

Biology of the Hair Follicle: The Basics

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The mammalian hair follicle represents a unique, highly regenerative neuroectodermal–mesodermal interaction system that contains numerous stem cells. It is the only organ in the mammalian organism that undergoes life-long cycles of rapid growth (anagen), regression (catagen), and resting periods (telogen). These transformations are controlled by changes in the local signaling milieu, based on changes in expression/activity of a constantly growing number of cytokines, hormones, neurotransmitters, and their cognate receptors as well as of transcription factors and enzymes that have become recognized as key mediators of hair follicle cycling. Transplantation experiments have shown that the driving force of cycling, the “hair cycle clock,” is located in the hair follicle itself. However, the exact underlying molecular mechanisms that drive this oscillator system remain unclear. These controls of hair follicle cycling are of great clinical interest because hair loss or unwanted hair growth largely reflect undesired changes in hair follicle cycling. To develop therapeutic agents for the management of these hair cycle abnormalities, it is critical to decipher and pharmacologically target the key molecular controls that underlie the enigmatic “hair cycle clock.”

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The hair follicle is one of the most complex miniorgans of the human body. This exquisitely productive protein fiber factory, which doubles as a sensory organ and serves as an instrument of psychosocial communication, excretion, and protection, undergoes cyclic transformations between phases of rapid growth (anagen), apoptosis-driven regression (catagen), and relative quiescence (telogen).¹ With this “hair cycle,” the follicle demonstrates the unique ability to cyclically regenerate itself during our lifetime, based on epithelial–mesenchymal interactions that drive waves of daughter cell populations, derived from resident epithelial, neural, and mesenchymal stem cells, into defined strata of differentiation.^{2,3}

Hair loss, as well as unwanted hair growth (hirsutism, hypertrichosis), is a widespread problem. According to one calculation, androgenetic alopecia on its own eventually affects approximately 50% of the world’s adult population.^{4,5} The hair shaft, the main product of the hair follicle, serves as an instrument of social communication, a protective device, and as a container for sequestering and excreting unwanted compounds.^{2,4}

Given the role of hair in psychosocial communication, (as a symbol of youth, health, fertility, and sexual potency) hair loss often has an underestimated psychosocial impact on an individual’s self-esteem, interpersonal relationships, and positioning within a society.⁶ Telogen effluvium, androgenetic alopecia, and alopecia areata, the 3 most frequent hair loss disorders encountered in clinical practice, exemplify how a range of negative psychological and social experiences translate into significant stressors that possibly conspire to further aggravate hair loss.⁶⁻⁹ And yet, there are still many general practitioners, and even dermatologists, who mistakenly view hair loss as a largely cosmetic problem.

Most hair growth disturbances seen in clinical practice primarily result from changes in hair follicle cycling. Androgenetic alopecia (AGA) in men and women is caused by a shortening of the anagen phase, with the clinical consequence of increased hair loss (telogen effluvium), accompanied by a transformation of terminal to vellus hair follicles. Vice versa, a prolonged anagen period can be seen in the conversion of vellus hair follicles into terminal hair follicles during hypertrichosis and hirsutism.^{2,4,10} Thus, a more profound understanding of the molecular controls of hair follicle cycling and its underlying disturbances promises to lead to the development of more effective “hair drugs,” one of the prime challenges of modern hair research.

Apart from the clinical importance of basic hair research,

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the hair follicle also offers an excellent, well-defined, easily manipulated and widely available biological test system for studying many key problems of general biology exemplarily (morphogenesis, proliferation, apoptosis, epithelial differentiation, pigmentation, angiogenesis, wound healing, stem cell biology, extracellular matrix remodeling, immune privilege, antiinfection defense, hormone synthesis, and metabolism).² To emphasize just 2 examples, the hair follicle's unusual immune system, which has been almost completely ignored by mainstream immunological research, offers a unique opportunity for studying the generation, maintenance, loss, and restoration of areas of relative immune privilege.^{11,12} Its amazing capacity for the generation of neurohormones and its sensitivity to key mediators of systemic stress responses designate it an ideal testing ground for probing the "brain-skin connection."¹³

Basic Data

The human scalp, eyebrows, and lashes consist of long, thick, medullated and pigmented terminal hair shafts, whereas the body is covered with short, thin and often unpigmented vellus hairs. Each of us displays an estimated total number of 5 million hair follicles, of which 80,000 to 150,000 are located on the scalp. The hair length is defined by the duration of anagen, which lasts for 2 to 6 years. Approximately 85% to 90% of all scalp hairs are within anagen follicles. Catagen lasts only for a few weeks, followed by the telogen phase, which lasts 2 to 4 months. The usual growth of scalp hair follicles (ie, the rate of hair shaft elongation) lies between 0.3 and 0.5 mm per day and is dependent on proliferation and subsequent follicular-type differentiation of the matrix keratinocytes in the hair bulb. The thickness of the hair shaft is related to the size of the hair bulb,¹⁰ which in turn is dictated by the volume of the hair follicle's mesenchymal component.¹⁴

Functional Hair Follicle Anatomy

The mature anagen hair follicle is composed of a multicylindrical stem that contains the hair shaft in its center and originates as an oval hair bulb proximally (Fig. 1).¹⁵ Embraced by the hair bulb lies an onion-like structure, called the dermal papilla (DP) (sometimes referred to as the "follicular papilla" to avoid confusion with the most superficial region of the dermis). The DP functions as the "command center" of the hair follicle and determines thickness, length, and likely the hair cycle itself.³

Each hair follicle consists of epithelial and mesenchymal parts. The epithelium is divided into an upper permanent region, distal to the arrector pili muscle (APM) and an inferior region (including the hair bulb), which dramatically reforms itself over the cycle (Fig. 1). Apart from serving as hair shaft factory, the anagen hair bulb also provides the hair shaft's trichocytes with melanin granules. Within the hair bulb is a population of cells with the highest proliferation rate in the human body: the keratinocytes of the hair matrix. These can differentiate into trichocytes, or cells of the inner root sheath

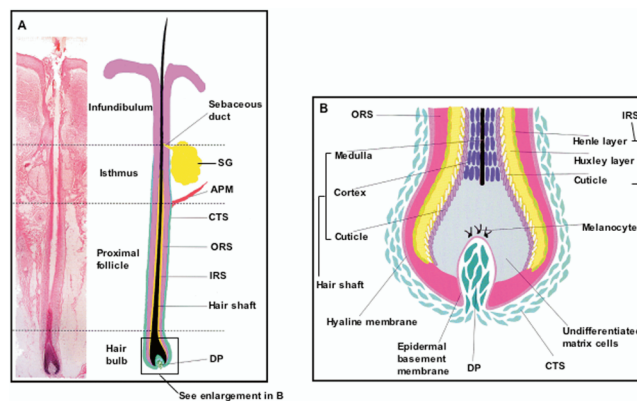


Figure 1 A, Anagen VI hair follicle. Histologic longitudinal section on the left hand side. Schematic drawing of an anagen VI follicle with anatomical details on the right hand side. B, Anagen VI hair bulb in detail (enlargement of schematic drawing in A). APM, arrector pili muscle; CTS, connective tissue sheath; DP, dermal papilla; IRS, inner root sheath; ORS, outer root sheath; SG, sebaceous gland (modified after Whiting, 2004).¹⁵

