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# Human Hair Follicle: An Update on Biology and Perspectives in Hair Growth Disorders Treatment

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## Abstract

The Hair Follicle (HF) is a vital component of mammalian skin and represents a unique, highly regenerative system that undergoes phases of rapid growth, regression, and resting periods. The hair cycling is of profound clinical relevance since majority of the hair growth disorders occur as a result of cycle changes. The influence of many molecules governing the formation of HF has been investigated and many of important cycle mediators have been identified. Cellular and molecular events during cycling are controlled by a network of sequential activation of autocrine, paracrine and endocrine signaling pathways. This implies variations in the expression or activity of the Wnt family molecules, Fibroblast Growth Factor (FGF), Transforming Growth Factor β (TGF-β), Hedgehog pathway, β-Catenin pathway, noggin, transcription factor Stat3, Epidermal Growth Factor (EGF), Insulin Growth Factor-1 (IGF-1), Vascular Endothelial Growth Factor (VEGF), Thyrotropin Releasing Hormone (TRH), Polyamine, Spermidine, Neurotrophins (NT3, NT4), prolactin, retinoids, Bone Morphogenetic Protein 4 (BMP4), cathepsin L, 17-β estradiol, dihydrotestosterone and many others. Despite considerable progress in this area, the key elements of cycle control have not been identified. Therefore, for the most common hair disorders several agents are available, even none of these is curative or preventive. The one of the prime challenges of hair research is a better understanding of the molecular controls of hair cycling and developing drug which would effectively manipulate the cycle. Future therapy strategies will be based on new and better knowledge about the HF biology. Until than, alopecia areata, telogen effluvium and androgenetic alopecia, will remain unsolved medical problems.

**Keywords:** Hair disorders; Hair follicle; Hair cycle; Alopecia areata; Androgenetic alopecia

## Introduction

The Hair Follicle (HF) is a vital component of mammalian skin. Thick scalp hair gives protection from actinic damage, while specialized nasal hairs, eyebrows and eyelashes have some environmental protective role. HF is also involved in sensory perception as a functionally distinct mechanosensory organ, giving the wide tactile sensation range of covered skin surface [1]. Beside the sensory activity role, hair exerts a function of thermoregulation, physical protection, tissue renewal and regeneration, and serves as an instrument of psychosocial communication [2].

Production of a hair is the primary and the most important function of HF. Hair growth does not take place continuously, but in a strictly defined cyclic model that includes periodic regeneration of follicles [3]. A synchronized cycle, seen in mammals, is preparing hair coat for environmental seasonal changes. The purpose of unsynchronized cycle which is seen in human species is not so obvious, but may include cleaning the skin surface of debris and parasites, and secretion of some chemical compounds via trichocytes [4].

Hair growth disorders can be attributed, at large, to a changes in the normal dynamic behaviour of the HF [5]. Since the cycle is regulated by various hormones and growth factors produced both inside and outside the follicles, even small environmental changes may lead to a shortening of the anagen, catagen phase induction, and increasing the number of telogen follicles [6].

Telogen effluvium, Androgenetic Alopecia (AGA), and Alopecia Areata (AA), the frequent hair loss disorders in clinical practice, exemplify how discrete cycling changes translate into significant clinical problems. Therefore, knowing the hair cycle is necessary for understanding the pathogenesis of hair diseases in general. Current hair treatment strategies are symptomatic and nonspecific so nowadays researches aim at developing new, targeted methods. Future strategies planning specific hair disorders therapy will be based on new and better knowledge about the HF biology.

## Hair Follicle: A Complex Miniorgan

The hair follicle is perfect and clinically relevant model for biology research. It represents a complex miniorgan that consists of multiple different cell populations which are distinct in their location, function and protein expression characteristics [4,7,8]. The HF is also a uniquely dynamic system that undergoes continuous cycling throughout adult life during which elements of its own morphogenesis are recapitulated [9]. This miniature organ during the normal human lifespan regenerates itself more than 8 to 10 times [2,10]. The transformation process of HF during the cycle arises under the dictates of an enigmatic oscillator system, "the hair cycle clock", and happens simultaneously with changes in the sebaceous gland, perifollicular dermis and subcutis [11-13].

