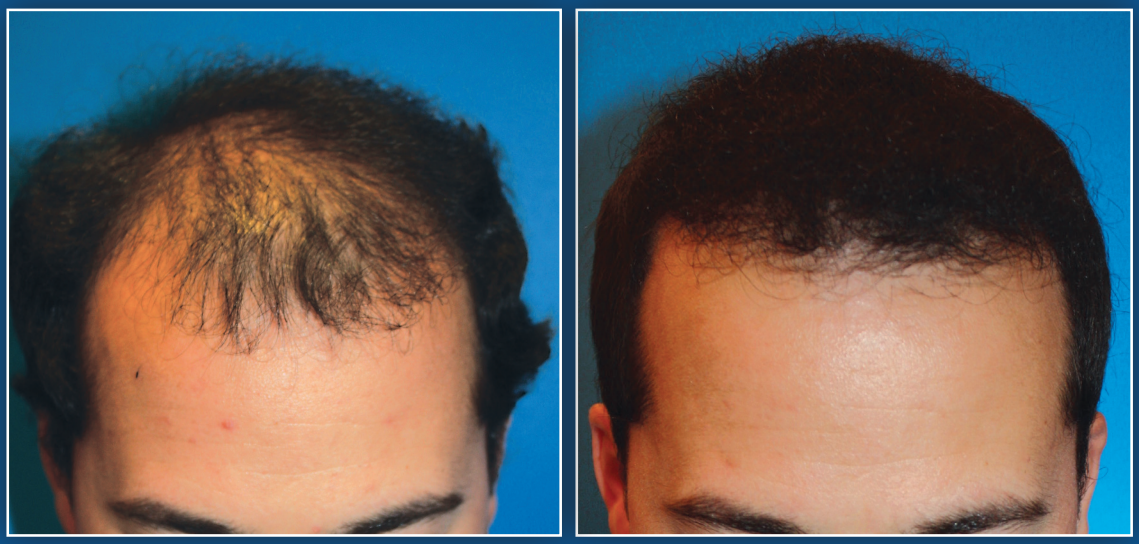
THE ALOPECIAS



DIAGNOSIS AND TREATMENTS

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Soigner et préserver ses cheveux : Les nouveaux traitements du cheveu, Editions ALPEN, Paris, 2006.

Les alopécies: de la clinique au traitement, Collection Guide Pratique de Dermatologie, Editions MED'COM, Paris, 2004.

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Chirurgie de la Calvitie, Editions Springer Verlag, Paris, 1994.

THE ALOPECIAS

DIAGNOSIS AND TREATMENTS

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Preface

The appearance of hair plays an important role in a person's overall physical appearance and self-perception. Physicians frequently encounter patients complaining about hair alterations and alopecia of various types, while the etiology of these conditions often remains unclear. In fact, disorders of hair growth are among the most common problems confronted in the practice of dermatology.

In this book, we review basic hair biology, the clinical features and pathophysiology of the major disorders of hair growth including alopecia, and the medical and surgical therapies available. We are fortunate to have internationally recognized experts contributing to this volume, and to them we express our appreciation. Special concentration has been placed on ethnicity and hair diseases, and specific medical–surgical treatments have been emphasized. Most men and women with pattern baldness will seek a remedy, and virtually all would have a full head of hair if all they had to do was snap their fingers to obtain it. As a result, we have dedicated a large portion of our practice to the restoration of hair for this group of patients.

This book is organized into 19 chapters that can be schematically divided into four major categories. The first category deals with biology and hair investigations. The second category is dedicated to clinical pathology; it describes various hair diseases including all major pathological conditions of the scalp affecting hair growth. The third category emphasizes the role of aesthetic and reconstructive hair transplantation or scalp surgery. The fourth category is devoted to hair cosmetology and hair cell treatments.

With this book, dermatologists, students, internists, hair transplant surgeons, endocrinologists, pediatricians, obstetricians–gynecologists, those in the pharmaceutical and cosmetic industries, laboratory workers, and any physicians who see hair loss in their regular practice are given the opportunity to understand the basic pathophysiology, clinical presentation, and various effective treatment options for patients with hair growth disorders. It is hoped that the general mission of this textbook to make the diagnosis and treatment of hair disorders concise, clear, and eminently practical, has been accomplished.