(IRS). The outer root sheath (ORS), hair matrix, and hair shaft derive from epithelial stem cells in the bulge area, functioning as a pluripotent epithelial stem cell population for the skin (Fig. 1).¹⁶⁻¹⁸ The bulge stem cells not only form the secondary hair germ, which is involved in the generation of the new hair, but they can even be reconstituted by dedifferentiating keratinocytes in response to wounding of the bulge area.¹¹

The size of the anagen hair bulb, the duration of anagen, and the hair shaft diameter are determined by the volume, the number of cells, and the secretory activity of the DP.^{19,20} Stringent coordination between epithelial and mesenchymal portions is needed to maintain the cyclic hair follicle growth.² Mesenchymal stem cells within the tissue sheath serve as a recruitment pool for new DP cells. Apart from mesenchymal stem cells, the hair follicle also contains mast cell precursors²¹⁻²³ and neuronal stem cells, the latter of which can develop into neurons and blood vessels.²⁴ The large numbers of stem cells make the hair follicle a fascinating organ in the field of stem cell biology.

The Hair Cycle

Hair cycling is the rhythmic change of the hair follicle through phases of growth (anagen), regression (catagen), and rest (telogen). *Synchronized* hair follicle cycling (in mammals) prepares the hair coat for seasonal changes in habitat conditions as well as procreational activities.² The purpose of hair cycling in mammals with individual (*asynchronous*) follicle waves (eg, humans) is not as obvious, but may include cleaning the skin surface of debris and parasites, and excretion of deleterious chemicals by encapsulation within trichocytes.² In addition, follicle cycling might serve as a regulator of paracrine or even endocrine secretion of hormones and growth modulators produced within the follicle and secreted into the skin or circulation.³ Finally, hair follicle cycling may act as a

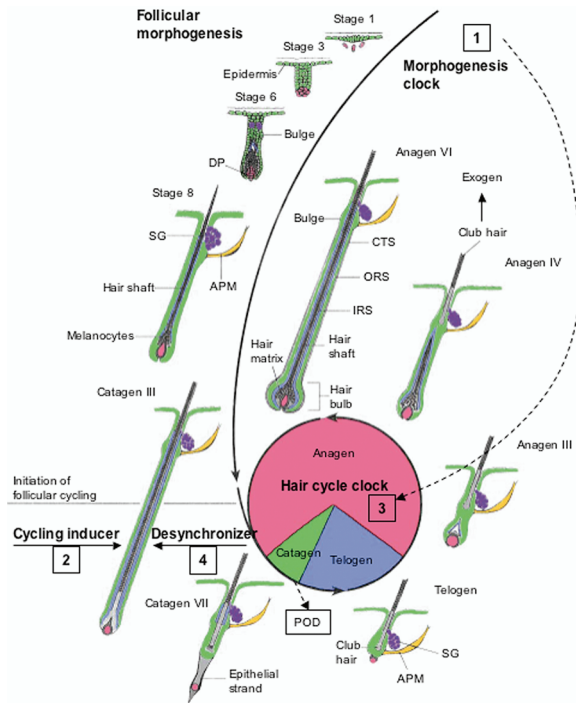


Figure 2 Chronobiology of the hair follicle. Every hair follicle is controlled by different timing devices. 1, morphogenesis clock; 2, cycling inducer; 3, hair cycle clock; 4, desynchronizer. The timing devices could be connected with each other and share molecular timing mechanisms (for example the hair cycle clock, which could be “set” already during morphogenesis and therefore incorporate parts of the morphogenesis clock). APM, arrector pili muscle; CTS, connective tissue sheath; DP, dermal papilla; IRS, inner root sheath; ORS, outer root sheath; SG, sebaceous gland; POD, programmed organ deletion (modified after Paus and coworkers, 1999).⁴

safe-guarding system against malignant degeneration by protecting rapidly dividing keratinocytes from oxidative damage by deletion during catagen.³

Anagen (the growth phase of the hair cycle) is divided into 6 different stages defined by specific morphologic criteria (Fig. 2).²⁵ The recurrent formation of the hair follicle displays morphologic and molecular analogies to fetal hair follicle morphogenesis.²⁶ Many molecular key regulators of hair biology (members of the transforming growth factor (TGF)- β /BMP family, WNTs, Shh, and neurotrophins) not only activate morphogenesis but also regulate anagen induction and duration.²⁷⁻²⁹ During anagen, epithelial stem cells differentiate into at least 8 different cell lines, forming the ORS, companion layer, Henle’s layer, Huxley’s layer, cuticle of the IRS, cuticle of the hair shaft, shaft cortex, and shaft medulla. The ORS probably is established by the downward migration of the regenerating epithelium.³⁰ IRS and hair shaft are tied together by their interlocked cuticle structures. The IRS-packaged shaft uses the innermost layer of the ORS (companion layer) as a slippage plane for orientation to move straight toward the skin surface.^{31,32}

Epithelial stem cells are located in the bulge area of the follicle. From there, stem cells ascend into the interfollicular epidermis and descend to differentiate into ORS cells. One

hypothesis suggests that derivatives of stem cells from the bulge area reach the hair germ, transform into matrix keratinocytes, and rebuild the hair shaft.³³ During catagen, this stem cell population is situated lateral to the DP, being secure from apoptosis and able to proliferate again in early anagen to produce a new hair shaft.

