The Biology, Structure, and Function of Eyebrow Hair

Jennifer V. Nguyen MD
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

ABSTRACT

Eyebrow hair serves many important biologic and aesthetic functions. This article reviews the structure and function of the hair follicle, as well as hair follicle morphogenesis and cycling. Eyebrow hair follicles share the same basic structure as hair follicles elsewhere on the body, but are distinguished by their shorter anagen (growing) phase. Knowledge of the hair follicle structure and cycle is important for understanding the pathophysiology of alopecia, as diseases affecting the stem cell portion of the hair follicle in the bulge region may cause permanent hair loss. Furthermore, therapeutic agents that target distinct phases and hormones involved in the hair cycle may be useful for promoting hair growth.

J Drugs Dermatol. 2014;13(suppl 1):s12-s16.

INTRODUCTION

Skin and hair possess many important biologic functions, serving as the body's first line of defense against the outside world. In continuity with the skin, the hair follicle functions to protect the skin from the environmental elements and disperses sweat gland products (eg, pheromones).[1] Eyebrow and eyelash hair protect the eyes from sweat and moisture. In addition, the hair follicle transmits sensory information to the nervous system via neuroreceptors that respond to mechanical stimuli above the skin surface. Hair also has essential immunologic functions, as Langerhans cells at the opening of the follicle detect surface pathogens and stimulate the immune system, in conjunction with perifollicular immune cells such as macrophages and mast cells.[1]

Furthermore, hair holds aesthetic importance, and conditions that result in hair loss (alopecia) or excessive hair growth can have devastating psychosocial effects. Eyebrows are vital for facial expression and, in conjunction with the eyelashes, cheekbones, hairline, and nose, eyebrows frame the eyes, thereby contributing to an individual's unique facial appearance.

DISCUSSION

Structure of Hair Follicles

Although hair follicles on the body vary in size and shape, they all share the same basic structure. The lower portion of the hair follicle comprises the hair bulb, which is composed of rapidly proliferating matrix cells that produce the hair shaft. The epithelial component of the hair follicle is composed of at least 8 concentric layers: the outer root sheath (ORS), the companion layer, the inner root sheath (IRS), which is subdivided into Henle's layer, Huxley's layer, and the cuticle of the IRS, and the hair shaft cuticle, the cortex, and the medulla (Figures 1 and 2). These layers are composed of characteristic intermediate filament keratins, enzymes, and adhesion molecules.[2] The ORS of the hair follicle is continuous with the epidermal basal layer and contains melanocytes, Langerhans cells (dendritic antigen-presenting cells), and Merkel cells (specialized neurosecretory cells).[1]

Pigment in the hair shaft is produced by melanocytes located in the hair bulb that transfer melanin to keratinocytes in the developing hair shaft cortex and medulla. As the matrix cells differentiate and move upward, they are compressed by the rigid IRS, whose structure determines the shape of the hair shaft.[1] The dermal papilla, which is composed of specialized mesenchymal cells located at the base of the follicle, is thought to control the proliferation of matrix cells and thus the size of the hair shaft.[1]

The bulge consists of a cluster of biochemically distinct cells located in the ORS, near the insertion of the arrector pili muscle. Bulge cells have the characteristic properties of epithelial stem cells: they are slow-cycling (quiescent) and are thought to persist for the lifetime of the hair follicle.[3,4] It is believed that the bulge population contributes to epithelial cells that proliferate and regenerate the new lower follicle during the growing stage of the hair cycle. Epithelial stem cells in the bulge portion of the ORS may also serve as a reservoir for epidermal and sebaceous-gland cells.[5,6] The bulge region of the hair follicle is especially rich in nerve endings and Merkel cells.[1] Hair follicle bulge cells express CD34 in mice and keratin 15 in humans.[3]

