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Hair Follicle Stem Cells: An Overview And Therapeutic Applications

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ABSTRACT

Stem cells are characterized by their capacity for self-renewal and differentiation. This makes them essential components of tissue regeneration. Among adult populations, multipotent hair follicle stem cells (HFSCs), which are located primarily in the follicular bulge, show significant regenerative potential. This is due to their ability to differentiate into multiple lineages. This review examines HFSC biology and evaluates their therapeutic potential in wound healing, neural repair, and cardiovascular tissue engineering. Clinical applications of HFSC based therapies show evidence of success in treating androgenetic alopecia and chronic ulcers. While applications in neuroregeneration and vascular engineering remain mainly within the preclinical and in vitro stages. This article reviews recent advances in follicular compartmentalization and the discovery of actively dividing subpopulations. While also addressing the technical limitations and evidentiary gaps that must be solved before these therapies can transition into clinical practice.

INTRODUCTION

Stem cells have the capacity for self-renewal and differentiation into specialized cell types, serving as the necessary components for tissue maintenance and repair. These populations are broadly categorized by their developmental origin and potency. Embryonic stem cells (ESCs) and adult (somatic) stem cells. ESCs are pluripotent, they can differentiate into all cell types derived from the three primary germ layers - ectoderm, mesoderm, and endoderm. Although, their clinical application is often constrained by ethical considerations and potential immunogenicity. In contrast, adult stem cells are typically multipotent, having a more restricted differentiation profile, limited to their tissue of origin. Despite this, adult stem cells offer advantages for regenerative medicine. Some such examples are: fewer ethical conflicts and a reduced risk of immune rejection when autologous cells are used.(Rehman)

Among adult stem cell niches, the hair follicle has emerged as an accessible and potent source for regenerative therapy. Hair follicle stem cells (HFSCs) are located primarily within the "bulge" region. This is a specialized microenvironment located near the attachment site of the arrector pili muscle. (Wang et al.)(Peterson and Nair). These cells are essential to the cyclical regeneration of the hair follicle through the anagen (growth), catagen (regression), and telogen (resting) phases.

Recent advancements in lineage tracing have shown that HFSC organization is more intricate than previously thought. Identifying prominent subpopulations such as actively dividing Lgr5+ cells.(Huddlestone)(Talebzadeh and Nojan Talebzadeh) The regenerative capacity of HFSCs was traditionally associated with hair production and epidermal repair. Now, emerging research suggests broader potential in neuroregeneration, wound healing, and cardiovascular engineering. (Heidari et al.)(Cao et al.)This review examines HFSC biology and evaluates the current state of their therapeutic applications, focusing on distinguishing between established clinical practices and early, preclinical findings

HAIR FOLLICLE STEM CELLS

2.1 Location of hair follicle stem cells

The hair follicle is a multi-layered organ made up of approximately 20 different cell types. These extend from the epidermis through the dermis and into the subcutaneous tissue. The follicle is divided into three primary segments: the *infundibulum* (going from the epidermal surface to the sebaceous duct), the *isthmus* (between the sebaceous duct and the bulge), and the *inferior segment*, which ends in the hair bulb.(Hoagland) The hair bulb contains the dermal papilla, a cluster of specialized mesenchymal cells that regulate hair growth. The hair bulb is surrounded by the hair matrix, where keratinocytes and melanocytes generate the hair shaft and provide pigmentation.(Martel) The follicles structure includes the inner root sheath (which has Henle's layer, Huxley's layer and the cuticle). Along with the outer root sheath, which is connected with the epidermis. The structure is covered by a dermal sheath. Each follicle has sebaceous glands and the arrector pili muscle which forms the full pilosebaceous unit (Martel)

The bulge region located near the attachment site of the arrector pili muscle was traditionally viewed as the sole location of HFSCs. Although recently, research has identified a more intricate organization of stem cell niches.(Jaks et al.)

- Lgr5+ stem cells**:** A subpopulation of actively dividing but long living cells. These are located in the lower bulge and secondary hair germ during the telogen phase.(Ito et al.)(Panteleyev)
- Secondary hair germ cells**:** Progenitors found at the base of the follicle. These initiate the transition to the anagen phase.
- Outer root sheath progenitors**:** Populations in the upper and middle segments of the outer root sheath. These may serve as parent cells to give rise to bulge stem cells.(Li et al.)
- Melanocyte stem cells: Inactive, unpigmented cells within the bulge that activate during the growth cycle to provide pigment to the hair shaft.. (Zhang et al.)