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1 Biology of the hair follicle

Ulrike Blume-Peytavi, Varvara Kanti, and Annika Vogt

INTRODUCTION

The spectrum of physiological functions of hair ranges from protection, e.g., from ultraviolet (UV) radiation, insulation against cold, and mechanical protection, to sensory and tactile as well as decorative and gender defining functions. Hair growth plays an important role in social and sexual communication, and hair loss may have a detrimental impact on quality of life, with significant impairment of life perceived by the affected patients. Understanding the biology of the hair follicle, its growth activity, including hair cycle regulation, is key for hair loss counseling and management.

Despite the development of new treatments, hair cycle regulation and its dysregulation leading to alopecia are not yet fully understood and controllable. A greater understanding of hair biology and pathogenetic mechanisms of hair disorders could lead to new therapeutic approaches for the management of hair disorders. The majority of clinically relevant hair diseases are caused by disturbances of hair cycle regulation, differentiation and keratinization, pigmentation, and immunology of the hair follicle. Generally, the complex mechanisms of hair follicle biology are only rudimentarily understood; our current knowledge is predominantly based on structural and morphological investigations as well as on functional characterization of single cell populations. The identification of mediators and elucidation of the complex cell–cell interactions in hair cycle regulation could open up new diagnostic and therapeutic possibilities. The aim of this chapter is to present current aspects of hair follicle biology and pathophysiology and carve out their clinical relevance.

HAIR FOLLICLE DEVELOPMENT

The hair follicle is composed of epidermal and dermal components; the latter includes the dermal papilla and the dermal fibrous sheath that are derived from an aggregate of mesenchymal cells that forms directly beneath the epithelial hair germ at the onset of follicular development. The epidermal hair germ grows downward and forms the hair peg as a result of complex epidermal–dermal interactions, which involve many pathways known from embryonic development, e.g., Hedgehog (Hh) and Wingless (Wnt) signaling. The full development of the hair follicle further requires a complex sequence of autocrine, paracrine, and endocrine signals both within and between the epidermis and the dermis. The development and differentiation of hair follicles during embryogenesis are classically divided into eight stages, characterized by distinct morphologies (Figure 1.1).

ANATOMY OF THE PILOSEBACEOUS UNIT AND HAIR FOLLICLE TYPES

More than 20 different cell populations are involved in the structure of the pilosebaceous unit, which includes the hair follicle, together with the sebaceous gland and the arrector pili muscle as well as the adjacent vascular supply of the hair follicle (Figure 1.2).

Hair follicles compose a permanent upper segment of follicular infundibulum and isthmus and a

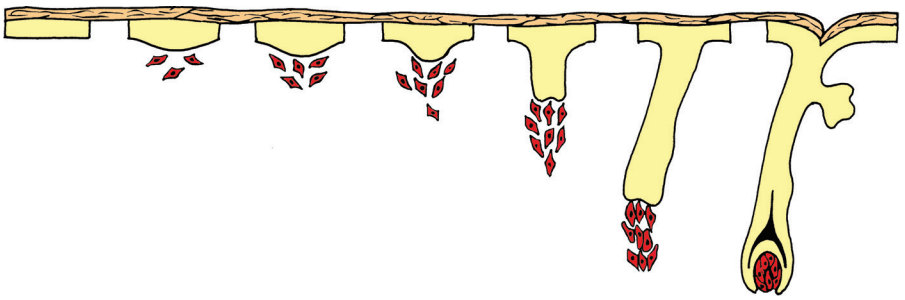

Figure 1.1 **Morphogenesis of the human hair follicle. Hair follicle formation is the result of complex sequential signaling events between the dermal mesenchyme and the overlying epithelium. Morphologically, induction, organogenesis, and cytodifferentiation phases can be determined. (With kind permission from Springer Science+Business Media: *Hair Growth and Disorders*, Biology of the hair follicle, 2008, 1–22, Berlin: Springer, Vogt A, McElwee KJ, and Blume-Peytavi U.)**

