The hair cycle

Laura Alonso[1] and Elaine Fuchs[2,*]

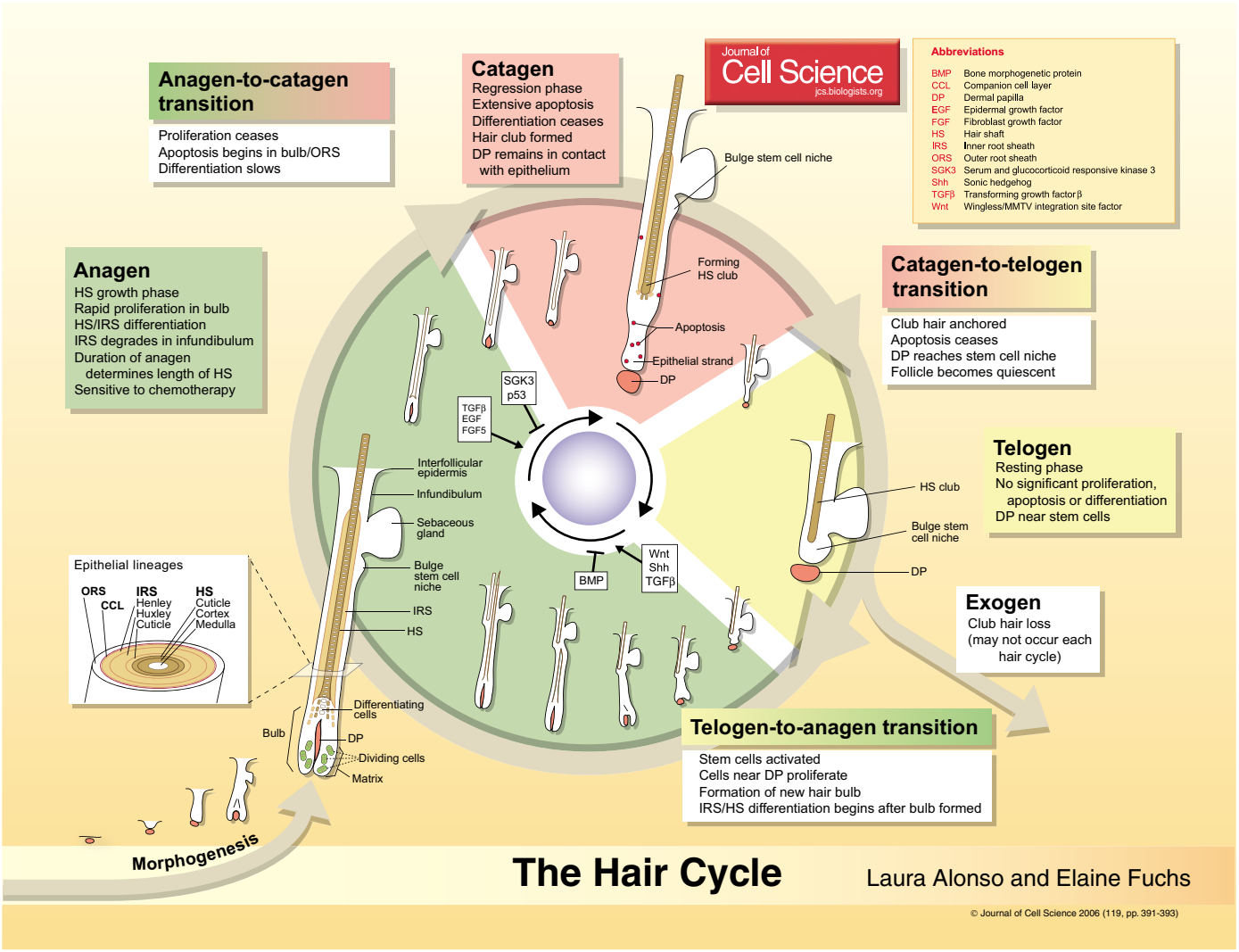
[1]Department of Medicine, Division of Endocrinology, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15261, USA
[2]Howard Hughes Medical Institute, Laboratory of Mammalian Cell Biology and Development, The Rockefeller University, 1230 York Avenue, New York, NY 10021, USA
*Author for correspondence
(e-mail: fuchslb@rockefeller.edu)

Journal of Cell Science 119, 391-393
Published by The Company of Biologists 2006
doi:10.1242/jcs02793

The hair coat, which keeps most mammals warm, dry and protected from harmful elements, requires a constant supply of new hairs throughout the lifetime of the animal. To produce new hairs, existing follicles undergo cycles of growth (anagen), regression (catagen) and rest (telogen). During each anagen phase, follicles produce an entire hair shaft from tip to root; during catagen and telogen, follicles reset and prepare their stem cells so that they can receive the signal to start the next growth phase and make the new hair shaft. The hair cycle represents a remarkable model for studies of the regulation of stem cell quiescence and activation, as well as transit-amplifying cell proliferation, cell-fate choice, differentiation and apoptosis in a regenerative adult epithelial tissue. Here we summarize the major events of the hair cycle, and touch on known regulators of the transitions. Detailed reviews of the hair cycle and its regulation can be found elsewhere (Lavker et al., 2003; Millar, 2002; Muller-Rover et al., 2001).