Hair shaft synthesis and pigmentation only take place in anagen. The cyclic reconstruction of an intact hair follicle pigimentary unit works optimally in scalp follicles during the first 10 hair cycles, meaning until approximately 40 years of age. Afterward there appears to be a genetically regulated exhaustion of the pigimentary potential of each individual follicle leading to “hair greying.”³⁴ Apart from the melanocortins, α -MSH and ACTH and also stem cell factor, nerve growth factor (NGF), and hepatocyte factor (HGF) are involved in the regulation of pigmentation.³⁵⁻³⁷

The anagen period ends with a highly controlled involution of the hair follicle resulting in apoptosis and terminal differentiation. This process, called catagen, consists of 8 different stages. The hair follicle epithelium, neuroectodermal cell populations (melanocytes and Merkel cells), the mesenchyme, the perifollicular vascular system, and the follicular innervation all show cyclic changes in proliferation, differentiation, and apoptosis.³⁸⁻⁴⁰

The first sign of catagen is the cessation of melanin production in the hair bulb. Clinically, telogen follicles have a depigmented proximal hair shaft (club hair). Melanocytes involved in apoptosis are recruited from melanocytic stem cells of the secondary hair germ.³⁵ The programmed cell death of these stem cells might be an important factor for hair greying.⁴¹ In contrast to the ORS and the hair matrix (with their huge numbers of apoptotic cells), there is no programmed cell death in the DP because of the expression of the apoptosis suppressor *bcl-2*.^{38,42}

During catagen, the DP condenses, moves upward, and comes to rest beneath the bulge. The hairless gene (*Hr*) is responsible for the strong connection between the condensing DP and the diminishing hair follicle epithelium in catagen and telogen follicles. In its function as a safeguard of apoptosis control during catagen⁴³ *Hr* operates as a negative transcription repressor and insures that apoptosis only takes place in certain tissues in the correct order. The *Hr* gene encodes a zinc finger transcription factor whose disruption prevents the DP from ascending and interacting with stem cells of the bulge, resulting in permanent alopecia during the first catagen period. This effect also takes place in congenital atrichia with a missense mutation in the zinc-finger domain of the *Hr* gene.⁴⁴ Similarities between the phenotype of hairless knockout mice and those with mutations of the vitamin D or RXR alpha receptor (a retinoid receptor)⁴⁵ suggest that *Hr*, vitamin D, and RXR all use the same signaling pathways to activate catagen.

After regression, the hair follicle enters telogen, a phase of relative quiescence regarding proliferation and biochemical activity. The follicle remains in this stage until it is reactivated by intrafollicular and extrafollicular signals. The unpigmented club hair often remains stuck in the hair canal. In mice, this process takes place mainly in anagen IV follicles.

This hair cycle stage, named exogen, has its own regulations and control mechanisms.⁴⁶ Factors thought to participate in exogen regulation are the protease cathepsin L and Msx-2.⁴⁷

To our knowledge, the hair follicle has only one irreversible physiologic mechanism to break out of the hair cycle: programmed cell death. In the mouse, a few isolated hair follicles demonstrate perifollicular inflammation that destroys the bulge region and therefore the follicle's capacity to cycle.⁴⁸ This targeted destruction probably serves to remove degenerated and nonfunctioning hair follicles. It could also play a role in forms of scarring alopecia, in the physiologic, slowly progressing loss of hair follicles in the aging human scalp,¹⁰ or during the final stages of androgenetic alopecia.⁴

Locally Produced Growth Factors, Hormones, and Proteins

The hair follicle is not only a very productive source of pigmented hair shafts (keratins and melanin) but also of many growth-, pigment-, and immunomodulators. It can synthesize or metabolize an enormous number of hormones, neurotransmitters, neuropeptides and growth factors. For example, growth factors like TGF- β 1/2, IGF1, HGF^{28,49,50} and hormones like CRH, prolactin, cortisol, and melatonin⁵¹⁻⁵³ are all synthesized in the hair follicle. Androgens are metabolized to dihydrotestosterone or 17 β -estradiol, and proopiomelanocortin to ACTH, alpha-MSH, or β -endorphin within the hair follicle.² The exact biologic functions of the locally generated factors are not well understood. The hair cycle dependence of this great productive activity, as well as the expression of the specific matching receptors, suggests that these actions function as autocrine and paracrine mechanisms.

As the hair follicle is regulated by diverse systemic extracellularly generated hormones and growth factors and by a variety of self-generated substances, it is no surprise that even small changes in this sensitive milieu can lead to a shortening of anagen, an induction of catagen, and to an increased number of telogen follicles, resulting in telogen effluvium.

Key Factors in Hair Follicle Cycling

It is now widely accepted that hair follicle transformation during cycling is caused by alterations in the local signaling milieu. There are key regulators that build up local gradients with competing stimulating and inhibitory signals (Fig. 2). Rhythmic changes of signal transducers in the key compartments of the follicle (bulge, secondary hair germ, dermal papilla) are thought to drive cyclic hair follicle transformation.

Key factors known to induce anagen include soluble proteins of the WNT family, activation of the corresponding β -Catenin pathway, noggin, and the transcription factor STAT3.^{54,55} Sonic hedgehog, HGF, and FGF7 (KGF) support this process and stimulate the subsequent steps of anagen development.^{50,56,57} DP-induced keratinocyte differentiation occurs via β -catenin/lef1 signaling.⁵⁸ Hair shaft differentia-

tion seems to be mediated, at least in part, by desmoglein.⁵⁹ WNT signals (WNT3a and WNT7a) are capable of keeping the dermal papilla in anagen. IGF1, HGF, glial cell-derived neurotrophic factor, and vascular endothelial growth factor can prolong anagen (Fig. 3).^{39,47,50,54,60-64}

During the anagen–catagen transformation of the hair follicle, the transcription factor Hr is a central, indispensable element of navigation and coordination of signal transduction. Loss of Hr function leads to rapid degeneration of the hair follicle.⁶⁵ Certain members of the homeobox gene family also seem to control some of the named factors. Msx-deficient mice, for example, show premature anagen termination, prolonged catagen and delayed entry into the next hair cycle.⁴⁷ TGF- β 1, TGF- β 2, FGF-5, the neurotrophins NT3, NT4, BDNF, p75, also retinoids, prolactin, and several other candidates like thrombospondin 1 and vanilloid receptor 1 induce catagen.^{28,52,66-72} Interestingly, there are some factors that have been shown to exert their catagen inductive activity at least in part via TGF β 2. These include retinoids, IFN- γ and BDNF.^{67,73,74} Under the influence of BMP4 and 17 β -Estradiol (E2) the hair follicle stays in telogen (Fig 3).^{74,75}

An essential inhibition/disinhibition system in anagen development is the neutralization of BMP4 by noggin.⁷⁴ Anagen is terminated by the upregulation of hair growth inhibitors (TGF- β 1, TGF- β 2, FGF-5) and downregulation of anagen preserving factors (IGF-1, HGF, FGF-5S) at the same time. The fuzzy mutation, associated with congenital atrichia, has recently been implicated in controlling both anagen and catagen initiation (Fig. 3).⁷⁶

It seems confusing that some hair growth modulators have growth-stimulating effects during morphogenesis but inhibitory effects in the hair cycle. TGF- β 2, follistatin, and NT3, for example, accelerate hair follicle morphogenesis, but are catagen-inducing in mature anagen follicles.^{3,27,55,77}

Interestingly, many molecular hair growth manipulators also are known as key factors in wound healing (for example, members of the FGF family, EGF, IGFs, HGF, TGF- β , VEGF, NGF, and interleukins) and as critical components in the development of teeth and feathers.⁷⁸⁻⁸⁰

Some of the very potent signal transducers of anagen induction or termination could lead to specific pharmacologic agents that would manipulate the human hair cycle and treat hair growth disturbances more efficiently. However, none of these factors seems to be a key element of the hair cycle clock itself, which directs the factors to execute the cyclic hair follicle transformations.

