replenish the cells consumed at the onset of the anagen phase, thus supporting the long-term growth of the hair shaft [5].

3. Applications of Different Types of Stem Cells in Hair Regeneration

3.1. Adipose-Derived Stem Cells (ADSCs)

ADSCs are a type of mesenchymal stem cell isolated from individual adipose tissue and cultured in vitro. Compared with other stem cells, ADSCs have unique paracrine regulatory functions. Due to their low immunogenicity, ease of availability, multipotency, and strong angiogenic potential, ADSCs are a hot topic in regenerative medicine. Subcutaneous fat cells and the dermis surround hair follicles, playing an important role in maintaining the normal growth of follicular cells. ADSCs and their secretions mediate various skin regeneration mechanisms, such as wound healing, anti-androgenic effects, and antioxidant protection, which are enhanced under hypoxic conditions. The substances secreted by ADSCs, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and exosomes, stimulate hair follicle growth, regulate the hair cycle, and promote more hair follicles to enter the anagen phase, thereby promoting hair regeneration [6]. ADSCs can inhibit the proliferation and differentiation of immune cells and reduce antibody secretion, exhibiting anti-inflammatory and antioxidant effects that reduce damage to hair follicles. Won CH et al. [7] demonstrated through cellular and molecular biology experiments that ADSCs can antagonize androgens and reduce the apoptosis rate of hair follicle epithelial cells caused by reactive oxygen species from downstream androgen metabolites, promoting dermal papilla cell proliferation, increasing follicle survival, and enhancing hair growth. Scalp blood supply is also an important factor in hair loss.

3.2. Umbilical Cord Blood-Derived Mesenchymal Stem Cells (UCB-MSCs)

UCB-MSCs are multipotent stem cells found in neonatal umbilical cord tissue, capable of being induced to differentiate into various tissues and organs. UCB-MSCs are the preferred source for most stem cell clinical research in China due to their easy accessibility, lack of ethical restrictions, low immunogenicity, and high regenerative capacity and differentiation potential [8]. Additionally, Wharton's jelly is a tissue surrounding the umbilical cord blood vessels, containing a small number of cells and a large amount of extracellular matrix (ECM) components. Decellularized Wharton's jelly matrix contains TGF-β, collagen, fibronectin, and laminin, forming a natural biocompatible 3D matrix that ensures cell adhesion, infiltration, growth, and proliferation both in vitro and in vivo, making it useful in tissue engineering and regenerative medicine [9].

3.3. Induced Pluripotent Stem Cells (iPSCs)

iPSCs are derived from somatic cells or other types of cells that are reprogrammed in vitro. These cells possess self-renewal capabilities and the potential to differentiate into multiple lineages, offering a new regenerative medicine approach for nearly all human diseases, including hair loss [10]. Today, we can reprogram somatic cells from patients with hair loss (such as blood or skin cells) to generate autologous iPSCs, which can be induced to differentiate into various cell types, including dermal papilla cells, epithelial cells, melanocytes, and other cell types that form functional hair follicles, providing an unlimited cell source for hair follicle generation. Zhou Huating et al. studied the effects of iPSCs on HFSCs by reprogramming human urine cells into iPSCs through the regulation of four transcription factors (SOX2, KLF4, OCT4, and c-Myc), followed by inducing iPSCs to differentiate into HFSCs by modulating the RA, BMP-4, and EGF signaling pathways [11]. Veraitch O et al. successfully cultivated a cell population with dermal papilla characteristics by inducing mesenchymal stem cells from iPSCs and using a culture medium containing bFGF and Wnt and BMP signaling activators. After mixing these cells with human keratinocytes and injecting them into the subcutaneous tissue of mice, they observed hair structure regeneration [12]. Lee J et al. studied the characteristics of iPSCs induced to differentiate into hair follicle cells by regulating the TGFβ and FGF signaling pathways, inducing hiPSCs to differentiate into epithelial and neural sheath cells [13]. They successfully constructed a skin organoid with biological characteristics similar to normal hair follicle cells and tissues. However, there are certain risks, such as incomplete iPSC differentiation, and controversies remain regarding the purity and quantity of these cells. Understanding the interaction between iPSC-based clinical treatments and hair regeneration outcomes is crucial for advancing hair regeneration technology [14].

4. Combined Applications of Stem Cell Therapy with Other Methods

4.1. Combination with Pharmacological Treatments

In recent years, significant progress has been made in the research of novel drugs for promoting hair follicle development and new drug delivery systems utilizing nanotechnology. Several new pharmacological agents have been discovered that activate hair follicle stem cells. For instance, Flores et al. identified small molecules RCGD423 and UK5099, which promote lactate metabolism, and found that they can activate hair follicle stem cells to promote hair growth by modulating local lactate metabolism in the hair follicle [15]. Additionally, certain medications have been found to have novel effects on promoting hair growth. For example, the immunosuppressant ruxolitinib, a selective kinase inhibitor commonly used to treat inflammation and graft-versus-host disease, has been shown to promote hair growth and improve symptoms of alopecia areata in mice and patients [16]. Metformin, an antidiabetic drug, can upregulate autophagy levels and promote hair regeneration [17]. Regarding drug delivery methods, in addition to oral administration, there are transdermal delivery systems using nanomicroparticles, microneedles, and biofilms based on traditional Chinese medicine components. Compared to conventional delivery methods, these novel systems offer higher transdermal efficiency and lower toxicity.