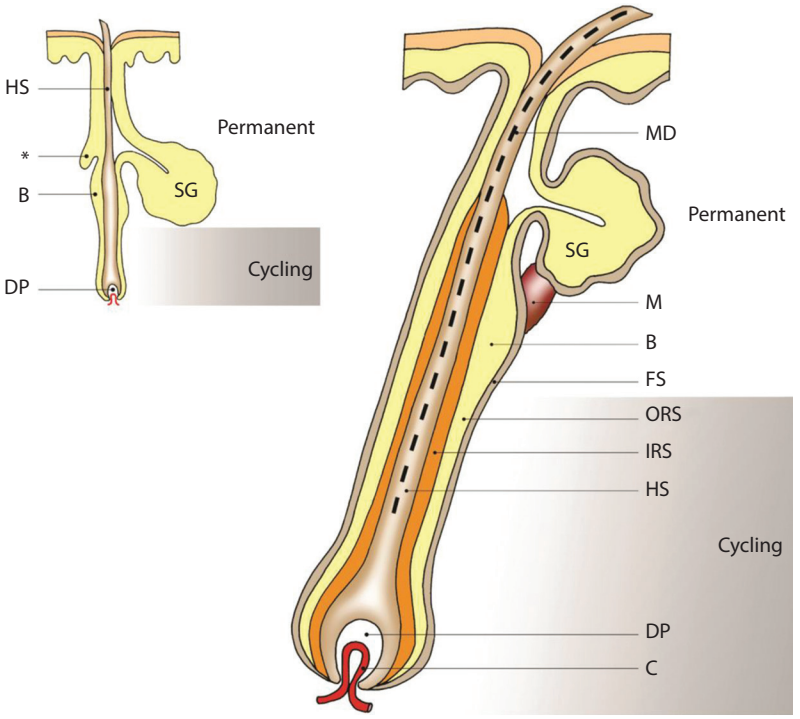

Figure 1.2 **Anatomy of the pilosebaceous unit. All hair follicles follow a common architecture. Together with the sebaceous gland (SG) and the arrector pili muscle (M), the hair follicle is part of the so-called "pilosebaceous" unit. The fibrous sheath (FS) and the epithelial outer and inner root sheaths (ORS, IRS) form concentric layers, which ensheathe the hair shaft (HS). Hair growth results from the proliferative activity of matrix keratinocytes in the bulb, which sit on the dermal papilla (DP). The dermal papilla is a condensate of specialized mesenchymal cells with important inductive properties. It also provides nutrition via a capillary loop (C), which is especially prominent in terminal hair follicles. The permanent, superficial component has to be differentiated from the transient cycling component of the hair follicle, which includes the bulb. The morphological dividing line between these two components lies below the bulge (B) region and the insertion of the arrector pili muscle (M). Size and shape of the hair follicles, however, vary with the body location and potential functions. In anagen phase, for example, vellus hair follicles from the retroauricular region (left) are approximately six times shorter than scalp hair terminal follicles (right). Each hair follicle has characteristic features. Vellus hair shafts, in contrast to terminal hair shafts, are usually devoid of a medulla (MD). Skirt-like epithelial structures (*), however, can only be found in vellus hair follicles. (With kind permission from Springer Science+Business Media: *Hair Growth and Disorders*, Biology of the hair follicle, 2008, 1–22, Berlin: Springer, Vogt A, McElwee KJ, and Blume-Peytavi U.)**

nonpermanent, variable lower segment of the hair follicle and bulb, which undergoes continuous renewal during the hair cycle. The morphological dividing line between these two components lies just below the bulge region and insertion of the arrector pili muscle.

The infundibulum extends from the skin surface to the point of the sebaceous gland duct opening to the hair canal. The superficial section of the hair follicle infundibulum, the acro-infundibulum, is lined by intact epidermis including a well-developed stratum corneum and a stratum granulosum. Continuous loss of epidermal differentiation occurs toward the isthmus of the lower infundibulum, the infrainfundibulum.

The isthmus extends from the arrector pili insertion (bulge area) down to the entry of the sebaceous duct. The bulge region represents a specialized compartment of the outer root sheath, which forms a niche for epithelial and neuroectodermal stem cells as well as various immature cell populations including immature Langerhans cells, mast cells, and melanocyte precursors.

The hair bulb is defined by the position of the dermal papilla and contains specialized mesenchymal cells with important inductive properties and a capillary loop to provide nutrition. The papilla is surrounded by undifferentiated, actively proliferating hair matrix cells, which give rise to the hair shaft and the inner root sheath. The

fibrous sheath and the epithelial outer and inner root sheaths form concentric layers, which ensheathe the hair shaft. The outer root sheath extends from the matrix cells in the hair bulb up to the entry level of the sebaceous duct. Outer root sheath cells contain clear vacuolated cytoplasm filled with large amounts of glycogen. Below the isthmus, the outer root sheath is not keratinized. However, at the level of the isthmus, where the inner root sheath disintegrates, the outer root sheath keratinizes without forming granules. Outer root sheath cells express a large diversity of mediators, hormones, and receptors. The inner root sheath consists of three layers, the Henle, Huxley, and cuticle, all of which keratinize and provide the form to the hair shaft. The mesenchymal sheath is separated from the epithelial root sheaths by a vitreous or basal membrane. This whole complex is surrounded by a dense vascular network. Free nerve endings form a cuff and provide the basis for intensive piloneural interactions.