Sex Hormones as Potent Hair Growth Modulators

Androgens are very potent, yet nonessential, hair growth modulators. In hair growth regulation, different types of hair follicles in diverse body areas have different underlying cycle control mechanisms. A common example is the paradoxical effect of androgens on terminal follicles of the scalp compared with vellus follicles on other parts of the body. Androgens stimulate hair growth in nonscalp areas like the beard,

Molecular players in hair cycle control

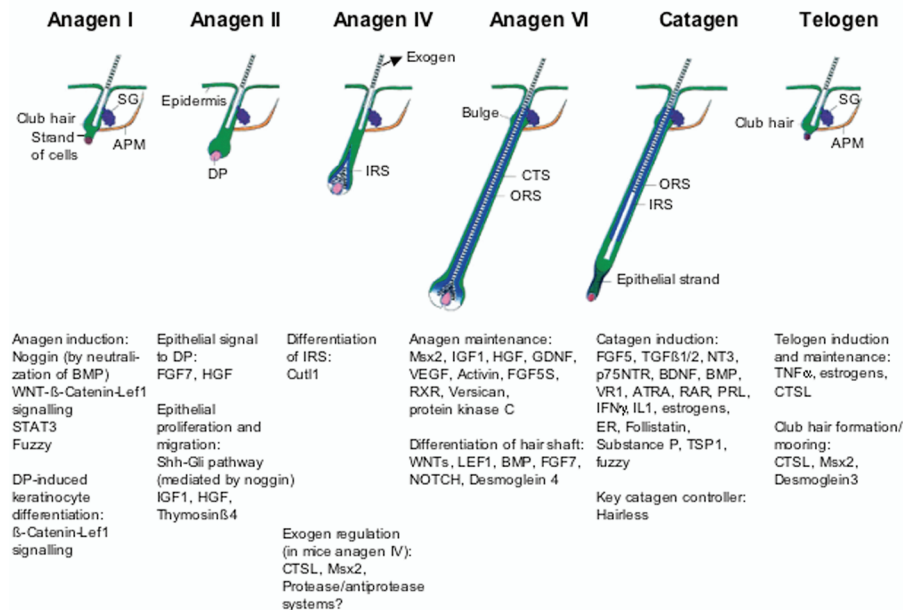


Figure 3 Molecular players in hair cycle control. The figure shows key factors of hair follicle cycling being employed by the HCC to drive the hair follicle from one stage to the next one or to keep it in a given stage. However, none of the named mediators are known to be key elements of the central pacemaker. (For references, see text,^{2,47,61-64}). APM, arrector pili muscle; CTS, connective tissue sheath; DP, dermal papilla; IRS, inner root sheath, ORS, outer root sheath; SG, sebaceous gland; BMP, bone morphogenic protein; WNT, wingless; STAT3, signal transducer and activator of transcription 3; FGF7, fibroblast growth factor 7; HGF, hepatocyte growth factor; Shh, sonic hedgehog; IGF1, insulin like growth factor; CTSL, cathepsin L; cutl, transcriptional repressor; GDNF, glial cell line-derived neurotrophic factor; BDNF, brain-derived nerve growth factor; VEGF, vascular endothelial growth factor; ATRA, all-trans retinoid acid; RXR, retinoid x receptor; RAR, retinoid acid receptor; NGF, nerve growth factor; Lef1, lymphoid enhancer-binding protein; TGF β , transforming growth factor β ; p75NTR, low affinity neurotrophin receptor; PRL, prolactin; PRLR, prolactin receptor; IFN γ , interferon γ ; ER, estrogen receptor; IL1, interleukin 1; VR1, vanilloid receptor 1; TNF α , tumor necrosis factor α ; TSP1, thrombospondin 1; (modified after Paus and Peler, 2003).

breast or abdomen (at least in part by upregulation of gene expression and secretion of IGF1).⁴⁹ In contrast, androgen sensitive hair follicles of the scalp become smaller under the influence of androgens (miniaturization) leading to the typical changes of androgenetic alopecia.^{10,81} Inhibition of hair growth in the fronto-temporal region can be demonstrated by TGF- β stimulation.⁸² Current theories suggest that scalp and body hair follicles react to androgen stimulation differently by triggering programmed gene regulation of defined hormones. These gene programs lead to potent hair growth stimulation in one follicle population and growth inhibition in others.⁸⁰

Localization and gender-specific regulation of hair follicle gene expression has also been demonstrated for estrogens. In vitro experiments show an inhibition of hair shaft elongation and anagen prolongation in human female occipital hair follicles, whereas in male frontotemporal scalp follicles, 17 β -estradiol (E2) stimulates hair shaft elongation.⁷⁵ In vivo E2 also leads to anagen prolongation in human hair follicles.⁸³ The role of estrogens in rodents, however, is completely different. Topical E2 induces not only premature catagen in mice, but also arrests murine hair follicles in telogen.^{84,85}

Stress and Hair Loss

Many patients notice increased hair loss after stress. Recently, chronic stress in mice was associated with highly significant inhibition of hair growth, increased mast cell degranulation, and perifollicular inflammation.^{8,86} Furthermore, in vivo and in vitro studies reveal that typical stress mediators like substance P, cortisol, ACTH, and prolactin inhibit hair growth.^{7,51,52} According to Botchkarev, neural signals can modulate hair growth but are not essential for the hair cycle.⁸⁷ Human isolated hair follicles directly respond to CRH stimulation (similar to the hypothalamic-pituitary-adrenal axis) with cortisol synthesis and neuroendocrine feedback loops.⁵¹ All of these data support the postulate that stress plays an important role in the development of hair loss.

