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Mechanisms Involved in Human Hair Growths Relevant for Regenerative Medicine Therapies

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Abstract

Hair forms a barrier to protect the skin from external insults and keep the body from temperature loss. Human hair, especially scalp hair, has important ornamental functions essential for social communication and well-being. Hair regeneration depends on activating hair follicle stem cells (HFSCs). As the hair follicle (HF) is an integral part of the skin, its growth, and the activity of HFSCs are regulated by various nearby cells of the HFSC niche in the skin. The component cells of the HFSC niche are categorized into three groups according to their functions: signaling, sensing, and message-relaying. This paper reviews how HFSC activity is regulated by different signaling cells and how sensing and message-relaying cells help HFs to initiate a regenerative attempt in the face of local injury and external environmental changes. Also, on diseased states, a focus is put on how the pathological changes of the niche lead to dysregulated hair growth. In addition, how the influx or emergence of non-preexisting cells within the HFSC niche affects hair growth and depletes HFSCs. Finally, it highlights the therapeutic implications of niche pathology intending to prevent hair loss and promote growth.

Keywords: Hair growth; Follicle; Regeneration; Wnt; β-Catenin; Stem cells; Perivascular niche; Alopecia.

Abbreviations: AGA: Androgenic alopecia; ALP: Alkaline phosphatase; APM: Arrector pili muscle; bFGF: Basic fibroblast growth factor; BIO: (2′Z,3′E) Bromoindirubin 3′oxime; BMP: Bone morphogenetic protein; CK15: Cytokeratin 15; CK19: Cytokeratin 19; Dkks: Dickkopfs; DP: Dermal papilla; DPSCs: Dermal papilla stem cells; Eda-A1: Ectodysplasin; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; GSK3: Glycogen synthase kinase 3; HF: Hair follicle; HFSCs: Hair follicle stem cells; HGF: Hepatocyte growth factor; HSC: Hair stem cells; IGF1: Insulin-like growth factor 1; IGFBP1: Insulin-like growth factor binding protein 1; IL6: Interleukin 6; MCSF: Macrophage colony-stimulating factor; MCSFR: Macrophage colony-stimulating factor receptor; MSCs: Mesenchymal stem cells; ORS: Outer root sheath; PDGF: Platelet-derived growth factor; PDGFRα: Platelet-derived growth factor receptor alfa; PDGFRβ: Platelet-derived growth factor receptor beta; PGD2: Prostaglandin D2; PGE2: Prostaglandin E2; SCs: Stem Cells; Shh: Sonic hedgehog; α-SMA: α-smooth muscle actin; TGFβ1: Transforming growth factor beta1; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; WIHN: Wound-induced hair neogenesis; Wnt3a: Wingless-type MMTV integration site family, member 3A

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Introduction

Hair is a defining feature of mammals and has critical functions, including skin protection, production of sebum, apocrine sweat and pheromones, social and sexual interactions, thermoregulation, and provision of stem cells (SC) for skin homeostasis, regeneration, and repair [1]. Unwanted hair loss can pose psychosocial distress to affected individuals, particularly women [2]. Hair regeneration depends on activating hair follicle SC (HFSCs) [3-5]. The hair follicle (HF) is considered a "*mini organ*," consisting of intricate and well-organized structures originating from the HF stem and progenitor cells [1]. Dermal papilla (DP) cells are the main components of the mesenchymal compartments in the hair bulb. They are instrumental in generating signals to regulate the behavior of neighboring epithelial cells during the hair cycle. Mesenchymal-epithelial interactions within the DP niche derive HF embryonic development and the postnatal hair growth and regeneration cycle [1]. Human and murine HFs share the same principal cell types and the same essential features of organization and function. While hair research in the mouse has long been the foundation of our understanding of hair biology, [6] recent work has provided insight into human HF biology, facilitating the development of novel therapies for skin disorders [7]. The HFSCs and the DP stem cells (DPSCs) interact in the hair's growth and guarantee appropriate hair recovery and regeneration conditions [8]. Nevertheless, despite the DPSCs being harmed, in the case of *androgenic alopecia* (*AGA*) patients, HFSCs are saved in *patchy*, for which this kind of hair loss can be reversible [8]. Due to the importance of this knowledge for hair loss therapy using SC from the HF in humans, we decided to do this bibliographic review to help develop regenerative medicine in Abu Dhabi.