Morphogenesis of Hair Follicles

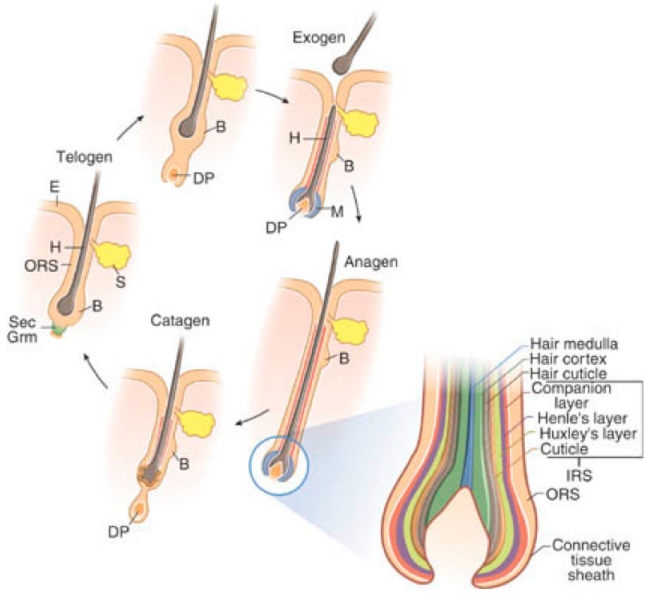
Hair morphogenesis is initiated in utero through complex interactions between the epithelium and underlying dermis.

An array of activating and inhibitory secreted molecules orchestrates follicular induction. The initiating signal is thought to arise from the dermal mesenchyme, which induces hair-follicle formation from the overlying epithelium during fetal development. The Wnt/β-catenin pathway is thought to be integral to this process, as it is first upregulated in the upper dermis, initiating the downgrowth of keratinocytes from the epithelium to form the epithelial hair follicle placode.[7,8] In the presence of a Wnt signal, cytoplasmic β-catenin translocates to the nucleus where it forms a transcription complex with deoxyribonucleic acid (DNA) binding factors of the lymphoid enhancer-binding factor/T-cell factor (LEF/TCF) family, and activates transcription of target genes.[7] An epithelial signal from the placode (likely Wnt and platelet-derived growth factor-A molecules) promotes the clustering of underlying mesenchymal cells, forming a dermal condensate.[7] Sonic hedgehog, a secreted protein downstream of Wnt signaling, is required for the proliferation of follicular epithelium and development of the dermal condensate into a dermal papilla.[7] In response to a signal from the dermal condensate, the epithelial placode cells proliferate and invade the dermis, eventually surrounding the dermal condensate, forming the hair follicle dermal papilla.[7,9] In addition to hair follicle morphogenesis, Wnt signaling is essential during the adult hair cycle, as Wnt activity is observed in the secondary hair germ during anagen onset and in the precortex of anagen follicles during hair shaft differentiation.[10]

Other genes that are thought to play a role in the spacing and distribution of the follicles during early morphogenesis include lymphoid enhancer-binding factor-1 (LEF1), bone morphogenetic protein 4, and the type II receptor for transforming growth factor β.[1,7] Ectodysplasin-A receptor (EDAR), fibroblast growth factor receptor, and bone morphogenetic protein receptor signaling contribute to hair follicle specification and patterning.[11] Reciprocal epithelial-mesenchymal interactions promote hair follicle differentiation and maturation of the adjacent dermal papilla, which becomes enveloped by proliferating matrix cells that differentiate into the IRS and hair shaft. The ORS is continuous with the epidermal basal layer and grows downward.[11] Hair follicle stem cells are thought to arise early during hair morphogenesis at the placode/germ stage. The stem cells localize to the upper ORS during development, forming the hair follicle bulge.[11]

Hair follicle development progresses in cephalocaudal direction, becoming first visible in the eyebrows, upper lip, and chin regions at 9 weeks of gestation, with the formation of hair shafts at 16 weeks.[12] Approximately 5 million hair follicles cover the human body at birth.[1] Although the number of hair follicles does not increase after birth, the size of the follicles and hairs can change (eg, transition of vellus to terminal hairs under the influence of androgens).