These follicle-derived populations are different from hair follicle-derived mesenchymal stem cells (HF-MSCs) and neural crest-like stem cells.(Wang et al.) HFSCs are mainly epithelial in nature and responsible for generating the hair follicle lineages. While HF-MSCs are found in the dermal sheath and dermal papilla and have a different differentiation profile. (Wang et al.)Additionally, hair follicle-associated pluripotent (HAP) stem cells, located in the upper part of the follicle, demonstrate a broader differentiation potential. This includes neural lineages, though they remain different from the embryonic pluripotency found in ESCs.(Obara et al.)

2.2 Potency

Hair follicle stem cells are multipotent cells capable of differentiating into all lineages within the hair follicle. Additionally , they contribute to the regeneration of the epidermis and sebaceous glands. During wound healing, HFSCs migrate from the bulge niche to the site of injury, where they differentiate into K14+ basal keratinocytes. This helps them facilitate re-epithelialization.(Kristo Nuutila) This response is stimulated by inflammatory signals, specifically from macrophages. These signals activate HFSC proliferation through AKT/β-catenin-dependent pathways.(Wang et al.)

Beyond their regular roles, HFSCs show significant neurogenic potential because they have shared ectodermal origin with the central nervous system. However, the efficiency of this differentiation depends on the experimental environment. In some *in vitro* induction models, researchers have determined the lineage-specific differentiation rates of HFSCs:

- Schwann cell differentiation: Studies utilizing rat-derived HFSCs have shown that approximately 84% of cells can differentiate into Schwann cells. These cells are very important for providing axonal support and myelination. (Najafzadeh)
- Neuronal differentiation: Under targeted neural induction protocols, HFSCs have exhibited the ability to differentiate into neuron-like cells at a rate of approximately 39%. (Najafzadeh)
- Oligodendrocyte formation: Around 23% of induced HFSCs, express markers consistent with oligodendrocytes. This includes receptor interacting proteins.(Najafzadeh)

These percentages represent results from isolated laboratory studies (in vitro) and do not represent the baseline efficiency of HFSCs in a living human system (in vivo).

THERAPEUTIC APPLICATION OF HSFCS

3.1 Preclinical applications : neuroregeneration and vascular engineering

Neural regeneration and spinal cord injury (SCI) models

In models of compression-induced spinal cord injury in rats, transplanted HFSCs have shown the ability to survive for a long time and differentiate into both neuronal and glial lineages. (Wang et al.) The rats showed improved functional recovery and motor coordination. This was measured by higher scores on the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale. (Nowruz Najafzadeh et al.)

More studies in rat models show that HFSC transplants contribute to the restoration of injured peripheral nerves, and help with the recovery of hind limb function.(Obara et al.) Treated rats regained the ability to walk normally. This suggests that the cells help in rebuilding neural networks that are damaged.

In a 2022 mouse study, HAP cells were encapsulated in polyvinylidene fluoride membranes and implanted into severed thoracic spinal cords, during the chronic phase. The cells differentiated into neurons, astrocytes, and oligodendrocytes. This resulted in functional improvements reflected in BMS scores. (Obara et al.) It is important to know that human clinical trials are necessary to confirm these effects in human patients.

Vascular and cardiovascular engineering

In cardiovascular tissue engineering, HFSCs have demonstrated the ability to differentiate into smooth muscle cells, and help in blood vessel formation. Studies have successfully used these cells to engineer human vessel walls *in vitro*. This offers a potential solution for patients where autologous vein grafts are unavailable. Their angiogenic properties and capacity to form functional vascular networks are currently being researched to help overcome the limitations of synthetic vascular grafts.(Xu et al.)

3.2 Early clinical trials: Androgenetic Alopecia and Ulcers

Some current clinical research has moved from animal models to human subjects. This is particularly in dermatology and wound management. The aim of these trials is to establish standardized protocols for the autologous transplantation of isolated HFSCs.

Androgenetic alopecia and hair density

Alopecia is a common condition affecting approximately 180 million people. (Zhou et al.) Early clinical trials have tested the effectiveness of HFSC micrografts. These are typically harvested from the occipital region of the scalp via a punch biopsy.(Gentile et al.) In this, the follicles undergo mechanical isolation to prepare a suspension of autologous HFSCs. This is done without the need for enzymatic digestion or laboratory cell culturing. (Gan et al.)(Katarzyna Krefft-Trzciniecka et al.)