Method

To compile this review, we conducted a comprehensive search of the Google Scholar and PubMed databases for relevant references from 2000 to 2024 using the following terms: "alopecia", "hair growth", "hair follicules stem cells", "dermal papilla", "stem cells therapy", and "cellular factor." To describe detectable cell therapies available and different possibilities for improvement, we based our review on analyses conducted by various authors. Our literature review primarily focused on the embryological development of human hair, human hair follicles, stem cells, stem cell factors and stem cells use in hair follicle regeneration. Also, the cited bibliography of each selected paper was revised to identify any further relevant publications that aligned with our search objectives. The full text of each article included in this review was examined. Finally, we selected only the articles written in English.

Embryological Development of Human Hair

Human HF develops in embryonic life in four distinct stages, beginning in the ninth week of intrauterine life [7]. The HF structure is preserved across multiple tissue types, including the nails, teeth, and most exocrine glands, [9] and reciprocal interactions between the epidermal placode and the underlying dermal cells crucially determine HF formation [10]. The coordinated interaction of the various cells that make up the body is key to multicellularity. Indeed, patterning embryos, establishing cell type diversity, and forming tissues and organs rely on cell-to-cell communication during development [11]. Thus, arguably, one of the most important principles of developmental biology involves "*one group of cells changing the behavior of an adjacent set of cells, causing them to change their shape, mitotic rate, or fate*." An array of signaling pathways is thought to mediate this communication. Although many of the key pathways have not yet been identified, it is understood that Wnt, Sonic hedgehog (Shh), transforming growth factor-β/bone morphogenic protein (TGF-β/BMP), fibroblast growth factor (FGF), and the various tumor necrosis factor (TNF) paracrine signaling factors have fundamental roles [12]. The mesenchyme initiates signaling, stimulating the thickening of the epidermis and the formation of a hair placode [13]. Once established, the placode cells induce the mesenchymal cells to form a dermal condensate that ultimately forms the HF dermal papilla [14]. Signals from the dermal condensate then promote the epithelial cells' ingrowth into the dermis [13]. Further reciprocal epithelial-mesenchymal signaling likely induces maturation and formation of the different HF lineages. These processes have been classically categorized into three phases: induction, organogenesis, and cytodifferentiation [15]. The surrounding dermal cells conjugate around the placode and form a hair bud. The hair bud proliferates, lengthens, and invaginates into the dermis, creating the hair peg. Mesenchymal tissue then accumulates in the area, resulting in the hair bulb. Differentiation of the surrounding epithelial cells results in the formation of the HF wall, hair epithelial sheath, and a small swelling that will eventually form the sebaceous gland. Proliferation and keratinization of central epithelial cells form the hair cone. The HF is complete after the sebaceous gland differentiation and when the hair protrudes through the skin. HFs throughout the body develop at different rates, but by 21 weeks of fetal life, all areas have at least one HF. The development of HF progresses in a cephalocaudal direction, and by the time there are long hairs on the face and scalp, many areas of the trunk and extremities have hairs within the cellular sheaths or hairs partially protruding through the epidermis [16]. Local gradients of HF activators and inhibitors govern the mechanisms determining HF fate [17]. Wnt, ectodysplasin-A1 (Eda-A1), and noggin induce placode formation [18]. Signals that

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inhibit HF development remain yet to be determined. Wnt activity within and around developing hair placodes is under tight control, which is important given its integral role in HF cycling [18] and the potential for skin tumor formation with overactive epidermal Wnt/β-catenin signaling [19]. As in the "Turing model of reaction-diffusion systems," previously described in feather development, extracelular secreted Wnt and Dickkopfs (Dkks) likely direct placode formation through a reaction-diffusion system. Small-molecular-weight Wnt inhibitor Dkk4, for example, easily diffuses and inhibits Wnt signaling in the interfollicular epidermis, whereas larger Wnt molecules remain within the placode [20].