The Hair Cycle Clock

Hair transplant experiments clearly show that follicles transferred from one place to another keep their original cycling behavior.^{2,25,88} Even isolated scalp hair bulbs go through the stages of anagen–catagen transformation in vitro^{60,89} without

the need for intact innervation, vascularization, or other extrafollicular components. These observations indicate that the basic oscillator system, which drives hair follicle cycling, is located in the skin, and likely the hair follicle itself. Based on an oscillating molecular pacemaker, this obscure hair cycle clock is responsible for the programmed cyclic transformation of the hair follicle and its surrounding structures (Fig. 2). There are differing theories about how the hair cycle clock works. In 1954, Chase postulated there could be endogenous mitotic inhibitors that accumulate during anagen, finally halting the anagen phase. Because of the subsequent endogenous mitotic inhibitors downregulation, the hair follicle is disinhibited, entering a new anagen phase.⁹⁰ Stenn later suggested an inhibition/disinhibition system that resides in the epithelial stem cell-containing bulge region as the central pacemaker.⁹¹ A current hypothesis locates the hair cycle clock in the DP (linked to the cell cycle of dermal fibroblasts). During the resting time of the cell cycle (G_0/G_1), there could be so-called “papilla morphogens,” that stimulate matrix keratinocytes and follicular pigmentation (as well as suppress apoptosis). In this mode, the beginning of the cell cycle (S, G2, M) would stop the secretion of morphogens (meaning anagen would be stopped by a lack of suppression of apoptosis) and lead to catagen transformation. While leaving the cell cycle, dermal fibroblasts would resume the secretion of morphogens and thereby induce a new anagen stage.¹⁹ None of these speculative theories has been proven. Figure 2 illustrates hair follicle morphogenesis and the hair cycle. Analogies in the regulation of morphogenesis and the adult hair cycle point to a connection between their underlying pacemakers. The equivalent of an inhibition/disinhibition system can be seen in the hair cycle inducer/desynchronizer system.

Management of Hair Growth Disorders: Principles, Current Options, and Future Prospects

The majority of the known hair growth disorders are a consequence of changes in the hair cycle. The most frequent growth disorder in men and women is androgenetic alopecia (AGA). AGA is characterized by a shortening of the anagen phase and a prolongation of telogen, combined with miniaturization of hair follicles.¹⁰ These changes are androgen dependent and genetically determined. The underlying molecular mechanism depends on the conversion of testosterone to dihydrotestosterone by 5α -reductase. Dihydrotestosterone binds to androgen receptors of the hair follicle and leads to a shortening of anagen and a reduced cell hair matrix volume.^{92,93} Men and women with AGA have a higher activity of 5α -reductase type II and androgen receptors in the frontal scalp area compared with the occipital area.⁹⁴

The common opinion that miniaturization from terminal to vellus follicles is a slow process over several hair cycles has been challenged by the hypothesis of an androgen-induced emigration of fibroblasts from the dermal papilla into the connective tissue sheath. A migration of this sort has been observed in mice,¹⁴ and it seems plausible that androgens

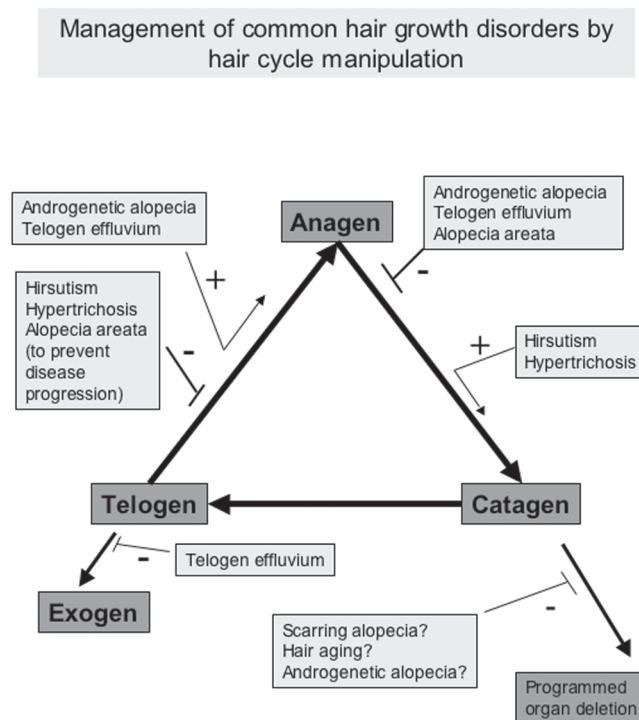


Figure 4 Common hair growth disorders frequently arise from changes of the hair cycle. They can be managed by manipulating the length of the different hair cycle stages. Anagen: growth phase with active production of a pigmented hair shaft, maximal length and volume of the follicle; catagen: apoptosis-driven phase of hair cycle regression with cessation of hair shaft production and pigmentation and club hair formation; telogen: phase of relative quiescence of hair follicle activity, while the club hair rests loosely anchored in the hair canal; exogen: active shedding of club hair which usually occurs in anagen IV in mice but can also take place in telogen; hair aging: number of predetermined hair cycles in life time could be slowed down; +, stimulate; -, inhibit (modified after Paus and coworkers, 1999).¹⁹

may influence a fibroblast transfer that leads to an increase or decrease of the dermal papilla volume. Clinically visible as terminal-to-vellus or vellus-to-terminal hair follicle conversion, this would explain the androgen dependent genesis of alopecia or hirsutism. Whiting also suggested the concept that miniaturization is an abrupt, large-step process which can be reversed in a single cycle. In his opinion, a marked reduction of DP cells leads to a reduction of DP size, follicle size and anagen length. This theory would explain the prompt appearance of vellus hairs in some cases of AGA, the rapid regrowth of terminal follicles after finasteride treatment, and the sudden vellus-to-terminal switch of body hairs at puberty.⁵

Figures 4 and 5 illustrates how common hair growth disorders can be managed by manipulating the hair cycle at different time points. AGA and telogen effluvium (caused by drugs, endocrine, and metabolic disturbances) could be treated by inhibiting premature catagen transition and/or stimulating the telogen/anagen transformation. Catagen induction and arrest of follicles in a prolonged telogen stage may be a therapy for hypertrichosis and hirsutism.

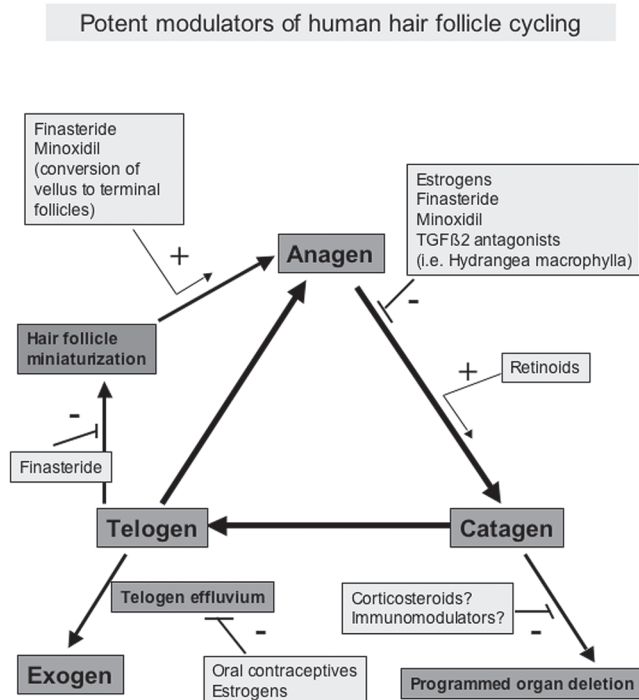


Figure 5 Potent modulators of human hair follicle cycling. The scheme demonstrates the mechanism of action of well-known drugs and conceivable future treatment options in the management of common hair cycle disorders like androgenetic alopecia and telogen effluvium. It shows how the hair cycle can be manipulated effectively at different hair cycle stages. +, stimulate; -, inhibit. (For references, see text.⁴)

Several agents are currently available for the treatment of AGA in both men and women. These are discussed at length elsewhere in this issue. Besides these, several theoretical approaches to alopecia therapy exist.

