



International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X

P-ISSN: 2664-9411

www.dermatologypaper.com

Derma 2024; 7(2): 16-21

Received: 22-05-2024

Accepted: 26-06-2024

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Autologous micrografts from scalp tissue in treatment of androgenetic alopecia

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DOI: <https://doi.org/10.33545/26649411.2024.v7.i2a.187>

Abstract

Androgenetic alopecia (AGA) is a prevalent hair loss condition affecting both genders, characterized by progressive hair follicle miniaturization and a decline in hair density and thickness. This condition impacts quality of life and is associated with psychological issues such as depression and anxiety. Current treatments include FDA-approved finasteride and minoxidil, alongside various other approaches like dutasteride and hair transplantation. Emerging therapies focus on hair follicle stem cells (HFSCs), which, despite their presence in balding scalps, exhibit reduced proliferative activity. Techniques using autologous cellular micrografts, which involve mechanical isolation of HFSCs from scalp biopsies, have shown promise in enhancing hair density and thickness. These micrografts, derived from the patient's own cells, offer a minimally invasive and effective solution for AGA, potentially reducing the need for ongoing treatments and mitigating patient non-compliance.

Keywords: Androgenetic alopecia (AGA), hair follicle stem cells (HFSCs), autologous cellular micrografts

Introduction

Androgenetic alopecia (AGA), which impacts both males and females, is the most prevalent form of hair loss. It predominantly manifests after puberty, although its incidence tends to rise with advancing age. AGA is distinguished by the gradual reduction in size of the hair follicle (HF), which ultimately results in the vellus transformation of the terminal hair^[1, 2]. Clinical manifestations of this miniaturization process include a reduction in hair density and thickness^[3]. This condition signifies an aesthetic concern; it often results in patients experiencing a decline in their overall well-being, serving as a significant risk factor for depression, and anxiety^[4, 5].

In cases of AGA, treatment aims to stabilize hair loss and prevent hair miniaturization^[6, 7]. In addition to finasteride^[9] and minoxidil,^[8] which are the sole medications approved for the treatment of hair loss by the US Food and Drug Administration (FDA), various other approaches have been implemented, such as dutasteride, spironolactone, platelet rich plasma (PRP), microneedling, low-level laser therapy (LLLT), and hair transplantation^[10].

Hair follicle stem cells (HFSCs), which are situated in the bulge region of the follicle, engage in interactions with dermal papilla (DP) mesenchymal stem cells^[11]. The quantity of HFSCs remains unaltered in a bald scalp, while the quantity of progenitor cells that are actively proliferating decreases significantly^[12]. The utilization of micrografts containing autologous HFSCs is beneficial for therapeutic hair regrowth. By utilizing HFSCs, which are acquired through mechanical centrifugation of scalp punch biopsies, the hair density of patients with AGA can be enhanced^[13].

Human stem cell use in androgenetic alopecia

There has been significant interest in stem cell-based therapies as potential innovative treatments; these therapies concentrate on reactivating HFSCs to enhance the development, growth, and regeneration of HFs^[14]. Multipotent SCs that have the capacity to regenerate HFs are derived from various sources, including adipose tissue, HFs from unaffected scalp regions, blood, bone marrow, and Wharton's jelly^[15].

Two primary varieties of SC transplants exist: allogeneic and autologous. Adult SCs and perinatal SCs were proposed as the two classifications of SCs by Anudeep *et al.* in 2022.^[15]

Adult SCs were classified as HFSCs, ADSCs (derived from adipose tissue), or BMSCs (derived from bone marrow). Perinatal SCs comprised MSCs derived from the placenta, umbilical cord blood derivatives, Wharton's jelly, and amniotic fluid.

Hair follicle structure and hair cycle

Throughout life, the HF is one of the few organs that experiences cyclical involution and regeneration^[16]. HF is an epithelial organ composed of two major components: a keratinocyte-filled epithelial cylinder and the mesenchymal cells comprising the dermal sheath and DP. HFs undergo anagen (growth), catagen (involution), and telogen (resting) phases before reentering anagen at the conclusion of the hair cycle (Fig. 1).^[17]