The hair fiber is formed of keratin proteins, which are organized as a two-phase intracellular composite consisting of the keratin fibers embedded in a sulfur-rich matrix. The visible hair shaft of terminal hair follicles consists of three layers: cortex, cuticle, and medulla. The hair fiber cortex contains melanosomes, which determine the color of the hair fiber. Homogenous oval eumelanin granules and lamellar pheomelanin granules, in variable composition and density, form the wide spectrum of dark to fair hair. The outermost layer of the hair fiber, the cuticle, consists of multiple layers of corneocytes. It is thin and translucent allowing light to penetrate to the cortex pigments.

The total number of hair follicles in an individual is determined at the time of birth to be between 2 and 5 million, 100,000–150,000 of which are located on the scalp. The number of scalp hair follicles varies depending on the individual's skin, hair color, and ethnicity (Table 1.1). All hair follicles form during embryonic development, and no additional follicles are formed after birth in humans. Consequently, hair follicle density changes in different body regions with age (Tables 1.2 and 1.3). Furthermore, the hair type varies depending on age, sex, and localization of the hair follicle (Table 1.4). Structurally and

Table 1.1 Typical Numbers of Scalp Hair Follicles

Type	Number
Blonde-haired Caucasian	130,000
Dark-brown/black–haired Caucasian	110,000
Red-haired Caucasian	90,000
African (African American)	90,000
Asian (Far East)	90,000

Source: With kind permission from Springer Science+Business Media: *Hair Growth and Disorders*, Biology of the hair follicle, 2008, 1–22, Berlin: Springer, Vogt A, McElwee KJ, and Blume-Peytavi U.

Table 1.2 Hair Follicle Density with Age (Absence of Alopecias)

Location	Mean Density of Hair Follicles in Skin
Full-term fetal scalp	1135/cm^2
Adult scalp	615/cm^2
Full-term fetal forehead	1060/cm^2
Adult forehead	765/cm^2
Full-term fetal thigh	480/cm^2
Adult thigh	55/cm^2

Source: With kind permission from Springer Science+Business Media: *Hair Growth and Disorders*, Biology of the hair follicle, 2008, 1–22, Berlin: Springer, Vogt A, McElwee KJ, and Blume-Peytavi U.

Table 1.3 Estimated Number of Hair Follicles in the Skin by Body Region

Location	Number of Follicles
Head	1,000,000
Trunk	425,000
Arms	220,000
Legs	370,000
Approximate total	2,000,000

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Table 1.4 Different Types of Terminal Hair in Humans

Type	Length—Typical Range	Description
Scalp hair	100–1000 mm	Medullated with tapered tip in uncut hair
Eyebrows and eyelashes	5–10 mm	Medullated and curved with punctuate tip
Beard and moustache	50–300 mm	Complex medullary processes, more irregular in structure, blunt tip
Body hair	5–60 mm	Irregularly medullated, fi e tip
Pubic hair	10–60 mm	Coarse, kinked, irregular, and asymmetrical cross section
Axillary hair	10–50 mm	Coarse, less kinked than pubic hair, blunt tip, often abraded due to friction

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functionally, a distinction is made between lanugo, vellus, and terminal hair, which are differentiated by means of hair shaft diameter, hair length, pigmentation, and characteristics of the multiple concentric cell layers forming the hair shaft (the fibrous sheath and the epithelial inner and outer root sheaths) (Table 1.5). All hair follicle types present the same compartments of the pilosebaceous unit but differ in size and relation of the pilus and the sebaceous contributing parts. Lanugo hair, the first body hairs formed in the embryo, are fine, soft, silky in texture, poorly pigmented, and have no central medulla. Vellus hairs have a diameter of up to 30 μm and are nonmedullated, fine, and poorly pigmented, and normally do not grow longer than 2 cm. Vellus hair follicles are small and reach down only in the upper third of the dermis. The mostly pigmented, terminal hair follicles reach into the lower dermis and often into the subcutaneous fat and produce hair with a diameter of typically 50–100 μm; average hair fiber diameters are smaller in blonde-haired than in dark-haired individuals and larger overall in African and Asian populations (Table 1.6). Furthermore, depending on ethnic origin, elliptical to round hair shafts can be found.