Hormones (eg, thyroid hormones and prolactin) have been underestimated in their function as hair growth modulators. Only small disturbances in the plasma level of T3 and T4 can lead to an associated telogen effluvium.¹⁰ Prolactin participates in the regulation of catagen and anagen initiation and is produced in the hair follicle itself.^{52,95} Thus, the role of prolactin receptor antagonists and thyroid hormone regulators in the pathogenesis of AGA and telogen effluvium deserves to be further explored.

Among the many molecular mediators of intra- and perifollicular signaling, neurotrophins have garnered particular interest. Neurotrophins 3, 4, and brain-derived neurotrophic factor (BDNF) have been shown to stimulate premature catagen induction. BDNF (and its receptor tyrosine kinase B) are expressed in a hair cycle-dependent manner in human hair follicles and act (at least in part) via TGF β 2 upregulation.⁷³ This observation suggests hair growth modulation by tyrosine kinase B mediated signaling as a possible future therapeutic strategy.

A better understanding of the stem cell rich bulge region and the induction of secondary hair germ by DP signals could help narrow the search for tools that would limit the hair follicle miniaturization and loss seen in AGA. Nevertheless,

all of the aforementioned hormones, factors and mediators simply execute the instructions derived from the overlying oscillator system. The discovery of the enigmatic hair cycle clock, more than 50 years after Chase's landmark work, is still the greatest challenge in hair research, and the one most likely to result in satisfactory treatment options in the field of hair growth disorders.

References

1. Dry FW: The coat of the mouse (*mus musculus*). *J Genet* 16:187-340, 1926
2. Stenn KS, Paus R: Controls of hair follicle cycling. *Physiol Rev* 81:449-494, 2001
3. Paus R, Foitzik K: In search of the "hair cycle clock": A guided tour. *Differentiation* 72:489-511, 2004
4. Paus R, Cotsarelis G: The biology of hair follicles. *N Engl J Med* 341:491-497, 1999
5. Whiting DA: Possible mechanisms of miniaturization during androgenetic alopecia or pattern hair loss. *J Am Acad Dermatol* 45:S81-S86, 2001
6. Hadshiew I, Foitzik K, Arck P, et al: Burden of hair loss: Stress and the underestimated psychosocial impact of telogen effluvium and androgenetic alopecia. *J Invest Dermatol* 123:455-457, 2004
7. Arck PC, Handjiski B, Hagen E, et al: Indications for a "brain-hair follicle axis (BHA)": Inhibition of keratinocyte proliferation and up-regulation of keratinocyte apoptosis in telogen hair follicles by stress and substance P: *FASEB J* 15:2536--2538, 2001
8. Arck PC, Handjiski B, Peters EM, et al: Stress inhibits hair growth in mice by induction of premature catagen development and deleterious perifollicular inflammatory events via neuropeptide substance P-dependent pathways. *Am J Pathol* 162:803-814, 2003
9. Arck PC, Handjiski B, Kuhlmei A, et al: Mast cell deficient and neurokinin-1 receptor knockout mice are protected from stress-induced hair growth inhibition. *J Mol Med* 83:386-396, 2005
10. Dawber R: *Diseases of the Hair and Scalp*. Oxford, Blackwell Science, 1997
11. Ito M, Kizawa K, Hamada K, et al: Hair follicle stem cells in the lower bulge form the secondary germ, a biomedically distinct but functionally equivalent progenitor cell population, at the termination of catagen. *Differentiation* 72:548-557, 2004
12. Paus R, Nickoloff BJ, Ito T: A hairy privilege. *Trends Immunol* 26:32-40, 2005
13. Paus R, Theoharides TC, Arck PC: Neuroimmunoendocrine circuitry of the "brain-skin connection." *Trends Immunol* (in press)
14. Tobin DJ, Gunin A, Magerl M, et al: Plasticity and cytokinetic dynamics of the hair follicle mesenchyme: Implications for hair growth control. *J Invest Dermatol* 120:895-904, 2003
15. Whiting DA: *The Structure of the Human Hair Follicle. Light Microscopy of Vertical and Horizontal Sections of Scalp Biopsies*. Pfizer, Canfield Publishing, 2004
16. Cotsarelis G, Sun TT, Lavker RM: Label-retaining cells reside in the bulge area of pilosebaceous unit: Implications for follicular stem cells, hair cycle and skin carcinogenesis. *Cell* 61:1329-1337, 1990
17. Morris RJ, Liu Y, Marles L, et al: Capturing and profiling adult hair follicle stem cells. *Nat Biotech* 22:411-417, 2004
18. Blanpain C, Lowry WE, Geoghegan A, et al: Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. *Cell* 118:635-648, 2004
19. Jahoda CA, Reynolds AJ: Dermal-epidermal interactions. Adult follicle-derived cell populations and hair growth. *Dermatol Clin* 14:573-583, 1996
20. Paus R, Müller-Röver S, Botchkarev VA: Chronobiology of the hair follicle: Hunting the "hair cycle clock". *J Invest Dermatol Symp Proc* 4:338-345, 1999
21. Oliver RF: Whisker growth after removal of the dermal papilla and lengths of follicle in the hooded rat. *J Embryol Exp Morph* 15:331-347, 1966