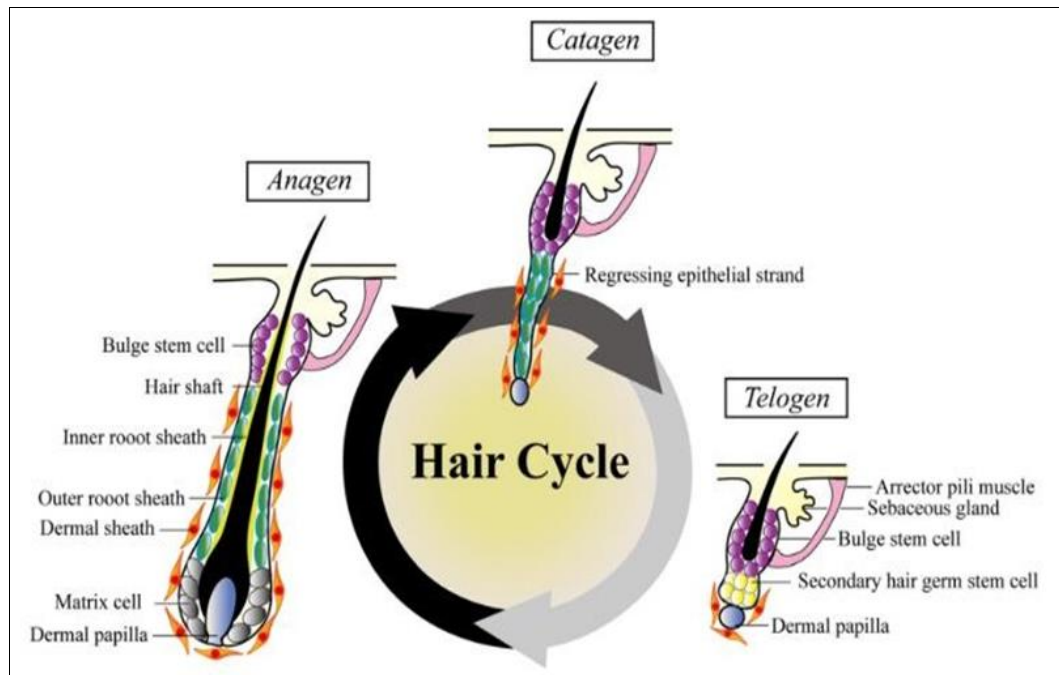


Fig 1: Hair follicle structure, hair follicle stem cell and hair cycle^[17]

Stem cells populations of the hair follicle

Elements of both epithelial and mesenchymal composition make up the HF. Its functional and cyclic activities are dependent on coordinated communication between distinct cell populations originating from the neural crest, epithelial, and mesenchymal origins. The epithelial cells are arranged in three concentric layers: the inner root sheath (IRS), the hair shaft (HS), and the outer root sheath (ORS), in that order from most external to internal^[18].

The bulge is a unilateral eccentric thickening is observed at the site of insertion of the arrector pili muscle in the ORS. The bulge is the geographical area where the most populous concentration of follicular SCs is found. SCs are a cell type that is capable of multilineage differentiation and self-renewal. The niche of SCs is an area characterized by particular conditions and a microenvironment that are sustained to sustain them. This niche differs between populations of SCs^[20]. Bulge's SCs, alternatively referred to as outer root sheath cells or HFSCs, exhibit multipotentiality through their capacity for multicellular differentiation. HFSCs are therefore capable of regenerating the epidermis and, at minimum, portions of the HF^[21]. Other epidermal SC populations exist in the HF besides bulge HFSCs; these include neuronal progenitor cells, sweat gland stroma derived SCs, sebaceous gland SCs, and melanocyte SCs. Additionally, SCs are situated in the isthmus and infundibulum. The former additionally aids in the maintenance of the interfollicular epidermis and the sebaceous gland, whereas the latter also provides support to the upper pilosebaceous unit. (Table 1)^[22] SCs that retain

the chromatin label for significantly longer durations than the surrounding cells in the tissue are referred to as label retaining cells^[20]. The bulge region of the HF is where the majority of label-retaining cells are located. Research has demonstrated that these cells are capable of proliferating in response to physical trauma or specific forms of stress^[24]. Each HF is situated on a DP consisting of a collection of mesenchymal-derived DP cells. Another mesenchymal component, the connective tissue sheath (DS) is situated between the ORS and the papillary dermis. Inducing inductive properties, DP cells are crucial to hair growth and the follicular cycle^[18].

The quiescent HFSCs are activated during the anagen phase, when DP stimulatory signaling exceeds the inhibitory bulge microenvironment's threshold. Thus, HFSCs proliferate and generate HF transit amplifying cells, which differentiate into eight distinct epithelial lineages and sebaceous glands to facilitate the growth of the HF. This procedure will ultimately produce a fully developed HF. When the proliferative capacity of the matrix cells is depleted, hair growth ceases and the follicle enter the catagen phase, during which the lower two-thirds of the follicle degenerate while the bulge zone remains intact. HFSCs are also capable of differentiating into interfollicular epithelial and sebaceous gland cells in response to injury^[24].

In their study, Liu *et al.* (2010)^[25] validated the mesenchymal stem cells immunophenotype and multilineage differentiation potential of DP cells and DS cells derived from human hair follicles (HFs). Consequently, these cells were called human hair follicle-derived

mesenchymal stem cells (hHF-MSCs). hHF-MSCs are capable of differentiating into osteogenic, myogenic, adipogenic, and hematopoietic lineages when they are not in their typical environment [26]. As a consequence, the HF

potentially represent an easily obtainable reservoir of autologous human MSCs suitable for applications in regenerative medicine and tissue engineering [27].