Regarding the origin of its structures, the mature HF can be divided into the mesenchymal part, consisting of the Dermal Papilla (DP) with connective tissue sheath, and the epithelial part, including transient amplifying cells of the hair matrix that envelope the DP, hair shaft, inner root sheath and outer root sheath. Coordination between epithelial and mesenchymal portions of HF as well as bi-directional communication between the pilosebaceous unit and its innervation and vasculature is needed to maintain the cyclic hair follicle growth [14-16].

Functionally, HF can be divided into upper permanent part and

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deep lower part (including the hair bulb) which is subject of great changes during the cycle. Morphologically, the two parts are divided by a line that lies below the "bulge zone", an eminent structure at the site of the arrector pili muscle attachment. Bulge zone is the lowest part of the permanent HF segment and it is histological evident as unilateral thickening of the outer root sheath [17]. It is inhabited by epithelial stem cells, precursors of melanocytes, mast cells and Langerhans cells. Thanks to bulge stem cells, HF regenerates itself [18,19].

Stem Cells (SCs), which reside in the adult HF, are the skin's elixir for regenerating hair, but also for maintaining tissue homeostasis and repairing the epidermis [20]. SCs are nonspecific and pluripotent, having the ability to self-renew and differentiate into multiple cell types. The classical view of SCs depicts them as slowly cycling, relatively undifferentiated cells, with the ability both for self-regeneration and for supplying the rapidly dividing progenitor population [9]. Until now, melanocytic SCs, mesenchymal SCs, mast cells precursors, immature Langerhans cells and neuronal SCs were recognized [21-27].

The Dermal Papilla (DP) functions as the hair signaling center, and represents as a pocket of mesenchymal cells that lies at the hair base [28-30]. The number of DP cells and their secretory activity determines the size of the anagen hair bulb, thickness, length, and the hair shaft diameter [31-33].

The HF can be considered an essentially autonomous organ as it is able to grow after dissection from its neurovascular supply and transplantation into another part of the integument [34]. In addition, isolated human HF can be maintained in organ culture, exhibiting emergent properties of great biological relevance: controlled cell proliferation, differentiation, apoptosis and organ regeneration [35,36].

## Hair Cycle

The hair cycle is traditionally divided into the growth phase (anagen I-VI), regression phase (catagen) and resting phase (telogen) [2]. Hair loss has recently been recognized as a separate active process that is called exogen, while kenogen is a brief interval in which the HF remains empty [37].

Anagen phase has significantly higher metabolic activity among matrix keratinocytes that produce the hair fiber and inner root sheath. It is divided into six subphases defined by specific morphological criteria, one of which is called pro-anagen, including phases I to V. The met-anagen phase follows, which leads to hair growth on the epidermis surface [38]. During the end of the anagen, follicle lies deep, firmly anchored in the subcutaneous tissue, while the bulb changes the position by moving more superficial, below the insertion of the arrector pili muscle. Anagen phase ends with the involution of HF, apoptosis and terminal differentiation [39-41].

Catagen is the time of involution. It is a short transitional phase of cycle between anagen and telogen, which lasts between two and four weeks. In this phase follicle undergoes a series of morphological and molecular changes that are associated with apoptosis. The first sign of involution is termination of bulb melanin production. Matrix melanocytes stop producing melanin and absorb dendrites, and keratinocytes cease proliferation and undergo terminal differentiation [5]. During catagen, the population of stem cells located lateral to the dermal papilla is spared from apoptosis, allowing the reproliferation in the early anagen [33].

After regression, the follicle enters the telogen phase, which is expressed by relative rest in terms of activation and proliferation. Telogen phase lasts three to four months. The hair is no longer firmly anchored in the tissue, the link between lower part of hair and follicular sac disappears, and the hair falls out.