22. Jahoda CA: Cell movement in the hair follicle dermis—more than a two-way street?. *J Invest Dermatol* 121:1267-1275, 2003
23. Kumamoto T, Shalheveth D, Matsue H, et al: Hair follicles serve as local reservoirs of skin mast cell precursors. *Blood* 102:1654-1660, 2003
24. Amoh Y, Li L, Katsuo K, et al: Multipotent nestin-positive keratin-negative hair follicle bulge stem cells can form neurons. *Proc Natl Acad Sci USA* 102:5530-5534, 2005
25. Paus R, Christoph T, Müller-Röver S: Immunology of the hair follicle: A short journey to terra incognita. *J Invest Dermatol Symp Proc* 4:226-234, 1999
26. Müller-Röver S, Handjiski B, van der Veen C, et al: A comprehensive guide for the accurate classification of murine hair follicles in distinct hair cycle stages. *J Invest Dermatol* 117:3-15, 2001
27. Foitzik K, Paus R, Doetschmann T, et al: The TGF β 2 isoform is both a required and sufficient inducer of murine hair follicle morphogenesis. *Dev Biol* 212:278-289, 1999
28. Foitzik K, Lindner G, Mueller-Roever S, et al: Control of murine hair follicle regression (catagen) by TGF-beta1 in vivo. *FASEB J* 14:752-760, 2000
29. Schmidt-Ullrich R, Paus R: Molecular principles of hair follicle induction and morphogenesis. *Bioessays* 27:247-261, 2005
30. Reynolds AJ, Jahoda CAB: Hair follicle stem cells? A distinct germinative epidermal cell population is activated in vitro by the presence of hair dermal papilla cells. *J Cell Sci* 99:373-385, 1991
31. Ito M: The innermost layer of the outer root sheath in human anagen hair follicle. Light and electron microscopy study. *Arch Dermatol Res* 279:112-119, 1986
32. Orwin DFG: Cell differentiation in the lower outer root sheath of the romney wool follicle a companion cell layer. *Aust J Biol Sci* 24:989-999, 1971
33. Panteleyev AA, Jahoda CA, Christiano AM: Hair follicle predetermination. *J Cell Sci* 114:3419-3431, 2001
34. Van Neste D, Tobin DJ: Hair cycle and hair pigmentation: Dynamic interactions and changes associated with aging. *Micron* 35:193-200, 2004
35. Tobin DJ, Paus R: Graying gerontobiology of the hair follicle pigmented unit. *Exp Gerontol* 36:29-54, 2001
36. Kausar S, Thody AJ, Schallreuter KU, et al: A fully functional proopiomelanocortin /melanocortin-1 receptor system regulates the differentiation of human scalp hair follicle melanocytes. *Endocrinology* 146:532-543, 2005
37. Slominski A, Tobin DJ, Shibahara S, et al: Melanin pigmentation in mammalian skin and its hormonal regulation. *Physiol Rev* 84:1155-1228, 2004
38. Lindner G, Botchkarev VA, Botchkareva NV, et al: Analysis of apoptosis during hair follicle regression (catagen). *Am J Pathol* 151:1601-1617, 1997
39. Mecklenburg L, Tobin DJ, Müller-Röver S, et al: Active hair growth (anagen) is associated with angiogenesis. *J Invest Dermatol* 114:909-916, 2000
40. Peters EM, Botchkarev VA, Botchkareva NV, et al: Hair cycle-associated remodeling of the peptidergic innervation of murine skin and hair growth modulation by neuropeptides. *J Invest Dermatol* 116:236-245, 2001
41. Nishimura EK, Granter SR, Fisher DE: Mechanisms of hair greying: incomplete melanocyte stem cell maintenance in the niche. *Science* 307:720-724, 2005
42. Müller-Röver S, Rossiter H, Lindner G, et al: Hair follicle apoptosis and Bcl-2. *J Invest Dermatol Symp Proc* 4:272-277, 1999
43. Panteleyev AA, Paus R, Christiano AM: Patterns of hairless (hr) gene expression in mouse hair follicle morphogenesis and cycling. *Am J Pathol* 157:1071-1079, 2000
44. Ahmad W, Faiyaz ul Haque M, Brancolini V, et al: Alopecia universalis associated with a mutation in the human hairless gene. *Science* 279:720-724, 1998
45. Zlotogorski A, Hochberg Z, Mirmirani P, et al: Clinical and pathologic correlations in genetically distinct forms of atrichia. *Arch Dermatol* 139:1644-1645, 2003
46. Milner Y, Sudnik J, Filippi M, et al: Exogen, shedding phase of the hair growth cycle: Characterization of a mouse model. *J Invest Dermatol* 119:639-644, 2002
47. Ma L, Liu J, Wu T, et al: 'Cyclic alopecia' in Msx2 mutants: Defects in hair cycling and hair shaft differentiation. *Development* 130:379-389, 2003
48. Eichmüller S, van der Veen C, Moll I, et al: Clusters of perifollicular macrophages in normal murine skin: Physiological degeneration of selected hair follicles by programmed organ deletion. *J Histochem Cytochem* 46:361-370, 1998
49. Itami S, Kurata S, Takayasu S: Androgen induction of follicular epithelial cell growth is mediated via insulin-like growth factor-1 from dermal papilla cells. *Biochem Biophys Res Commun* 212:988-994, 1995
50. Lindner G, Menrad A, Gherardi E, et al: Involvement of hepatocyte growth factor/scatter factor and met receptor signaling in hair follicle morphogenesis and cycling. *FASEB J* 14:319-332, 2000
51. Ito N, Ito T, Kromminga A, et al: Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal (HPA) axis and synthesize cortisol. *FASEB J* 19:1332-1334, 2005
52. Foitzik K, Krause K, Nixon AJ, et al: Prolactin and its receptor are expressed in murine hair follicle epithelium, show hair cycle-dependent expression, and induce catagen. *Am J Pathol* 162:1611-1621, 2003
53. Kobayashi H, Kromminga A, Dunlop TW, et al: A role of melatonin in neuroectodermal-mesodermal interactions: The hair follicle synthesizes melatonin and expresses functional melatonin receptors. *FASEB J* 19:1710-1712, 2005
54. Millar SE, Willert K, Salinas PC, et al: WNT signaling in the control of hair growth and structure. *Dev Biol* 207:133-149, 1999
55. Botchkarev VA, Botchkareva NV, Roth W, et al: Noggin is a mesenchymally derived stimulator of hair-follicle induction. *Nat Cell Biol* 1:157-163, 1999
56. Sato N, Leopold PL, Crystal RG: Induction of the hair growth phase in postnatal mice by localized transient expression of sonic hedgehog. *J Clin Invest* 194:855-864, 1999
57. Danilenko DM, Ring BD, Yanagihara D, et al: Keratinocyte growth factor is an important endogenous mediator of hair follicle growth, development, and differentiation. *Pathology* 147:145-154, 1995
58. Roh C, Tao Q, Lyle S: Dermal papilla-induced hair differentiation of adult epithelial stem cells from human skin. *Physiol Genomics* 19:207-217, 2004
59. Meyer B, Bazzi H, Zidek V, et al: A spontaneous mutation in the desmoglein 4 gene underlies hypotrichosis in a new lanceolate hair rat model. *Differentiation* 72:541-547, 2004
60. Philpott MP, Sanders D, Westgate GE, et al: Human hair growth in vitro: A model for the study of hair follicle biology. *J Dermatol Sci* 55:S72, 1994 (suppl)
61. Paus R, Piker S: Biology of hair and nail, in Bologna JL, Jorizzo JL, Rapini RP (eds): *Dermatology*, London, Mosby, 2003, pp 1007-1032
62. Ellis T, Smyth I, Riley E, et al: Overexpression of sonic hedgehog suppresses embryonic hair follicle morphogenesis. *Dev Biol* 263:203-215, 2003
63. Oro AE, Higgins K: Hair cycle regulation of hedgehog signal reception. *Dev Biol* 255:238-248, 2003
64. Hibino T, Nishiyama T: Role of TGF-beta2 in the human hair cycle. *J Dermatol Sci* 35:9-18, 2004
65. Panteleyev AA, Botchkareva NV, Sundberg JP, et al: The role of the hairless (hr) gene in the regulation of hair follicle catagen. *Am J Pathol* 155:159-171, 1999
66. Soma T, Tsuji Y, Hibino T: Involvement of transforming growth factor-beta2 in catagen induction during the human hair cycle. *J Invest Dermatol* 118:993-997, 2002
67. Suzuki S, Ota Y, Ozawa K, et al: Dual-mode regulation of hair growth cycle by two Fgf-5 gene products. *J Invest Dermatol* 114:456-463, 2000
68. Botchkarev VA, Botchkareva NV, Peters EMJ et al: Epithelial growth control by neurotrophins: Leads and lessons from the hair follicle. *Prog Brain Res* 146:493-513, 2004
69. Foitzik K, Spexard T, Nakamura M, et al: Towards dissecting the pathogenesis of retinoid-induced hair loss: all-trans retinoic acid induces