Table 1: Overview of the main stem cell populations located in the hair follicle. (22) Sca-1: Stem cell antigen-1

Stem Cell	Location	Main Markers	Origen
Interfollicular epidermal stem cells	Epidermis	Integrin $\alpha 6$ Keratin 5 (K5) Keratin 14 (K14)	Epidermal
Hair Follicle Stem Cells (HFSCs)	Bulge	CD34 Keratin 15 (K15) Leucine-rich G-protein-coupled receptor 5 (Lgr5) Integrin $\alpha 6$	Epidermal
Stem cells of the Isthmus	Isthmus	MTS24 Leucine-rich G-protein-coupled receptor 6 (Lgr6)	Epidermal
Stem cells of the Infundibulum	Infundibulum	Leucine-rich repeats and immunoglobulin-like domains protein 1 (Lrig1)	Epidermal
Dermal Papilla Cells (Hair follicle-derived mesenchymal stem cells)	Dermal Papilla	Nestin Vimentin Fibronectin Sca-1 Markers for fibroblasts, such as collagen I	Mesenchymal

A normal quantity of HFSCs is observed in AGA, whereas the pool of actively proliferating progenitor cells is diminished. This observation indicates that the pathology lies in the regulator of these SCs, whether it be activating or inhibiting them, and not in their quantity [12].

Signals and signaling cells within hair follicle stem cells niche

By definition, the presence of adjacent niche cells is not a prerequisite for the development of HF [28]. However, HFSCs acquire emergent functions through the integration of a variety of surrounding niche cells, most notably the ability to initiate a regenerative scheme or remain quiescent in response to changes in the local, systemic, and even external environments. Pathological infiltration of non-preexisting cells into the HFSC niche induces dysregulated hair growth in diseased states. As hair research continues to progress, an increasing number of cell types-including DP cells, adipose tissue, lymphatic vessels, nerves, and immune cells-are identified as contributors to the HFSC niche, revealing the sophistication and complexity of HFSCs' interactions with their environment [29-32].

Given the potential coexistence of activating and inhibitory signals within the HFSC niche, the likelihood of HFSC activation is calculated as the product of these two signal values [33]. The Wnt/ β catenin and bone morphogenetic protein (BMP) signaling pathways are the two primary counteracting signals [33, 34]. Strong BMP signaling inhibits the growth of HFSCs, whereas Wnt/ β -catenin signaling stimulates HFSC activation and sustains HF development. [32-34]. A number of variables that alter the proportions of Wnt/ β catenin and BMP signaling are capable of modulating HFSC activity, thus either inhibiting or promoting anagen entry [16].

Senescent characteristics are observed in dermal papillae cells derived from the balding scalps of patients with AGA. These include a decline in replicative potential, alterations in cell size and shape, and a reduction or elimination of the cell's distinctive markers or molecular signature [35]. DHT appears to accelerate the aging process in DP as a result of ongoing androgen receptor (AR) activation. In addition to losing the ability to promote the proliferation of HFSCs, the balding DP cells also generate inhibitory factors that inhibit the growth of HFSCs and impede the proliferation of keratinocytes [36, 37].

As an illustration, Wnt signaling is indispensable for both

anagen entry and progression. In balding DP cells, Dkk1, a negative regulator of Wnt signaling, is overexpressed. (36) An increase in TGF-1 secretion from DP in catagen facilitates the transition from anagen to catagen. Balding DP is characterized by increased TGF-1 production, which can inhibit keratinocyte proliferation. Furthermore, balding DP cells generate elevated levels of inflammatory cytokines, including IL6. In addition to impeding the entry of anagens, IL6 disrupts the regular progression of anagens [38].

Other uses of follicular stem cells in dermatology: Alopecia areata

Loss of immune privilege and the infiltration of CD4/CD8 lymphocytes and cytokines surrounding the HFs constitute the primary pathogenesis of AA [39].

Stem cells possess anti-inflammatory characteristics, which lead to immunomodulation. This property has been harnessed to treat cases of AA that are resistant and unresponsive. MSCs alter the function of additional immune cells and impede the proliferation of T and B cells. MSCs are capable of augmenting the release of immunosuppressive molecules such as PGE2 and TGF β 1. By stimulating the JAK1/STAT3 pathway and inhibiting dendritic cell maturation via IL-10, they promote the differentiation of regulatory dendritic cells and regulatory T cells [40, 41].

Telogen effluvium

Telogen effluvium is a hair cycle anomaly distinguished by an abundance of telogen hair loss. Numerous triggers, including stress, malnutrition, surgery, pregnancy, thyroid dysfunction, and others, contribute to the complete shedding of hair from the scalp. If this condition persists for a duration exceeding six months, it is classified as chronic telogen effluvium [41].