FIGURE 1. Hair follicle cycling and anatomy. The 4 stages of hair follicle cycling are follicle growth (anagen), regression (catagen), rest (telogen), and hair shedding (exogen). Matrix cells in the bulb generate 7 different hair follicle layers.



B, bulge; DP, dermal papilla; H, hair; IRS, inner root sheath; M, matrix; ORS, outer root sheath; S, sebaceous gland; Sec Grm, secondary germ. Reprinted with permission from Blackwell Publishing, Inc. *Journal of Investigative Dermatology*. 2006;126(7):1459-1468. ©2006.

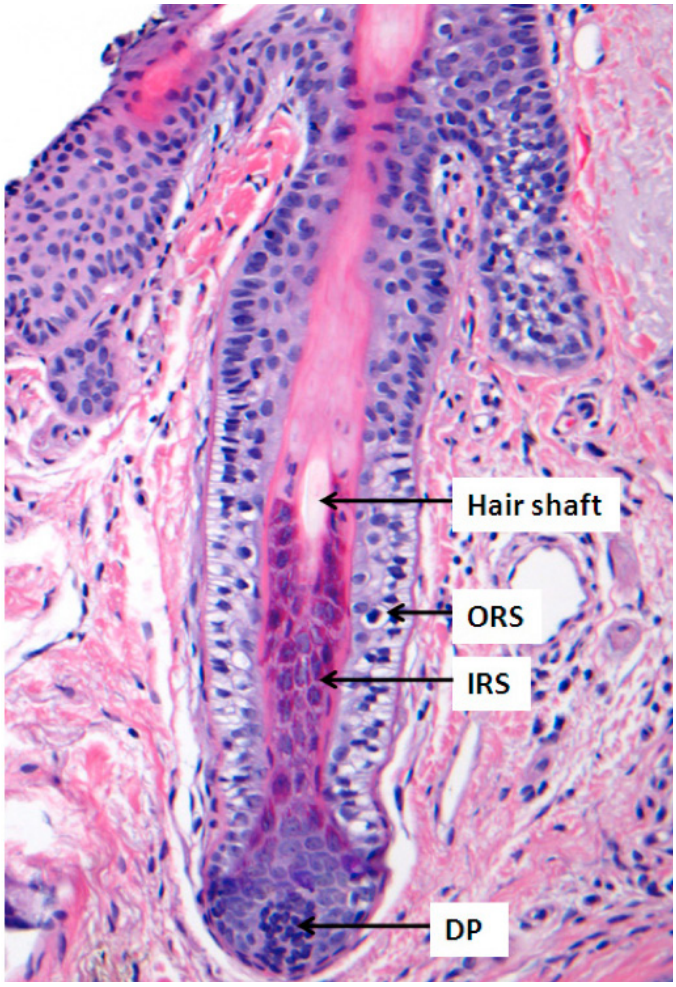
Hair Follicle Cycling

The hair shaft is continuously regenerated in a cycle that consists of 4 stages: hair follicle growth (anagen), regression (catagen), rest (telogen), and hair shedding (exogen) (Figure 1). The entire lower epithelial structure is formed during anagen, during which matrix keratinocytes in the bulb of the lower follicle rapidly proliferate. The duration of anagen is proportional to hair length. For example, human eyebrow hair follicles are short because they stay in anagen for only 2 to 4 weeks,[3] while scalp follicles have the capacity to grow long because they can remain in anagen for many years.

The lower portion of the hair follicle regresses during catagen, which occurs through programmed cell death (apoptosis) of follicular keratinocytes as well as melanocytes. Catagen usually lasts 2 to 3 weeks. Toward the end of the catagen stage, the dermal papilla condenses and moves upward, coming to rest underneath the hair follicle bulge.

During the telogen stage, the hair shaft matures into a club hair. Telogen typically lasts for 2 to 3 months. The percentage of follicles in the telogen stage varies substantially according to the region of the body (eg, 5% to 15% of scalp follicles are in the telogen stage at any one time, as compared with 40% to 50% of follicles on the trunk).[1] An increase in the percentage of scalp follicles in the telogen stage leads to excessive shedding.