Morphogenesis

In the embryo, the skin begins as a single layer of epidermal stem cells. Soon after, as mesenchymal cells populate the skin to form the underlying collagenous dermis, morphogenesis of the hair follicle begins (Schmidt-Ullrich and Paus, 2005). Specialized dermal cells organize in small clusters directly beneath the epidermal layer, stimulating the overlying epithelial stem cells to grow downward and produce a hair follicle. The follicle is contiguous with the epithelium; both are separated from the dermis by a basement membrane rich in extracellular matrix and growth factors synthesized and deposited largely but not solely by epithelial cells. As the follicle grows down, it assumes the shape of a rod several cell diameters wide. The inner layers begin to differentiate into concentric cylinders to form the central hair shaft (HS)



(See poster insert)

and the surrounding channel, the inner root sheath (IRS). An inductive mesenchymal cluster called the dermal papilla (DP) becomes a permanent part of the follicle base (Jahoda et al., 1984; Kishimoto et al., 2000). It travels with the epithelial downgrowth and becomes enveloped by the hair bulb. The follicle becomes fully mature as its bulb nears the bottom of the dermis. At this point (in mouse back skin around postnatal day 6 or P6), the proliferative cells (matrix) at the follicle base continue to divide, producing progeny cells that terminally differentiate to form the growing hair that exits the skin surface.

Anagen

Histologically, anagen follicles are long and very straight, but the follicles are angled to permit the hair coat to lie flat along the body surface. The proliferating matrix cells have a cell-cycle length of approximately 18 hours (Lavker et al., 2003). Daughter cells move upwards, adopting one of six lineages of the IRS and HS; from outermost to innermost, the layers include Henley, Huxley and cuticle layers of the IRS, and the cuticle, cortex and medulla layers of the HS. As HS cells terminally differentiate, they extrude their organelles and become tightly packed with bundles of 10-nm filaments assembled from cysteine-rich hair keratins, which become physically cross-linked to give the hair shaft high tensile strength and flexibility. The IRS also keratinizes so that it can rigidly support and guide the hair shaft during its differentiation process, but its dead cells degenerate as they reach the upper follicle, thereby releasing the HS that continues through the skin surface. The duration of anagen determines the length of the hair and is dependent upon continued proliferation and differentiation of matrix cells at the follicle base.

Anagen-to-catagen transition

The matrix cells are referred to as transit-amplifying cells because they undergo a limited number of cell divisions before differentiating. As the supply of matrix cells declines, HS and IRS differentiation slow and the follicle enters a destructive phase called catagen. The timing of the first catagen onset varies slightly between strains of mice and varies significantly from one skin region to another. In pigmented mice, the progression of catagen is evident from the color of the skin, which changes from the dark gray to black of anagen to pale pink by telogen. As with morphogenesis, the first catagen begins in a wave, spreading from the top of the head caudally towards the tail and laterally down the sides of the animal. In back skin taken from the midline, the onset of the first catagen ranges from P14 at the upper back near the head to P18 in the lower back near the tail. Catagen lasts 3-4 days in mice.

Some molecular regulators of the anagen-catagen transition have been identified, although how they work together to promote catagen or terminate anagen is not yet understood. Molecules that promote the transition to catagen include the growth factors FGF5 and EGF, neurotrophins such as BDNF and possibly the p75-neurotrophin receptor, p53 and TGFβ-family pathway members such as TGFβ1 and the BMPRIa (Andl et al., 2004; Foitzik et al., 2000; Hansen et al., 1997; Hebert et al., 1994; Schmidt-Ullrich and Paus, 2005). Factors known to maintain anagen include SGK3 and Msx2 (Alonso et al., 2005; Ma et al., 2003).

Catagen

Catagen is the dynamic transition between anagen and telogen (Muller-Rover et al., 2001). During catagen, the lower 'cycling' portion of each hair follicle regresses entirely in a process that includes apoptosis of epithelial cells in the bulb and outer root sheath (ORS), the outermost epithelial layer (Lindner et al., 1997). HS differentiation ceases, and the bottom of the HS seals off into a rounded structure called a club, which moves upward until it reaches the permanent, non-cycling upper follicle, where it remains anchored during telogen. As the lower follicle recedes, a temporary structure forms – the epithelial strand – which is unique to catagen. This connects the DP to the upper part of the hair follicle, contains many apoptotic cells and is completely eliminated by the time the DP reaches the cells that surround the remnant club hair.