- premature hair follicle regression (catagen) by upregulation of TGF- β 2 in the dermal papilla. *J Invest Dermatol* 124:1119-1126, 2005
70. Yano K, Brown LF, Lawler J, et al: Thrombospondin-1 plays a critical role in the induction of hair follicle involution and vascular regression during the catagen phase. *J Invest Dermatol* 120:14-19, 2003
 71. Bodo E, Biro T, Telek A, et al: A hot new twist to hair biology: Involvement of vanilloid receptor-1 (VR1/TRPV1) signaling in human hair growth control. *Am J Pathol* 166:985-998, 2005
 72. Ito T, Ito N, Saathoff M, et al: Interferon-gamma is a potent inducer of catagen-like changes in cultured human anagen follicles. *Br J Dermatol* 152:623-631, 2005
 73. Peters EM, Hansen MG, Overall RW, et al: Control of human hair growth by neurotrophins: Brain-derived neurotrophic factor inhibits hair shaft elongation, induces catagen, and stimulates follicular transforming growth factor beta2 expression. *J Invest Dermatol* 124:675-685, 2005
 74. Botchkarev VA, Sharov AA: BMP signaling in the control of skin development and hair follicle growth. *Differentiation* 72:512-526, 2004
 75. Conrad F, Paus R: The role of estrogens in hair biology. *J Dtsch Dermatol Ges* 2:412-423, 2004
 76. Mecklenburg L, Tobin DJ, Cirilan MV, et al: Premature termination of hair follicle cycling in lasi congenital atrichia (fz) mice points to fuzzy as a key element of hair cycle control. *Exp Dermatol* 14:561-570, 2005
 77. Nakamura M, Sundberg JP, Paus R: Mutant laboratory mice with abnormalities in pilosebaceous unit development, growth and/or function. *Exp Dermatol* 10:369-390, 2001
 78. Werner S, Grose R: Regulation of wound healing by growth factors and cytokines. *Physiol Rev* 83:835-870, 2003
 79. Chuong CM, Hou L, Chen PJ, et al: Dinosaur's feather and chicken's tooth? Tissue engineering of the integument. *Eur J Dermatol* 11:286-292, 2001
 80. Mayer JA, Chuong CM, WidELITZ R: Rooster feathering, androgenetic alopecia, and hormone-dependent tumor growth: what is in common? *Differentiation* 72:474-488, 2004
 81. Hoffmann R: Enzymology of the hair follicle. *Eur J Dermatol* 11:296-300, 2001
 82. Inui S, Fukuzato Y, Nakajima T, et al: Identification of androgen-inducible TGF-beta1 derived from dermal papilla cells as a key mediator in androgenetic alopecia. *J Invest Dermatol Symp Pro* 8:69-71, 2003
 83. Schumacher-Stock U: Estrogen treatment of hair diseases, in Orfanos CE, Montagna M, Stuttgen G (eds): *Hair Research*. Berlin/Heidelberg, Germany, Springer-Verlag, 1981, pp 318--321
 84. Ohnemus U, Uenalan M, Conrad F, et al: Hair cycle control by estrogens: catagen induction via estrogen receptor (ER)-{alpha} IS CHECKED BY ER{beta} signaling. *Endocrinology* 146:1214-1225, 2005
 85. Smart RC, Oh HS, Chanda S, et al: Effects of 17-beta-estradiol and ICI 182 780 on hair growth in various strains of mice. *J Invest Dermatol Symp Proc* 4:285-289, 1999
 86. Peters EMJ, Handjiski B, Kuhlmai A, et al: Neurogenic inflammation in stress-induced termination of murine hair growth is promoted by nerve growth factor. *Am J Pathol* 165:259-271, 2004
 87. Botchkarev VA: Stress and the hair follicle: exploring the connections. *Am J Pathol* 162:709-12, 2003
 88. Ebling FJ: the hair cycle and its regulation. *Clin Dermatol* 6:67-73, 1988
 89. Philpott MP, Green MR, Kealey T: Human hair growth in vitro. *J Cell Sci* 97:463-471, 1990
 90. Chase HB: Growth of hair. *Physiol Rev* 34:113-126, 1954
 91. Stenn KS, Nixon J, Jahoda CAB, et al: What controls hair follicle cycling? *Exp Dermatol* 8:229-33; discussion 233-6, 1999
 92. Cowper SE, Rosenberg AS, Morgan MB: An investigation of apoptosis in androgenetic alopecia. *Am J Dermatopathol* 3:204-208, 2002
 93. Messenger AG: The control of hair growth: an overview. *J Invest Dermatol* 101:4S-9S, 1993
 94. Price VH: Androgenetic alopecia in women. *J Invest Dermatol Symp Proc* 8:24-27, 2003
 95. Pearson AJ, Ashby MG, Wildermoth JE, et al: Effect of exogenous prolactin on the hair growth cycle. *Proceedings of First Intercontinental Meeting of Hair Research Societies* 62:358-360, 1997