FIGURE 2. Histology of eyebrow hair.



DP, dermal papilla; IRS, inner root sheath; ORS, outer root sheath.

After telogen, the lower, hair-producing portion of the follicle regenerates. As the new hair shaft grows in, the old hair is shed during exogen, and the cycle is repeated.

The exact molecular mechanisms of hair follicle cycling are still being elucidated, and numerous growth factors and growth factor receptors are implicated. Stem cells from the bulge region are believed to be integral to the initiation of anagen and formation of the new hair shaft with each hair cycle. The onset of the anagen stage recapitulates hair follicle development, as the formation of the new lower hair follicle is initiated by signals derived from secondary germ cells. Secondary germ cells are found at the base of the telogen follicle, and are believed to arise from the lowermost portion of the bulge at the end of catagen.[13] During late telogen/anagen onset, the dermal papilla stimulates secondary hair germ cells to proliferate, which initiates hair growth and generates the matrix, IRS, and hair shaft. The bulge cells respond by undergoing activation and proliferation later, during the anagen phase. The bulge cells continue to cycle slowly during the anagen phase to extend the ORS and maintain the matrix to support hair growth.[14] Many of the mesenchymal-epithelial interactions and secreted signaling molecules critical for hair follicle morphogenesis, such as Wnt ligands and Sonic hedgehog, are required to promote anagen onset and hair follicle growth during the adult hair cycle. The cessation of the anagen stage is controlled by various factors, including epidermal growth factor and fibroblast growth factor 5, which is first expressed in the follicle just before the end of this stage.[5]

The most common hair disorders are related to aberrations in hair follicle cycling. Telogen effluvium manifests as a transient period of hair shedding, often associated with medications, fever, endocrine abnormalities, parturition, anemia, and malnutrition. It occurs when an increased number of hair follicles prematurely enter the telogen stage, resulting in subsequent hair shedding. Transient shedding typically begins 2 to 4 months after the inciting event and lasts for several months.[1] Hair regrowth usually follows, assuming the precipitating trigger is removed. Telogen effluvium is typically limited to the scalp, but may affect other areas, such as the eyebrows or pubic region.

> "Prostaglandin analogues, such as bimatoprost, have been shown to induce eyelash growth, although the mechanism is unclear."

Hormones Controlling Hair Growth

Many hormones play a role in controlling hair growth, the most significant of which are androgens. Androgens contribute to the most common type of hair loss, androgenetic alopecia (AGA), eg, male and female pattern hair loss. Androgenetic alopecia is due to the progressive miniaturization of the hair follicle (transition from terminal hairs to vellus hairs) and shortening of the anagen cycle duration. This miniaturization is due to testosterone and its active metabolite, dihydrotestosterone, acting upon androgen receptors in the dermal papilla.[1] These hormones convert vellus hairs to terminal hairs in androgen-dependent areas such as the beard, axillary, and pubic areas during adolescence, yet later in life they can cause miniaturization of follicles in the scalp (resulting in AGA).

The conversion of testosterone to the more potent dihydrotestosterone is catalyzed by the enzyme 5α-reductase (types I and II). The type I enzyme is found predominantly in sebaceous glands and the liver, and the type II enzyme is predominant in hair follicles of the scalp, beard, and chest, as well as in the liver and the prostate gland. Finasteride, which inhibits 5α-reductase type II, slows the progression of AGA by inhibiting 5α-reductase.