Human hair follicular stem cells

Human HFSCs (hHFSCs) are less known than murine HFSCs (mHFSCs). A variety of molecules are involved in the networks that critically regulate the fate of hHFSCs, such as factors in HF growth and development -in the Wnt, Shh, Notch, and BMP pathways, and that suppress apoptotic cues (the apoptosis pathway)-It appears that specific markers are normal in both human and mouse HFSCs: CD34, [21, 22] Cytokeratin 15 (CK15), [7, 21], Ctrokeratin 19 (CK19), [21, 23], and CD200. [21, 22] T he presence of different markers (i.e., Sox9 and LHX2) requires further examination. [24] Markers found in hHFSCs are PHLDA1 and EpCAM/Ber-EP4, valuable markers of the telogen-optional hair germ [21]. Although PHLDA-1 is not specifically expressed in hHFSCs, it can also be expressed in sweat glands and epidermal melanocytes [25]. DP cells present distinctive markers, including the cells from HF, dermal fibroblasts, and alkaline phosphatase (ALP) that is critical for both human and murine HFs, and it is the most explicit of the markers, wherein its high action is considered a marker of DP cells separation [26]. Additionally, α-smooth muscle actin (α-SMA), laminin, fibronectin, and CD133 expression have been observed in DP cells [26]. Marker expressions are modified in disease states. For instance, the immunoreactivity of CK15 is diminished in individuals with *patchy alopecia*. It is also identified in *AGA* [27]. HF of the scalp's front part displays a reduced CD34 in *AGA*, whereas its appearance is conserved in HF of the occipital locale [28]. In *patchy alopecia*, CD200, another marker of matrix cells, is expressed ineffectively, which might indicate a low immune benefit contributing to pathogenesis (i.e., the response of auto-reactive lymphocytes) [27]. Hair stem cells (HSCs) in the bulge remain resting for most of their lives, yet they can be actuated by relying upon the hair circle stage. The interpretation of the hair circle in humans has a few constraints due to the distinctive lengths of anagen, asynchrony of the human cycle, or the alternate response to the impact of hormonal variables [29]. Different papers reported the results of human scalp skin xenografted onto immune-compromised mice to set up the hair circle course *in vivo* in people [29].

The action of SCs in the bulge is controlled by its microenvironment (i.e., a supposed niche). This microenvironment incorporates the daughter cells of the SCs in the bulge, which enact their self-recovery ahead of schedule and in the late anagen stages [31]. SCs are fundamentally influenced by the DP's mesenchymal stem cells (MSCs), which are in close contact with the germinal matrix cells isolated by the basal membrane [32]. They appear to be of vital significance in the activation of hair growth and signal transmission during recovery [33]. Investigations have demonstrated that hair recovery is impossible after laser treatment because the HF cycle stops at the telogen stage without advancing to the anagen stage [32].Infusions of exosomes obtained from DP cells to HFs have been found to accelerate the passage of anagen and catagen delay employing the β-catenin and SHH pathways. [34] HFSCs are additionally influenced by fibroblasts in the reticular and papillary layers of the dermis, in addition to the subcutaneous tissue [32]. Inside

Table 1: The main phases of hair growth.