In a clinical study, patients treated with these HFSC micrografts showed a 29% increase in hair density in the targeted areas after 23 weeks. While, the control areas showed an increase of less than 1%. (Gan et al.)These results suggest that immediate transplantation of mechanically isolated HFSCs can effectively stimulate follicular regrowth in thinning areas.

Ulcer management

Beyond just hair regrowth, early phase clinical trials are analysing the potential of HFSCs to treat chronic, non healing wounds. A 2024 monocenter study examined 37 patients with refractory ulcers. These included venous, diabetic, and traumatic types. The treatment involved the application of isolated follicular units directly on to the wound bed.

After a 12 week follow-up period, the study reported:

- An average area reduction of 68% across all ulcer types. (Jansen et al.)
- Complete wound closure in 57% of the participants. (Jansen et al.)

While these outcomes are promising, they are currently only based on small sample sizes or single center designs. Larger, multi center randomized controlled trials (RCTs) are necessary to validate these findings. Then, these delivery methods may be able to be standardised and transition into established clinical practice.

3.3 Established clinical practices : grafting and burns

Follicular unit punch grafting for chronic ulcers

The transplantation of autologous follicular units has become a recognized and established method for speeding up the healing of persistent wounds such as venous leg ulcers. This technique involves harvesting small scalp punches (2–4 mm) containing terminal hair follicles. These are then grafted into the ulcer bed. In a randomized controlled trial (RCT) comparing these grafts to standard skin grafts which did not have hair follicles, the follicle containing grafts showed a 75% reduction in ulcer area over 18 weeks.(Luisa et al.)

This procedure is driven by the migration of HFSCs from the transplanted bulge niche to the wound edge within 48 hours after the procedure has been done. The cells then differentiate into K14+ basal keratinocytes to rebuild a multilayered epidermis.(Kristo Nuutila) HFSCs also contribute to the healing environment by secreting pro-regenerative cytokines. These include vascular endothelial growth factor and several chemokines.(Dekoninck and Cédric Blanpain) (Hegde et al.) They recruit endothelial cells and fibroblasts, promoting angiogenesis and matrix deposition. (Hegde et al.)(Dekoninck and Cédric Blanpain)(Zhang et al.)

Scalp derived grafts for severe burns

The scalp is a very effective donor site for split-thickness skin and dermal grafts (0.4–0.5 mm epidermis and 0.2 mm dermis). This is because of its high follicular density. Clinical practice has shown us that utilizing these scalp-derived grafts for burn patients leads to site re-epithelialization in an average of 10 days.(Oh)

Outcomes show that these grafts lead to significantly faster closure and reduced visible scarring compared to grafts taken from traditional donor sites, such as the thighs or buttocks. This fast repair is mainly due to the dense population of HFSCs that repopulate the injury site. This illustrates the proven use of hair follicle-rich tissue in modern reconstructive surgery .(Oh)

CONCLUSION AND FUTURE PERSPECTIVES

Hair follicle stem cells are a versatile and accessible multipotent population with significant potential in regenerative medicine. Beyond their main role in follicular cycling, the evidence presented in this review depicts their use in treating a wide variety of conditions. Spanning from androgenetic alopecia to chronic ulcers. Clinical studies have depicted success in autologous transplantation. The findings showed up to a 29% increase in hair density and faster re-epithelialization in venous leg ulcers and severe burns.

While the neurogenic and angiogenic potential of HFSCs offers promising potential for treating spinal cord injuries and cardiovascular diseases, these applications remain within the preclinical and in vitro stages.(Abadie et al.) The transition of these findings into established clinical practice requires solving technical and regulatory challenges. Future research has to prioritize the development of standardized and large-scale protocols for cell harvesting, processing, and delivery.(Shimizu et al.)

The integration of strategies including exosome-based therapies, tissue engineering, and personalized medicine is expected to improve the therapeutic effectiveness of HFSCs.(Huddlestone) As long term clinical trials continue to tune and refine these methods and address current gaps, HFSC-based interventions are positioned to become a significant part of the regenerative medicine field. (Poddar et al.)

AUTHOR'S CONTRIBUTIONS

Anusha Srivastava conceptualized this study, did the literature survey, wrote and corrected the manuscript

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