Eyelashes constitute a specialized hair type: they have the largest diameter of all body hair, they have a relatively short active growth phase, and their strong pigmentation is normally preserved into old age.

Table 1.5 Typical Hair Characteristics

Type	Diameter	Length
Lanugo hair	<30 μm	>2 cm
Vellus hair	<30 μm	<2 cm
Intermediate hair	30–60 μm	>2 cm
Terminal hair	>50 μm	>2 cm

Source: With kind permission from Springer Science+Business Media: *Hair Growth and Disorders*, Biology of the hair follicle, 2008, 1–22, Berlin: Springer, Vogt A, McElwee KJ, and Blume-Peytavi U.

Table 1.6 Terminal Hair Diameter

Type	Diameter—Typical Range
Blonde-haired Caucasian	40–80 μm
Dark-brown/black–haired Caucasian	50–90 μm
Red-haired Caucasian	50–90 μm
African (African American)	60–100 μm
Asian (Far East)	80–120 μm

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HAIR GROWTH CYCLE

The hair cycle (Figure 1.3) includes a complex remodeling and regeneration of the complete inferior nonpermanent portion of the hair follicle. In humans, hair cycle regulation is not synchronized; each individual hair follicle cycles continuously during its life span through stages of growth (anagen), regression (catagen), and rest (telogen). Recently, an additional phase was recognized, during which the hair shaft is actively shed from the telogen follicle (exogen). The following interval of the hair cycle, in which the hair follicle remains empty after the telogen hair has been extruded and before a new anagen hair emerges, has been named *kenogen*.

Anagen

During the anagen phase, the hair is actively growing and materials are deposited in the hair shaft by cells found in the follicle. Metabolically active and dividing cells above and around the dermal papilla of the follicle, arising from the matrix keratinocytes grow upward during this phase to form the hair shaft. The anagen phase includes hair growth and proliferation of all hair follicle cells in all epithelial compartments, with the highest activity and sensitivity to noxes and toxic events observed in matrix cells.

Catagen

The anagen phase is followed by a short regression phase, the catagen, characterized by a cessation of protein and pigment production, involution of the hair follicle, and fundamental restructuring of the extracellular matrix. Massive apoptosis (programmed cell death) in the infrabulbar transient portion of the hair follicle leads to regression of the hair follicle and formation of a fibrous streamer. Catagen is the first component of the first hair cycle after morphogenesis.

Telogen

In telogen, the hair follicle has completely regressed, leading to total interruption between the permanent and the nonpermanent compartments of the hair follicle, to about half of its previous size and does not extend beyond the upper dermis. The hair root sheaths have retracted to form the club hair. The rounded up dermal papilla is located distantly, having migrated downward in the dermis waiting for the next signal in early anagen to migrate via the down-growing lower portion of the permanent hair follicle compartment. Epithelial cells of the lower telogen follicle do not show significant DNA or RNA synthesis, and the volume of the dermal papilla extracellular matrix is much reduced. The telogen club hair can be retained for months in this epithelial sac until the exogen starts.

Exogen

Recent research suggests that shedding of the hair fiber is a highly controlled, active process (exogen phase)