Stage	Key Features
ANAGEN	**Active growth phase:** Early anagen: hair matrix forms new hair. Nourishment of HF from the blood supply enables hair growth. Lasts 2-6 years.
CATAGEN	**Intermediate or "transition" phase:** A deeper portion of the HF starts to collapse. HF detaches from the nourishing blood supply. Lasts 1-2 weeks.
TELOGEN	**Resting phase:** Remains of the hair bulk are inactive. Papillary cells are entirely separate from HF. Lasts 5-6 weeks.
EXOGEN	**Shedding phase:** Hairs at the end of their life fall out. It is mainly coupled to early anagen but also occurs in telogen.
HF: HAIR FOLLICLE. **Reference: https://www.sciencedirect.com/science/article/pii/s0022202x15417737** [30]	

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the niche, melanocyte SCs oversee the formation of mature melanocytes that confer color to maturing hair. The survival and growth of MSCs relies on signs transmitted by the HF epithelial cells (HFECs), for instance, the TGF-β or the Wnt pathway [32]. The extracellular matrix is another part of the microenvironment. It explicitly influences the SCs through the arrangement of the basal layer, in which undifferentiated cells are in contact and regulated, for instance, by integrins [33]. Adult neural, mesenchymal, and hematopoietic SCs neighbor the vasculature, supplying oxygen and nutrients and providing molecular signals to the SCs [6,35,36], mainly through endothelial cells [37]. Intimate molecular communication from the vascular niche to the SCs contributes to tissue homeostasis and repair. Reverse signaling, from SCs to the neighboring niche, was also shown in zebrafish, where hematopoietic SCs can remodel the perivascular niche [38]. Little is known about skin vasculature cross-talking with adult HFSCs. HFSCs reside in the upper segment of the HF, known as the bulge, and are embedded deep into the skin dermis. During the hair circle, bulge HFSCs periodically regenerate the temporary lower HF region (bulb), which grows downward into the hypodermis [39]. HFs undergo morphologically recognizable and synchronous phases of remodeling, known as anagen (Bulb growth), catagen (bulb destruction), and telogen (quiescence and rest) [37].

At catagen, a subset of quiescent HFSCs leave the bulge and form the secondary hair germ, which replaces the apoptotic hair bulb. The skin loses most of its fat in the hypodermis, shrinks considerably in thickness, and the HFs enter the resting phase or telogen. In anagen, signals from the environment, including the fat progenitors [40], activate the quiescent HFSCs in the hair germ to produce a new hair bulb with a newly growing hair shaft [39] The bulge HFSCs that go into the hair germ are subsequently replenished at anagen by self-renewing symmetric divisions of the bulge SCs [41,42] The fat layer in the hypodermis and surrounding the growing hair bulb also regenerates in parallel with the HF at anagen [40]. Although poorly understood, the skin vasculature is remodeled along with the massive changes in the skin structure and thickness that result in the destruction and reconstruction of the highly vascularized hypodermis. In human skin, vasculature-associated cells known as pericytes may promote stem cell proliferation of the inter-follicular epidermis [43], although any effects on HFSC activation have not been addressed. Furthermore, a permanent vascular structure, known as the upper venule annulus, neighbors the upper hair bulge region at all hair circle stages [44], but the significance of this association is not understood. Importantly, angiogenesis and recruitment of blood vessels promote more robust hair shaft production, presumably by providing nutrients to rapidly dividing hair matrix progenitor cells in the bulb during full anagen [45,46]. However, these studies have not examined the potential cross-talk of vasculature with quiescent HFSC at earlier hair circle stages (catagen/telogen). Hormones such as androgens are an essential regulator for hair growth, and they have paradoxical effects on HFs in different body regions. It is known that vellus hair refers to our body's thin, tiny hairs. We can find them if we look closely at seemingly hairless areas, such as our ear lobes or faces. Androgens can stimulate the transformation of small vellus HFs in some regions of our body into large terminal HFs after puberty, such as the beard, pubic hair, and axillary hair [47,48]. On the contrary, in the scalp, genetically predisposed individuals of androgenic alopecia or male pattern baldness, androgens inhibit hair growth, leading to progressive HF miniaturization. [49] Hyperandrogenism in females can lead to hirsutism with excessive male pattern hair growth. [50] These paradoxical effects of androgens on human hair growth have long been a puzzle [51,52]. Androgens act through the intracellular androgen receptor. In HFs, androgen receptors are mainly expressed by DP [53,54] In contrast, keratinocytes do not express androgen receptors or show androgen receptor-dependent signaling activation, suggesting that keratinocytes may not be the primary responding cells in HFs [55,56]. It is already demonstrated that Piloerection (goosebumps) requires concerted actions of the HF, the arrector pili muscle (APM), and the sympathetic nerve, providing a model to study interactions across epithelium, mesenchyme, and nerves. It was shown that APMs and sympathetic nerves form a dual-component niche to modulate HFSC activity. Sympathetic nerves form synapse-like structures with HFSCs and regulate HFSCs through norepinephrine, whereas APMs maintain sympathetic innervation to HFSCs. Without norepinephrine signaling, HFSCs enter deep quiescence by downregulating the cell cycle and metabolism while upregulating quiescence regulators Foxp1 and Fgf18. During development, HFSC progeny secretes Shh signals to direct the formation of this APM-sympathetic nerve niche, which controls adult HF regeneration. Those results reveal a reciprocal interdependence between a regenerative tissue and its niche at different stages. They demonstrate that sympathetic nerves can modulate SCs through synapse-like connections and neurotransmitters to couple tissue production with demands [57]. Some SC factors and small molecules promote hair growth by different mechanisms (See Table 2).