Recent researchers have found that the hair loss is controlled; active process that significantly differs from inaction during telogen [42]. Even the nature of the process is not yet solved; the morphology of hair root suggests that this process, called exogen, involves proteolytic events among cells in the base of telogen hair [43].

Kenogen is interval in which the hair follicle remains empty after the telogen hair loss and before the outbreak of a new anagen hair. Number of hairs in kenogen increases parallel with the number of vellus hair and reducing normal hair cycles, which is the main feature of AGA deterioration [44].

## Regulation of Hair Cycle

Since the majority of hair growth disorders occur as a result of the hair cycle changes, HF cycling is of profound clinical relevance. The concept that skin appendage formation at a given location and time is the result of interacting stimulatory and inhibitory signals exist for the long time; these not only consist of secreted molecules and changes in the expression of receptors, but also of changes in tissue biology and underlie prominent epigenetic controls [45,46].

By recent theory, the cycling is caused by rhythmic signal transducers changes in the bulge zone and dermal papilla region, with complex processes that are the consequences of follicular stem cells and dermal papilla cells interactions. Although HF 'system' is highly sensitive to extra-follicular neural and vascular signals thus increasing the level of system complexity, basic autonomous clock driving the HF cycle reside in the HF itself [10,15,47,48].

In any case, cellular and molecular events during differentiation of HF are controlled by a complex network of sequential activation of autocrine, paracrine and endocrine signaling pathways. This implies variations in the expression or activity of numerous cytokines, hormones, neurotransmitters, transcription factors and enzymes in the key compartments of HF.

The development of skin appendage such as hair is regulated by signaling molecules of the Wnt family, Fibroblast Growth Factor (FGF), transforming growth factor β (TGF-β), and Hedgehog pathways [49]. Hair follicle regeneration begins when signals from the mesenchyme-derived dermal papilla cells reach multipotent epidermal stem cells in the bulge region. Key inducers of anagen, the rapid growth hair cycle phase, including Wnt family proteins, β-Catenin pathway, noggin, and the transcription factor Stat3 [50]. Signal transducer and activator of transcription 3 (Stat3) plays critical roles in biological activities and contributes to HF growth. Stat3 is a latent cytoplasmic protein that conveys signals to the nucleus upon stimulation with IL-6, Epidermal Growth Factor (EGF), and many other cytokines/growth factors [51]. EGF probably triggers multiplication and proliferation of outer root sheath follicle cells that leads to the formation of new hair follicles. Another EGF role is probably anagen to catagen transition [52].

Wnt/β-catenin signaling is also known to positively affect mammalian hair growth. For example, HF stem cell differentiation is inhibited through a cross talk between Wnt/β-catenin and androgen signalling in dermal papilla cells from patients with androgenetic alopecia [53].

Sonic Hedgehog Proteins (Shh) and Hepatic Growth Factor (HGF) furthermore promote anagen development. Upregulation of Shh activity functions as a biologic switch that induces resting hair follicles

to enter anagen with consequent hair growth. Sonic hedgehog is one of the earliest genes found to be expressed in the hair placode. Continuous labeling of Shh-expressing cells showed that their progeny, with rare exceptions, form all structures in the HF. Shh expression is necessary also for the embryonic development of hair follicles [10,54-58].

The duration of anagen phase prolong Insulin Growth Factor-1 (IGF-1), Vascular Endothelial Growth Factor (VEGF) and Thyrotropin-Releasing Hormone (TRH). IGF-1 and IGF-2 are dose-dependent HF growth stimulators that also prevent the entry of follicles into catagen. It is possible that both of these growth factors are key physiological hair cycle regulators. Hypothesis is supported by a noticeable decline in the expression of mRNA for IGF-1 during early catagen [59,60].