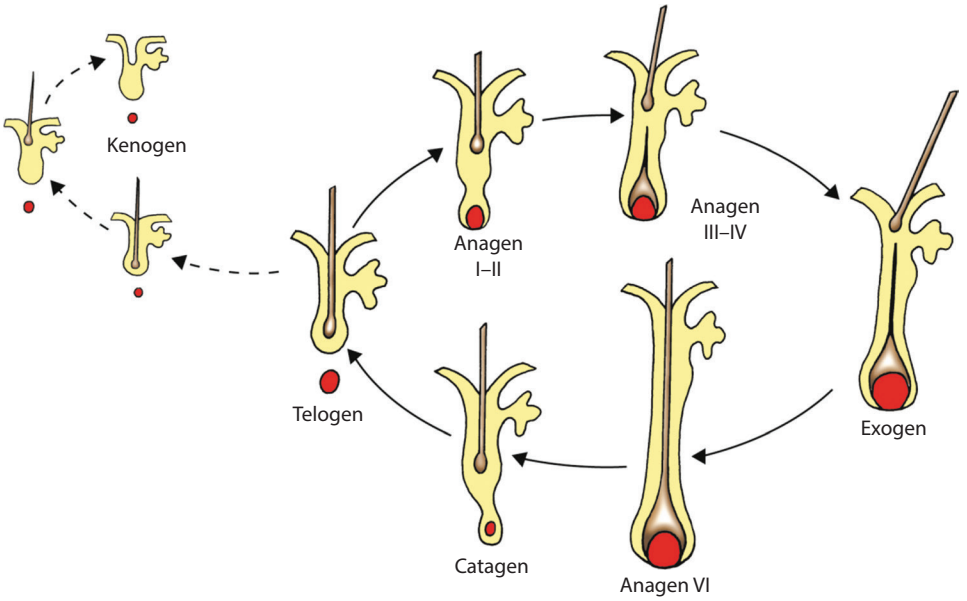

Figure 1.3 **Hair cycle. During one hair cycle a complete remodeling of the nonpermanent portion of the hair follicle occurs, which is controlled by finely tuned changes in the local signaling milieu. Traditionally, three phases of hair growth are recognized: growth phase (anagen I–III), regression phase (catagen), and resting phase (telogen). Recent research suggests that the shedding of the hair fiber is an active process, which has led to the introduction of the term *exogen* to describe this event. As another novel phenomenon in hair cycling, empty hair follicles after shedding of the hair fiber were reported. This interval of the hair cycle in which the hair follicle remains empty after the telogen hair has been extruded and before a new anagen hair emerges has been named *kenogen*. (With kind permission from Springer Science+Business Media: *Hair Growth and Disorders*, Biology of the hair follicle, 2008, 1–22, Berlin: Springer, Vogt A, McElwee KJ, and Blume-Peytavi U.)**

that differs from the quiescence normally found during the telogen phase. In fact, more detailed studies on this process suggest that the former concept, based on the assumption that the newly formed hair fiber pushes the resting shaft outward to effect shedding, is unlikely. It was shown that while anagen and telogen hairs are firmly anchored to the follicle, exogen hairs are passively retained within the follicles. The different morphology of the exogen and telogen hair root suggests that the exogen process involves a proteolytic event that occurs between the moving cells of the telogen shaft ase.

Kenogen

Empty hair follicles after shedding of the hair fiber have been found using phototrichograms, and the term *kenogen* has been suggested to describe this interval of the hair cycle in which the hair follicle remains empty after the telogen hair has been extruded and before a new anagen hair emerges. Kenogen can be reproducibly observed in healthy skin; however, frequency and duration have been reported to be greater in men and women with androgenetic alopecia, and only a portion of the hair follicle undergoes this phase. It is yet unclear which signals decide for the occurrence of kenogen.

Duration of the hair cycle

Durations of the different phases depend on the type and localization of the hair follicle (Tables 1.7 and 1.8). Normally, 80%–85% of the scalp hair is in anagen, with the rest either in catagen (2%) or telogen phase (10%–15%). The anagen phase of scalp hair follicles typically persists for 2–6 years and is a major determinant of maximal hair length. But anagen may persist for just a few weeks in terminal hair follicles on the extremities. The anagen phase of hair follicles of the eyebrows is only 70 days, while eyelashes grow for 100–150 days. The duration of telogen in hair follicles is also an important consideration in understanding the consequences of changes in the hair growth cycle. Body hair follicles are characterized by an increased telogen frequency and duration as compared to scalp hair follicles. Under physiological conditions, each hair follicle continues to cycle throughout life, but with reduced anagen phase duration while undergoing the aging process.

HAIR GROWTH REGULATION

Cyclical growth is a characteristic of the hair follicle. Even though all scalp hair follicles are in the same hair cycle phase during the fetal period, the hair cycles of the

Table 1.7 Hair Cycle Duration Depending on Body Location

Location	Hair Growth State	Typical Time Duration
Scalp	Anagen	2–6 years
	Catagen	2–3 weeks
	Telogen	3 months
Beard	Anagen	4–14 weeks
	Telogen	10–18 weeks
Arms	Anagen	6–12 weeks
	Telogen	7–13 weeks
Legs	Anagen	19–26 weeks
	Telogen	13–34 weeks

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Table 1.8 Rate of Terminal Hair Growth in Adults

Location	Typical Hair Growth per Day
Chin	0.38 mm
Scalp	0.35 mm
Axillary	0.30 mm
Thi h	0.20 mm
Eyebrows	0.16 mm

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individual hair follicles run asynchronously in humans, as opposed to in other mammalian species. The regulation of hair growth has been extensively revised in current literature. We aim to summarize key knowledge of the involvement of the major signaling pathways in hair cycling. Essential for the coordinated regulation of the hair cycle are epithelial–mesenchymal interactions between hair follicle stem cells and dermal papilla cells. The inner root sheath has essential pattern formation functions. The outer root sheath perceives regulatory functions through close contact with antigen-presenting cells and melanocytes.