Stem Cell Use in Hair Follicle Regeneration

HF are immunologically privileged places, like the brain, eyes, and testicles, under the influence of the neuroendocrine-immune network [59].

In physiological conditions, this is characterized by:

(1) Low expression or absence of the main MHC I antigens,

(2) The presence of malfunctioning *Langerhans* cells,

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Table 2: Stem cell factors and small molecules that promote hair growth and their mechanisms of action Ref [58].

Factor	Mechanism of Action
HGF and HGF ACTIVATOR	Factor secreted by DP cells that promotes proliferation of epithelial follicular cells
EGF	Promotes growth and migration of follicle ORS cells by activation of Wnt/β-catenin signaling
BFGF	Promotes the development of HF
IL 6	Involved in WIHN through STAT3 activation
VEGF	Promotes perifollicular angiogenesis
TGFB	Stimulates the signaling pathways that regulate the hair cycle
IGF1	Promotes proliferation, survival, and migration of HF cells
IGFBP1 TO 6	Regulates IGF1 effects and its interaction with extracellular matrix proteins at the HF level
BMP	Maintains DP cell phenotype, which is crucial for stimulation of HF stem cell
BMPR1A	Maintains the proper identity of DP cells that is essential for specific DP cell function
MCSF	Involved in wound-induced hair regrowth
M CSFR	Involved in wound-induced hair regrowth
PDGF AND PDGFR B/A	Upregulates the genes involved in HF differentiation. Induction and regulation of anagen phase. PDGF and its receptors are essential for follicular development
WNT3A	Involved in HF development through β catenin signaling
PGE2	Stimulates anagen phase in HFs
PGD2 RECEPTOR D2/ GPR44	Promotes follicle regeneration Iron and l
PGF2A and ANALOGS	Promotes transition from telogen to anagen phase of the hair cycle
BIO	GSK 3 inhibitor
PGE2 or INHIBITION of PGD2 or PGD2 RECEPTOR D2/	Promotes follicle regeneration
GPR44	Under investigation
IRON and L-LYSINE	

(3) Local expression of immunosuppressive substances (TGF-β1 and α-melanocytes MSH) [59].