Other hormones that modulate hair growth include estrogens, thyroid hormones, glucocorticoids, retinoids, prolactin, and growth hormone.[1]

Minoxidil has been used for patients with severe hypertension and was incidentally observed to result in hair growth. The mechanism by which minoxidil induces hair growth is not fully elucidated, but may be related to its action on opening of the adenosine triphosphate (ATP) sensitive potassium channel (K[ATP] channel). K(ATP) channel opening in dermal papilla cells at the base of the follicle is thought to play a role in stimulating hair growth.[15] As a vasodilator, it may promote more oxygen, blood, and nutrients to the proliferating dermal papilla cells. Other studies have shown that minoxidil stimulates the production of growth factors such as vascular endothelial growth factor in cultured dermal papilla cells, and that these growth factors might stimulate hair growth.[16] It has also been shown that minoxidil promotes the survival of human dermal papilla cells, thereby prolonging anagen, through proliferative and anti-apoptotic effects.[17]

Prostaglandin analogues, such as bimatoprost, have been shown to induce eyelash growth, although the mechanism is unclear. It is suggested that hypertrichosis is probably a result of the induction of the anagen phase in the telogen phase follicles of the eyelashes and prolonging the anagen phase.[18] Anecdotal cases describe significant eyebrow hair growth after use of topical prostaglandin analogues for eyebrow hypotrichosis.[19]

"Knowledge of the hair follicle structure and cycle is key to understanding the pathogenesis of the different types of alopecia, as well as developing targeted therapies for hair loss."

Other Hair Follicle Disorders

In contrast to AGA, hirsutism and hypertrichosis result from a prolonged anagen stage with an abnormal enlargement of hair follicles; small, fine vellus hairs transform into large, terminal hairs. This can be caused by medications or hormonal factors (eg, dysfunction in the adrenal glands or ovaries resulting in hyperandrogenism).

Anagen effluvium is caused by the cessation of anagen, often due to antineoplastic/chemotherapeutic drugs, which disrupt the rapidly proliferating bulb matrix cells. As a result, the hair shaft becomes narrower, with subsequent breakage and loss of the hair. Because the stem cells of the hair follicles are typically spared, a new hair bulb may be regenerated once the medication is stopped. Hair loss usually begins 1 to 2 weeks after chemotherapy is started and is most noticeable by 1 to 2 months.[20] The scalp hair is usually most affected, but all body hair, including eyelashes and eyebrows, can be affected.[21]

Inflammatory alopecias (such as lichen planopilaris and discoid lupus erythematosus) can lead to permanent scarring hair loss, whereas others (such as alopecia areata and telogen effluvium) are nonscarring and potentially reversible. In scarring alopecias, the inflammation usually involves the superficial portion of the follicle, including the bulge area, resulting in permanent destruction of the stem cells necessary for the regeneration of the follicle. In contrast, the acute follicular inflammation in alopecia areata targets the hair bulb in the subcutaneous fat, resulting in disruption of the anagen stage. Because the bulge area is spared, the hair follicle has the potential to generate a new hair bulb and hair shaft once the inflammation has resolved.

Hair disorders associated with rare congenital hair defects, such as Netherton's syndrome and ectodermal dysplasias, are caused by mutations in keratins or other structural proteins. Netherton's syndrome is an autosomal recessive disease caused by mutations in serine protease inhibitor Kazal-type 5, encoding the serine protease inhibitor lympho-epithelial Kazal-type-related inhibitor. It presents with an atopic diathesis, allergic reactions, and icthyosiform dermatitis. A clue to diagnosis is the examination of eyebrow hairs, which will characteristically show trichorrhexis invaginata, in which the distal portion of the shaft is invaginated into the proximal portion.[22] Eyebrows may be the sole site of involvement in many patients with Netherton's syndrome, and the findings more prominent than in the scalp.[22]

CONCLUSION

In summary, eyebrow hair serves many important biologic functions, including sensory transmission and protection from the elements, as well as playing an important role in cosmesis and expression. The hair follicle originates from complex mesenchymal-epithelial interactions during embryogenesis. Similar molecular mechanisms underlie hair follicle cycling during one's lifetime. Knowledge of the hair follicle structure and cycle is key to understanding the pathogenesis of the different types of alopecia, as well as developing targeted therapies for hair loss.