Reciprocal interactions between epithelial and mesenchymal cell populations are well known from the organogenesis; accordingly, components of signal transduction pathways concerned with pattern formation are expressed in the adult hair follicle. The ligand "sonic hedgehog" (Shh) is expressed in the distal part of the epithelial section of the hair follicle, and the expression of associated target genes, such as transcription factor Gli, could be found in adult hair follicles. The coordination of the different signaling pathways is essential for the proper course of the hair cycle. The transient expression of Shh can induce the anagen phase, but the permanent activation of this signal transduction pathway is an important factor in the pathogenesis of basal-cell carcinoma. A wide spectrum of growth factors, including EGF, FGF, HGF, IGF, and TGFβ, as well as various cytokines, play a role in hair cycle regulation, while overlapping interactions between the different signal transduction pathways are mostly the case, e.g., convergence between EGFR and Wnt/β-catenin signaling pathways: EGF regulates transcription of E-cadherin through Src kinase activation, thus enabling the regulation of Wnt-mediated signals through β-catenin.

The dermal papilla is the central place of regulation, supplying the adjacent germinative epithelial cells and the matrix keratinocytes via the strongly pronounced vessel system. The mesenchymal cells of the dermal papilla express vascular endothelial growth factor (VEGF) and are probably involved in the cyclical restructuring of the vascular system and the extracellular matrix. Dermal papilla cells show in vitro basal expression of nitrogen monoxide (NO). This could be stimulated by 5α-dihydrotestosterone, thereby highlighting the importance of hormonal stimuli for hair cycle regulation.

Hormonal infl ence

The same hair follicle is able to produce lanugo hair in the fetal period, vellus hair in infancy, and terminal hair in adulthood. Abnormal increases in the serum levels of androgens, such as in the case of hirsutism in adrenal hyperfunction, or of estrogens, progesterone, and prolactin, lead to a prolongation of the anagen stadium. The different receptors and hormone-metabolizing enzymes determine the complex and partially contradictory reaction pattern of the hair follicle depending on age, localization, and gender. For example, there is a graded response of regional hairs to androgens: temporal and occipital scalp hairs as well as eyebrows and eyelashes are insensitive to androgens. Inguinal and axillary follicles are stimulated to grow under low androgen levels, while the androgen-dependent facial hairs in men are stimulated to grow only under high levels of androgen. The inherent specific sensitivity to hormonal stimuli is retained after hair transplantation, a principle called *donor dominance*. Therefore, androgen independent/insensitive hair follicles from the occipital scalp can be successfully transplanted to sites of androgen-sensitive hairs, affected by male pattern baldness (frontal, parietal, coronal areas) and retain their occipital growth behavior. Human hair follicles express a wide variety of steroid metabolizing enzymes, such as aromatase, 5α-reductase, steroid sulfatase, 5,3β-hydroxysteroid dehydrogenase, and 17β-hydroxysteroid dehydrogenase. The activity of these enzymes can locally influence the perifollicular hormone level, depending on the particular isoform as

well as availability of the substrate. Hence, usually local imbalances in this equilibrium without changes in the hormone serum levels can lead to clinically relevant hair growth disorders like androgenetic alopecia.

Hair pigmentation

Pigmentation is also hair cycle dependent and underlies endocrine, paracrine, and autocrine regulatory mechanisms. Although melanocytes can be found in different compartments of the anagen hair follicle, melanogenetically active cells are primarily located in the hair bulb. Hair follicle melanogenesis is tightly coupled to the hair growth cycle as a result of closely coordinated epithelial, mesenchymal, and neuroectodermal interactions. Toward the end of each hair cycle, melanocytes reduce melanin production and retract their dendrites, thus leading to a transient "canities"—an unpigmented proximal end of telogen hair fibers. During aging, melanocyte activity decreases, as does the number of dopa-positive melanocytes, resulting in gray and white hair. Furthermore, follicular melanocytes are able to replace interfollicular melanocytes. In pigmentation disorders, such as vitiligo, follicular melanocytes are actively involved in the repigmentation of the interfollicular epidermis. Proopiomelanocortin (POMC) α-, β-, and γ-MSH, and corticotropin (ACTH) are important pigmentation regulators, and polymorphisms of the melanocortin 1 receptor are associated with hair color characteristics. Apart from this receptor, the coexpression of corticotropin-releasing hormone (CRH) and mRNA from α-MSH and even ACTH could be found in the human hair follicle. These findings support results from experimental studies in animals, indicating that the hair follicle is not only a target organ for melanocortins, but also a synthesis site for CRH and POMC peptide. This could be considered as an expression of a potential follicular control system, involved not only in pigmentation regulation but also in hair growth, the perifollicular immune system, and local mediation of the stress response. The dense perifollicular adrenergic and sensory nerve network, as well as the presence of perifollicular Merkel cells and neurotrophin-sensitive mast cells all being with the highest density around the bulge region, also highlights the importance of piloneural interactions in hair follicle cycling and control.