Owing to this, they can be easily used in transplantation. Multipotent SCs can regenerate HF with sebaceous glands in the skin. In the current state of knowledge, SCs can be used to regenerate hair in several therapeutic strategies:

(1) Reversing the pathological mechanisms that contribute to hair loss (especially in AGA)

(2) Regeneration of complete HF from their parts (cells in the bulge can regenerate a whole hair)

(3) Neogenesis of HF from a stem cell culture with isolated cells or tissue engineering [60,61].

The presence of SCs in somatic tissues has been well established using functional tissue cell transplantation assays. [62] However, their isolation and propagation have proven difficult.

Methods to isolate and expand SCs from somatic tissue, particularly without significant differentiation, are highly desirable. Some questions have been raised regarding how multipotent adult SCs relate to embryonic SCs. Thus, obtaining and cultivating many types of somatic SC is essential. In particular, the availability of a method for producing HFSCs and melanocyte SCs from adult tissues would significantly contribute to cell replacement therapies and tissue engineering. For example, HFSCs can produce hair, sweat glands, sebaceous glands, and skin cells [63]. One of the problems encountered with artificial skin is that it does not have sweat glands or sebaceous glands, leading to problems with thermo-regulation and dryness, respectively, when large segments are grafted. It would be desirable to have other cells that could be used in tissue engineering applications, such as generating functional skin grafts. There has been considerable difficulty in obtaining human somatic HFSCs that can be propagated and cultured *ex vivo*. One factor is the predominant way somatic SCs divide is by asymmetric cell kinetics. During asymmetric kinetics, one daughter cell divides with the same kinetics as its stem cell parent, while the second daughter gives rise to a differentiating non-dividing cell lineage. The second daughter may differentiate immediately, or, depending on the tissue, it may undergo a finite number of successive symmetric divisions to give rise to a larger pool of differentiating cells.

Such asymmetric cell kinetics significantly hinder cell expansion *in vitro*. [64-66] In culture, continued asymmetric cell kinetics results in dilution and loss of an initial relatively fixed number of SCs by accumulating much greater numbers of their terminally differentiating progeny. If a sample includes exponentially growing cells and somatic SCs, their growth will rapidly overwhelm the somatic SCs, leading to their dilution. Even in instances where it is possible to select for relatively purer populations, for example, by cell sorting, asymmetric cell kinetics prevent expansion. Another factor

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is that during the hair growth cycle, the cells are believed to migrate from the bulge region to a place at the base of the HF known as the bulb [67]. These migratory patterns and the general difficulty of dissecting these regions from HF have foiled attempts to establish HFSC lines.

Conclusions

SCs are being investigated in applications in male pattern baldness and other forms of alopecia of the human scalp. Stem cells are being studied to see if the hair can be replenished using patients' MSCs from the base of the existing follicles, fat cells, and bone marrow SCs or embryonic umbilical SCs to stimulate hair growth or replacement. Other modalities, such as SC-derived nutrient medium and SC-derived exosomes, are novel approaches to future hair loss therapy [68]. Recent studies revealed that SCs may be directly injected into the scalp to allow the growth of new HF in males or females and correct alopecia. SCs may also be used in growth factor stimulation of existing inactive and atrophic follicles to become viable and active follicles yet again [68]. Additional studies indicate that various regulatory mechanisms may be utilized to reinitiate the existing inactive follicle cells to regrow hair in male pattern baldness. SCs injected into the scalp could aid these regulatory mechanisms. Nevertheless, we have developed a simple, reliable, and safe method in our laboratory to isolate such SCs from an individual and expand them as primary culture *ex vivo* for hair loss therapy without establishing a cell line but only for autologous use.

Author contributions

All authors contribute to this review. RARJ and AABH conceived and designed the study. RARJ wrote the manuscript. RARJ, MTH, URM, YVC, and AABH reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Not applicable; all information is gathered from published articles.

Code Availability

Not applicable

Declarations

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Ethical approval

Not applicable

Consent to participate

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Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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