DISCLOSURES

Jennifer V. Nguyen MD has no conflicts of interest to disclose.

REFERENCES

1. Paus R, Cotsarelis G. The biology of hair follicles. *N Engl J Med.* 1999;341(7):491-497.
2. Langbein L, Schweizer J. Keratins of the human hair follicle. *Int Rev Cytol.* 2005;243:1-78.
3. Cotsarelis G. Epithelial stem cells: a folliculocentric view. *J Invest Dermatol.* 2006;126(7):1459-1468

4. Cotsarelis G. Gene expression profiling gets to the root of human hair follicle stem cells. *J Clin Invest*. 2006;116(1):19-22.
5. 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*. 1990;61(7):1329-1337.
6. Ito M, Liu Y, Yang Z, et al. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. *Nat Med*. 2005;11(12):1351-1354.
7. Millar SE. Molecular mechanisms regulating hair follicle development. *J Invest Dermatol*. 2002;118(2):216-225.
8. Zhang Y, Tomann P, Andl T, et al. Reciprocal requirements for EDA/EDAR/NF-kappaB and Wnt/beta-catenin signaling pathways in hair follicle induction. *Dev Cell*. 2009;17(1):49-61.
9. Hardy MH. The secret life of the hair follicle. *Trends Genet*. 1992;8(2):55-61.
10. Myung PS, Takeo M, Ito M, Atit RP. Epithelial Wnt ligand secretion is required for adult hair follicle growth and regeneration. *J Invest Dermatol*. 2013;133(1):31-41.
11. Myung P, Andl T, Ito M. Defining the hair follicle stem cell (Part I). *J Cutan Pathol*. 2009;36(9):1031-1034.
12. Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology*. 2nd ed. St. Louis, MO: Mosby Elsevier, 2008.
13. Ito M, Kizawa K, Hamada K, Cotsarelis G. Hair follicle stem cells in the lower bulge form the secondary germ, a biochemically distinct but functionally equivalent progenitor cell population, at the termination of catagen. *Differentiation*. 2004;72(9-10):548-557.
14. Myung P, Ito M. Dissecting the bulge in hair regeneration. *J Clin Invest*. 2012;122(2):448-454.
15. Buhl AE, Conrad SJ, Waldon DJ, Brunden MN. Potassium channel conductance as a control mechanism in hair follicles. *J Invest Dermatol*. 1993;101(suppl 1):s148-s152.
16. Lachgar S, Charveron M, Gall Y, Bonafe JL. Minoxidil upregulates the expression of vascular endothelial growth factor in human hair dermal papilla cells. *Br J Dermatol*. 1998;138(3):407-411.
17. Han JH, Kwon OS, Chung JH, et al. Effect of minoxidil on proliferation and apoptosis in dermal papilla cells of human hair follicle. *J Dermatol Sci*. 2004;34(2):91-98.
18. Law SK. Bimatoprost in the treatment of eyelash hypotrichosis. *Clin Ophthalmol*. 2010;4:349-358.
19. Schweiger ES, Pinchover L, Bernstein RM. Topical bimatoprost for the treatment of eyebrow hypotrichosis. *J Drugs Dermatol*. 2012;11(1):106-108.
20. Sinclair R, Grossman KL, Kvedar JC. Chapter 9: Anagen hair loss. In: Olsen EA, ed. *Disorders of Hair Growth: Diagnosis and Treatment*. 2nd ed. New York, NY: McGraw-Hill Publishing, 2003:275-302.
21. Tosti A, Pazzaglia M. Drug reactions affecting hair: diagnosis. *Dermatol Clin*. 2007;25(2):223-231.
22. Boussofara L, Ghannouchi N, Ghariani N, Denguezli M, Belajouza C, Nouira R. Netherton's syndrome: the importance of eyebrow hair. *Dermatol Online J*. 2007;13(3):21.

AUTHOR CORRESPONDENCE

Jennifer V. Nguyen MD
E-mail:..... JenniferV.Nguyen@uphs.upenn.edu