Immune system

The hair follicle represents a physiological break in the skin barrier. Accordingly, antigen-presenting cells can be found at particularly high densities around the upper portion of the hair follicle, which is thus acting as a site for intensive interactions between the immune system and microbial invaders or allergens. The hair follicle constitutes a reservoir of dendritic cells, from which follicular Langerhans cells can contribute to the repopulation of areas of skin that are exposed to UVB. In contrast to the high density of antigen-presenting cells in the upper portion of the hair follicle, very low numbers of intraepithelial T cells, Langerhans cells, and major-histocompatibility-complex-I-(MHC-I-)molecules are found in the anagen hair bulb. Ultrastructural investigations indicate a potential role of Langerhans cells in pigment sequestration in the early catagen stage. An overexpression of MCH-I as well as melanogenesis-associated autoantigen presentation with activation of CD 8^+ cells was found in hair follicles of patients with alopecia areata. Therefore, dysfunctions with collapse of the peribulbar immune privilege have been suggested as a possible factor in the pathogenesis of alopecia areata.

Follicular stem cells

The hair follicle is able to regenerate a variety of cell populations during each new hair cycle. This enormous plasticity is accomplished by the presence of multipotent adult stem cells, which reside in rather undifferentiated, quiescent states and form precursors, transient amplifying cells, which provide further proliferation and differentiation into the different cell types. Furthermore, the reepithelialization of epidermal defects often emanates from the hair follicle. The exact localization of the responsible stem cells has not yet been clarified. Experimental data revealed that the slowest cycling cells within the skin reside in the bulge region. The outer root sheath has also been discussed as the location of the stem cell reservoir. The possible role of mesenchymal stem cells is becoming the focus of scientific interest. In experimental studies in animals with high follicle density, cycle-related/dependent differences were found in wound healing. Mesenchymal hair follicle cells also seem to positively influence the quality of wound healing, so that the fibrous sheath has been suggested to be a possible site for progenitor cells. The mesenchymal cells of the dermal papilla exhibit a high inductive potency and are capable of inducing folliculogenesis after transplantation through interaction with epithelial cells of the host tissue. Moreover, mesenchymal cells of the dermal papilla and the fibrous sheath actively produced hematopoietic cells in vivo and in vitro, whereas follicle epithelial cells did not.

Follicular penetration

With a density of more than 400 vellus hairs per square centimeter on the forehead and more than 93 per square centimeter on the back, hair follicles account for a significant share of the skin surface area. The epithelium of the acro-infundibulum is keratinized and relatively impermeable, like the epithelium of the interfollicular epidermis, whereas the corneocytes in the underlying portions of the follicle are rather fragile and small and only form an incomplete barrier. Experimentally, it could be shown that implantation of dissected hair follicles into reconstructed skin significantly increases the penetration of substances like hydrocortisone. Furthermore, a

correlation has been observed between penetration of topically applied substances and sebum production as well as growth activity of the hair follicle. This observation provided the rationale for the development of particular drug formulations and carrier systems to specifically target hair follicles. Therefore, these findings on penetration in and through the hair follicle depending on localization, gender, and growing activity are of high practical relevance and provide implications for the dermatological external therapy and for the development of transcutaneous application systems.

CLINICAL RELEVANCE

The development of new strategies to control the hair follicle cycle is currently in the spotlight of hair research, and a wide range of novel molecules and delivery systems are currently being developed. The investigative challenges in alopecia treatment involve understanding and controlling signal transduction events and their regulatory genes in order to induce and/or prolong anagen and to shorten telogen. A profound knowledge of hair follicle biology could facilitate the targeted control/selective influence of the local regulation systems and the development of novel hair loss therapeutic approaches based on molecular evidence rather than pure empirical evidence.

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