4.1.1 Janus Kinase Inhibitors

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway is a signal transduction pathway stimulated by cytokines that regulates the growth, activation, differentiation, and apoptosis of various cells, playing a crucial role in the body's inflammatory response [18]. Recent studies have shown that the JAK/STAT pathway is important in the pathogenesis of alopecia areata. Ruxolitinib is a selective inhibitor of JAK1 and JAK2, previously used for treating inflammation and graft-versus-host disease. JAK inhibitors can reduce the generation and release of inflammatory factors by blocking the JAK/STAT signaling pathway, thereby decreasing inflammatory mediators in hair follicles and awakening dormant follicles, which may represent a new and effective treatment for alopecia areata [19, 20].

4.1.2 Autophagy Modulators

Autophagy is a process by which the body engulfs aging organelles or macromolecules and transports them to lysosomes for degradation, achieving cellular metabolism and renewal by removing damaged proteins or organelles. Through the autophagic process, these substances are degraded into amino acids, fatty acids, and nucleotides within lysosomes, which are then reused. Autophagy plays an important role in maintaining cellular material balance and homeostasis. Research indicates a close relationship between autophagy and hair follicle development; certain synthetic or natural autophagy activators can activate the autophagic process, alleviating oxidative stress, skin aging damage, and clearing free radicals [21]. Autophagy levels increase during the anagen phase of the natural hair follicle cycle and remain low during the telogen phase. During the telogen phase, local application of autophagy-inducing small molecules, such as α-ketoglutarate (α-KG), α-ketobutyrate (α-KB), rapamycin, and olaparib, can induce autophagy by inhibiting ATP synthase and mTOR pathways. Metformin can activate AMP-activated protein kinase (AMPK), reducing cellular energy intake and inhibiting the respiratory chain, thereby inducing autophagy and stimulating hair follicles in the telogen phase to enter the anagen phase, promoting hair growth.

4.2. Combination with Physical Stimulation

Local physical stimulation of the skin, such as mechanical stretching, acupuncture, and photostimulation, can also induce the activation of hair follicle stem cells and promote hair growth. Unlike pharmacological stimulation, physical stimulation does not involve the introduction of foreign substances; instead, it activates the hair follicle stem cells through mechanisms inherent to the skin's immune and metabolic responses, minimizing systemic side effects and enhancing safety. Research on mechanical stretching has shown that methods such as mechanical tension applied to the skin or hair plucking at specific densities can effectively activate hair follicle stem cells. Chu et al. designed a device for stretching the skin, adjusting the intensity and duration of the force applied to regulate hair regeneration [22]. They found that continuous skin stretching at 33% for 7 days produced optimal results, with hair growth completing within 21 days. This mechanical stretching can stimulate the production of chemokines, recruiting macrophages to the stretched area. Following stretching, 29.4% of the recruited macrophages underwent M2 polarization and released growth factors that activated hair follicle stem cells (HFSCs), inducing hair regeneration. The activation of hair follicle stem cells through mechanical stretching is closely associated with immune cells in the hair follicle. The hair follicle serves as an entry point for immune cells into the epidermis, which release inflammatory factors in response to external stimuli, “summoning” immune cells (such as macrophages) and triggering an immune response [23]. Once activated, macrophages release a variety of active factors that promote the activation of the Wnt signaling pathway in the skin, inducing the regeneration of hair follicles in the damaged epidermis. Additionally, regulatory T cells (Tregs), a subset of T cells that control autoimmune responses, accumulate in the niche of hair follicle stem cells in the skin. Following inflammatory stimulation, these cells express high levels of the Notch signaling protein Jagged 1, initiating the Notch signaling pathway that triggers the activation of hair follicle stem cells, promoting their transition from the telogen phase to the anagen phase and enhancing hair follicle regeneration under hair loss stress [24].

4.2.1 Skin Needle Stimulation

Clinically, different intensities of skin needle stimulation are employed, such as plum blossom needles, electroacupuncture, and fractional microneedle radiofrequency, for treating alopecia. Animal experiments in mice have demonstrated similar therapeutic effects, with ongoing research into the underlying mechanisms. Electroacupuncture stimulation can enhance the immune function in various inflammatory disease animal models [25]. In a mouse model of alopecia areata, severe mast cell degranulation and the accumulation of inflammatory cells around anagen hair follicles were observed; after 14 days of electroacupuncture, degranulation levels were reduced by one-fifth, effectively suppressing inflammation and alleviating symptoms of alopecia areata [26]. Fractional microneedle radiofrequency stimulates hair follicle stem cells through the Wnt signaling pathway and inflammatory response, promoting hair growth in mice. In this process, macrophages play a crucial role. When the inflammatory response is inhibited and macrophages are removed, the hair growth-promoting effect disappears [27].