Twenty female cases of telogen effluvium caused by COVID-19 that were treated with HFSC micrografts injected from scalp tissues were evaluated in a study. Patients were assessed at the initiation of the intervention and were scheduled for follow-up appointments three and six months later. The treatment's effectiveness was evaluated through a combination of clinical assessment and trichoscopy. A notable enhancement in both the density and thickness of the hair was observed between the initiation of the treatment and the six-month follow-up period [42].

Vitiligo

Vitiligo develops due to a complex interplay of genetic and non-genetic factors that contribute to the autoimmune destruction of melanocytes^[43].

Co-cultivating melanocytes with adipose tissue-derived stem cells (ADSCs) improved melanocyte survival, according to a study by Kim *et al.* (2012)^[44]. It has been hypothesized that the immunomodulatory properties of SCs, which inhibit the infiltration of CD4/CD8 T cells and inflammatory cytokines, may account for the aforementioned phenomenon.

Thirty patients with stable vitiligo participated in a randomized, controlled trial in which the lesions were divided into two groups: those who received a fusion of epidermal cell suspension and follicular cell suspension transplant, or those who received epidermal cell suspension alone. The outcomes of combination therapy were superior at the sixteen-week mark in comparison to the control group, as measured by mean repigmentation (76% versus 57%), rapidity of repigmentation (48% versus 31%), and color match (73% versus 61%).^[45]

Wound healing

Fundamentally, wound healing consists of two phases: early and late. A cascade of events occurs during the initial phase of wound healing, encompassing homeostasis, inflammation, proliferation, and remodeling. The late phase is characterized by continuous remodeling to restore the tissues to an architecture close to normal. Deviations in this procedure may occasionally give rise to an excessive accumulation of fibrous tissue, which can manifest as hypertrophic scarring and keloids. An overproduction of collagen results from an imbalance between the anti-inflammatory and inflammatory processes, wherein dermal fibroblasts are stimulated by an excess of inflammatory cytokines and cells. SCs can aid in the treatment of chronic non-healing wounds due to their cellular differentiation, regeneration, ability to release growth factors, and immunomodulatory properties^[40, 46].

When scalp punch grafts are used for autologous transplantation of terminal HFs, healing is enhanced compared to punch grafts obtained from non-hairy regions. A minimally invasive surgical technique, hair punch grafting appears to be an effective treatment for chronic venous leg ulcers^[47].

Autologous cellular micrografts from the scalp

Autologous cellular micrografts (ACM) are obtained from scalp biopsies of patients via preparation system that filters and mechanically disintegrates scalp tissues, thereby no need for cell expansion or enzymatic digestion. By mechanical aggregation, injectable micrografts comprised of cells (SCs and progenitor cells), extracellular matrix, and growth factors derived from the patient's own cells were produced^[48]. Proposed mechanisms of action for ACM in AGA include the reactivation of progenitor cells and existing SCs of miniaturized follicles through the injection of growth factors and the enhancement of HF regeneration via transplantation of mature multipotent SCs^[48]. Dermal progenitor SCs may also have immunomodulatory and anti-inflammatory properties, which may promote hair regrowth given that AGA is known to have an inflammatory infiltrate that is accountable for the release of inflammatory cytokines. Multipotent SCs are capable of regenerating HFs in conjunction with sebaceous glands in the skin. Based on

existing knowledge, SCs have the potential to be utilized in The treatment approach utilizing autologous cellular micrografts combines a single session of cell harvesting, minimal manipulation, and immediate injection and the availability and safety of utilizing the patient's own cells, which do not induce an adverse reaction, are two advantages of this method. By omitting costly cell extension and *in vitro* cell control, the necessity for sterile manufacturing facilities, cell culture preparation, the risk of contamination, and the need for an additional method to collect the cells, this treatment circumvents a substantial number of restrictions previously associated with exogenous cell treatment. Moreover, it reduces the duration of the medical procedure's waiting period^[51]. Although autologous therapies may alleviate the patient of some daily responsibilities, the increased invasiveness of the procedures may result in decreased patient compliance^[52].

Conclusion

Autologous cellular micrograft is a rational, minimally invasive, efficacious, and remanence-beneficial long-term technique for the treatment of AGA that can also liberate the patient from their daily treatment of AGA.

Acknowledgement

Not available.

Author's Contribution

Not available.

Conflict of Interest

Not available.

Financial Support

Not available.

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How to Cite This Article

Mohammed MAAR, Doghaim NN, El-Ashmawy AA, Mohammed DAA, Hawwam SA. Autologous micrografts from scalp tissue in treatment of androgenetic alopecia. *International Journal of Dermatology, Venereology and Leprosy Sciences*. 2024;7(2):16-21.