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 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, random 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 cyclic 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 undergoes a series of seasonal changes, determines the hair coat function, “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 epidermal 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].

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Hair follicles go through a cycle divided into three phases: anagen, catagen, and telogen. The anagen phase, the longest in the cycle, involves the active growth of the hair. Catagen is the transition phase where the follicle enters a resting state, and telogen is when the hair is shed.

Recent research has focused on understanding the mechanisms that control hair follicle regeneration. Key players in this process include Stem Cells (SCs), which reside in the adult hair follicle and are responsible for regenerating hair. These SCs are pluripotent and can give rise to multiple cell types, including melanocytes, keratinocytes, and fibroblasts.

The Dermal Papilla (DP) plays a crucial role in hair follicle development and maintenance. DP cells are responsible for producing growth factors and cytokines that stimulate hair growth. The DP also functions as a biologic switch that induces resting hair follicles to enter the growth phase.

EGF (Epidermal Growth Factor) is another key factor in the regulation of hair growth. EGF is responsible for stimulating the proliferation of hair follicle cells and promoting hair growth in mice. EGF is present in the anagen phase, including Wnt family proteins, β-Catenin pathway, noggin, and transforming growth factor β (TGF-β), and Hedgehog pathways.

Another EGF role is probably anagen to catagen transition. EGF probably triggers multiplication and proliferation of outer root sheath keratinocytes called dermal papilla cells reach multipotent epidermal stem cells during this period.

It is important to note that the hair follicle system is under epigenetic control. Recent research has shown that Sonic Hedgehog Proteins (Shh) and Hepatic Growth Factor (HGF) further promote anagen development.

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. Hair follicle regeneration begins when signals from the mesenchymal-dermed 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.

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 growth.
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 HF s 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 HF s 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-55) 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 play an important role in the regenerating hair follicle, play hair follicle stem cell marker nestin, located in the dermal papilla [64].

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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 identify 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. However, 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 prednisolone, 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 available 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 nowadays [92].

New drug treatment opportunities for AA also include use of drugs that block the NKG2D-activating ligand and NKG2D receptor interaction, halt activated T cells, or modify 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.

References