TRH promotes hair-shaft elongation, prolongs the anagen and antagonizes its termination by Transforming Growth Factor-β2 (TGF-β2) [59]. Human HFs are direct targets of thyroid hormones and demonstrate that T3 and/or T4 modulate multiple hair biology parameters, ranging from HF cycling to pigmentation. Human scalp HFs are both a source and a target of TRH, which operates as a potent hair-growth stimulator [59,61].

Important anagen prolongator/catagen inhibitor is also the key polyamine-spermidine. Polyamines are multifunctional polycationic aliphatic amines which except serving as metabolic and nutrients regulators, also have been implicated as mediators of key cell functions, such as proliferation, migration and differentiation. Spermidine is a potent stimulator of human hair growth and a previously unknown modulator of human epithelial stem cell biology [62,63].

Finally, an important role in the regenerating hair follicle, play hair follicle stem cell marker nestin, located in the dermal papilla [64].

Anagen is terminated by the concurrent decreasing of anagen upholding factors (IGF-1, HGF, FGF-5S) and increasing of hair growth inhibitors, like members of the transforming growth factor (TGF- β1, TGF- β2), fibroblast growth factor. Inhibition of TGF-β2 activity at receptor level significantly impairs the maturation of follicles and folliculogenesis [65].

Dickkopf 1 (DKK-1) is involved in anagen-to-catagen transition in the hair cycle by regulating the activity of follicular keratinocytes. Moreover, it is observed that recombinant human DKK-1 (rhDKK-1) blocks canonical Wnt-mediated activation of β-catenin signaling and induces the proapoptotic protein Bax, resulting in apoptosis in outer root sheath keratinocytes [66]. Besides, the molecular interaction between downregulating effectors of TNF-asignalling and keratin 17 (K17) may be partly responsible for controlling catagen entry by regulating the rate of apoptosis [2]. Last decade has revealed a pivotal role for the TNF family ligand Ectodysplasin (Eda) in multiple steps of hair morphogenesis, from initiation to differentiation. Other members of the TNF superfamily such as Rank ligand, lymphotoxins and TNF have recently been linked with sp ecific aspects of skin appendage biology including hair shaft formation, and hair follicle cycling [49].

Other involved controlling anagen-catagen transformation molecules are neurotrophins NT-3, NT-4, as well as prolactin and retinoids. Prolactin participates in the regulation of anagen and telogen initiation, and is produced by the follicle itself. Recent studies identifie PRL as a major, clinically relevant, novel neuroendocrine regulator of both human keratin expression and human epithelial stem cell biology in situ [10,50,67,68].

The signaling that controls hair cycle resting phase is only partly understood. Telogen concurs with major gene activity changes and some proteins, like estrogen receptor, are noticeably increased, so this phase is not really quiescent as traditionally described. On the contrary telogen probably represents a key stage in hair cycle control.

The follicle in telogen arrest Bone Morphogenetic Protein 4 (BMP4) and 17-β estradiol [50]. BMPs are diffusible molecules involved in a variety of cellular interactions during development. It is proposed that about the stage of terminal division, the balance between BMP and BMP-inhibitory signals regulates survival and specification of hair-cell precursors [69].

Hair cycle resting phase is regulated also by cyclic epithelial Fibroblast Growth Factor (FGF18). Signaling FGF18 is expressed in a hair stem cell niche throughout telogen, and that it regulates the hair cycle through the non-growth phases. FGF affects follicular morphogenesis, participates in the regulation of mitotic activity and differentiation. Receptors for this growth factor have been identified in the follicular papilla and in the basal layer of epidermal keratinocytes [70].

The cycle stage, called exogen, has its own control mechanisms and it is presumed that its regulators are protease cathepsin L and Msx-2 [2].