4.2.2 Photostimulation

Instances of hair regrowth have been observed in cases of laser hair removal, suggesting that light-induced skin stimulation may be an effective treatment for hair loss. Due to the large size of conventional laser devices and their limited use in daily life, researchers have designed a high-performance, flexible red vertical light-emitting diode (LED) wearable stimulator to promote hair growth [28]. This light stimulator is easy to manufacture, boasts excellent flexibility for wearable bio-stimulation, and features high light output with low forward voltage. Moreover, light stimulation can rapidly activate hair follicle stem cells through the suprachiasmatic nucleus's sympathetic nervous circuit. When M1-type intrinsically photosensitive retinal ganglion cells receive light signals, they transmit signals to the suprachiasmatic nucleus via melanopsin, which activates sympathetic nerves, increasing the release of norepinephrine in the skin and thereby activating hair follicle stem cells [29]. The 308 nm excimer light, a medium-wavelength ultraviolet light source, can induce apoptosis of T lymphocytes, alleviating the attack on hair follicles by inflammatory cells and factors, thereby effectively treating alopecia [30]. Lu et al. targeted senescent cells with nanoparticles modified with β2-microglobulin antibodies, using photothermal effects to selectively eliminate these cells and mitigate doxorubicin-induced hair loss [31]. As individuals age, the aging of hair follicle stem cells leads to gradual miniaturization of the follicles and extended telogen phases, resulting in increasingly robust resistance to activation and, ultimately, thinning and loss of hair, characterized as an aging phenotype [32]. Transplanting aged skin into a younger environment can partially rescue the aging phenotype of the skin [33]. Related research has proposed a “senescence-stem lock model”: senescent cells secrete pro-inflammatory factors that maintain adjacent cells in a persistent stem-like state, preventing appropriate tissue renewal [34, 35].

5. Challenges Faced by Stem Cell Therapy in Hair Regeneration

5.1. Uncertainty of Long-Term Effects

The long-term effects of stem cell therapy for hair regeneration are uncertain. Although initial studies show promise, they mainly consist of preclinical and preliminary clinical trials, lacking sufficient long-term follow-up data to evaluate efficacy and safety. For example, combining adipose-derived stem cell-conditioned media with microneedle therapy has been shown to enhance hair growth in mice; however, these findings require further clinical validation. Factors such as patient-specific conditions and individual differences may also influence treatment outcomes. While studies have not reported severe adverse reactions, the long-term safety of stem cell therapy is still a concern, necessitating further investigation. Overall, more clinical research is needed to assess the long-term effectiveness, safety, and applicability of stem cell therapy in hair regeneration.

5.2. Ethical and Regulatory Issues

The ethical and regulatory challenges surrounding stem cell therapy for hair regeneration are complex. Ethical concerns arise from the use of embryonic or adult stem cells, particularly regarding embryo use and destruction, which are subject to strict regulations in many regions. Additionally, potential risks and uncertainties, including side effects and long-term health impacts, must be addressed. Regulatory policies vary across countries; for instance, the U.S. and Europe maintain stringent oversight, while China is still working to improve regulations. Furthermore, emerging technologies, such as adipose-derived stem cell exosomes (ADSC-Exos), show promise but require more clinical trials for validation. To ensure patient rights and public safety, it is crucial to enhance ethical reviews and regulatory frameworks for stem cell therapy.

6. Conclusion

HFSCs possess self-renewal capabilities and can differentiate into all cell types within the hair follicle, including keratinocytes and sebaceous gland cells. This multipotency positions HFSCs as an ideal cellular source for hair regeneration research. Hair loss is a common dermatological issue, and current treatment options have limitations; however, studies on HFSCs provide hope for the development of novel therapies. HFSCs are relatively easy to isolate and culture from hair follicles compared to other stem cell types, facilitating both laboratory research and clinical applications. Moreover, HFSCs have the potential to contribute not only to hair regeneration but also to the regeneration of skin, bone, cardiovascular, and nervous tissues.

Despite the significant potential of HFSCs in hair regeneration, challenges remain, including effective expansion of HFSCs, enhancing their survival and functional restoration in vivo, and understanding their specific mechanisms of action in various types of hair loss disorders. In conclusion, stem cells play a crucial role in hair regeneration research and offer broad application prospects. As our understanding of HFSC biology deepens and related technologies advance, it is anticipated that more effective hair regeneration therapies will emerge in the future.

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