Regarding hormonal influence, autocrine and paracrine factors produced by balding DP cells following Dihydrotestosterone (DHT)-driven alterations are believed to be key factors involved in male pattern baldness. IL-6 is upregulated in balding DP cells compared with non-balding DP cells. Dihydrotestosterone-inducible IL-6 inhibits elongation of human hair shafts by suppressing matrix cell proliferation and promotes regression of hair follicles [71]. 17β-estradiol (E2) inhibits hair shaft elongation and anagen prolongation in human female occipital hair follicles, whereas in male stimulates hair shaft elongation of frontotemporal scalp follicles [50].

In conclusion, even mostly through mouse models studies, our knowledge of the HF biology is continuously increasing. The promising research approach would be to screen the human HF for the expression of yet recognized mammalian clock genes [72].

## The Perspectives in Hair Growth Disorders Treatment

It is perfectly clear that a hair growth disorders can be attributed, at large, to a changes in the normal dynamic behaviour of the HF. Logical conclusion appears that the hair growth disorders could be treated by inhibiting premature transition to catagen phase and/or stimulating the transition from telogen into the anagen phase. Hovewer, the key elements of cycle regulation have not been identified. Although all yet recognized molecules offering themselves to be exploited as chemical tools for hair disorders treatment, still remains to synthesize drugs which would effectively manipulate the cycle [6].

Plenty therapeutic agents have been tried as a potent hair cycle-modulators with with variable efficacy and safety profiles. These agents among others include Cyclosporin A (CsA), topical immunophilin ligands, prostaglandin, ezetimibe and simvastatin, minoxidil, retinoids, estrogen, adenosin, calcitriol, estradiol, and prednisolon, zinc, and candida antigen [73-84].

For the most common hair disorders several agents are currently available. The first line of treatment in AGA is still minoxidil, despite of low success rate and speculative mechanism of action. The finasteride inhibits the production of the male hormone dihydrotestosterone but as with minoxidil, one's previous degree of hair loss returns when finasteride is discontinued [85]. Treatment options for female AGA

also include the androgen receptor antagonists spironolactone and cyproterone acetate [86,87]. Considering AA treatment, except for topical immunotherapy and corticosteroids, there are few published studies on long-term therapeutic success of avaliable therapeutic agents. Biologics have also been tried, but shown either development of AA or complete failure to respond to different TNF alpha inhibitors, including adalimumab, infliximab and etanercept [88-91].

Regarding perspectives, a studies have focused on various innovative pharmacologic targets, but also on some well known molecules. The role of prolactin receptor antagonists, as well as the regulators of thyroid hormones, deserves to be the subject of further research . Also, the relation between vitamin D levels, vitamin D receptor and hair cycling, specifically anagen initiation, represent an attractive area of research nowdays [92].

New drug treatment opportunities for AA also include use of drugs that block the NKGD-activating ligand and NKG2D receptor interaction, halt activated T cells, or modificate the cytokine network [93].

Calcitonin Gene-Related Peptide (CGRP) may award relative protection from interferon-γ-induced collapse of human hair follicle immune privilege and might help to retard AA progression [94]. Also, Fuzzy (fz), an autosomal recessive mutation that is involved in controlling catagen and anagen initiation, is an exciting target that maybe drives HF cycling [95].

Recently, autologous platelet-rich plasma (PRP) has attracted attention in plastic surgery and dermatology, for its ability to promote wound healing and to increase hair density [96].

The new studies also make a substantial contribution towards the development of transplantation therapy for skin and skin appendages, even the autologous transplantation of HF is already an accepted treatment for AGA [97].

There are also numerous ongoing studies, that explore the possibilities of using stem cells in treating hair growth disorders. Theoretically it would be possible to regenerate HF cultivating autologous dermal papilla cells and transplanting them to the hairless skin. This hypothetical process of breeding HF would enable the efficient compensation of the lost hair when all other options fail [98].

## Conclusion

Recent years have witnessed a considerable progress in the research focused on treatment of hair disorders, but with limited success. Therefore, one of the prime challenges of modern hair research is a more profound understanding of the molecular controls of hair follicle cycling. Common diseases such as alopecia areata, telogen effluvium and AGA, until than will remain the unsolved medical problems.

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