Telogen

Following catagen, follicles lie dormant in a resting phase (telogen). In mice, the first telogen is short, lasting only 1 or 2 days, from approximately P19 to P21 in the mid back. The second telogen, however, lasts more than 2 weeks, beginning around P42.

The follicle stem cell compartment

Although no new hair follicles are made postnatally, the lower portion of the hair follicle regenerates in order to produce a new hair. For this purpose, and for the maintenance of the epidermis and sebaceous gland, reservoirs of multipotent epithelial stem cells are set aside during development. These precious cells are found in the lowest permanent portion of the hair follicle – the 'bulge' (Oshima et al., 2001; Taylor et al., 2000). Follicle stem cells are activated at the telogen-to-anagen transition, to initiate a new round of hair growth.

Telogen-to-anagen transition

The transition from telogen to anagen occurs when one or two quiescent stem cells at the base of the telogen follicle, near the DP, are activated to produce a new hair shaft (Blanpain et al., 2004; Tumbar et al., 2004). These cells now begin to proliferate rapidly, and become the transit-amplifying daughter cells that are fated to form the new hair follicle. The new follicle forms adjacent to the old pocket that harbors the club hair, which will eventually be shed (exogen). This creates the 'bulge' and adds a layer to the stem cell reservoir. The new hair emerges from the same upper orifice as the old hair. In many ways, the telogen-to-anagen transition resembles the activation of embryonic skin stem cells that are stimulated to make the follicle de novo. Signaling by Wnts (Gat et al., 1998; Huelsken et al., 2001; Lo Celso et al., 2004; Lowry et al., 2005; Van Mater et al., 2003) and Shh (Callahan et al., 2004; Mill et al., 2003; St-Jacques et al., 1998) is indispensable for new anagen, whereas Bmps (Botchkarev et al., 1999; Kulessa et al., 2000) have been implicated in follicle differentiation. The molecular steps involved are likely to hold clues to understanding the activation and specification of stem cells.

References

Alonso, L., Okada, H., Pasolli, H. A., Wakeham, A., You-Ten, A. I., Mak, T. W. and Fuchs, E. (2005). Sgk3 links growth factor signaling to maintenance of progenitor cells in the hair follicle. *J. Cell Biol.* **170**, 559-570.

Andl, T., Ahn, K., Kairo, A., Chu, E. Y., Wine-Lee, L., Reddy, S. T., Croft, N. J., Cebra-Thomas, J. A., Metzger, D., Chambon, P. et al. (2004). Epithelial Bmpr1a regulates differentiation and proliferation in postnatal hair follicles and is essential for tooth development. *Development* **131**, 2257-2268.

Blanpain, C., Lowry, W. E., Geoghegan, A., Polak, L. and Fuchs, E. (2004). Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. *Cell* **118**, 635-648.

Botchkarev, V. A., Botchkareva, N. V., Roth, W., Nakamura, M., Chen, L. H., Herzog, W., Lindner, G., McMahon, J. A., Peters, C., Lauster, R. et al. (1999). Noggin is a mesenchymally derived stimulator of hair-follicle induction. *Nat. Cell Biol.* **1**, 158-164.

Callahan, C. A., Ofstad, T., Horng, L., Wang, J. K., Zhen, H. H., Coulombe, P. A. and Oro, A. E. (2004). MIM/BEG4, a Sonic hedgehog-responsive gene that potentiates Gli-dependent transcription. *Genes Dev.* **18**, 2724-2729.

Foitzik, K., Lindner, G., Mueller-Roever, S., Maurer, M., Botchkareva, N., Botchkarev, V., Handjiski, B., Metz, M., Hibino, T., Soma, T. et al. (2000). Control of murine hair follicle regression (catagen) by TGF-beta1 in vivo. *FASEB J.* **14**, 752-760.

Gat, U., DasGupta, R., Degenstein, L. and Fuchs, E. (1998). De Novo hair follicle morphogenesis and hair tumors in mice expressing a truncated beta-catenin in skin. *Cell* **95**, 605-614.

Hansen, L. A., Alexander, N., Hogan, M. E., Sundberg, J. P., Dlugosz, A., Threadgill, D. W., Magnuson, T. and Yuspa, S. H. (1997). Genetically null mice reveal a central role for epidermal growth factor receptor in the differentiation of the hair follicle and normal hair development. *Am. J. Pathol.* **150**, 1959-1975.

Hebert, J. M., Rosenquist, T., Gotz, J. and Martin, G. R. (1994). FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. *Cell* **78**, 1017-1025.

Huelsken, J., Vogel, R., Erdmann, B., Cotsarelis, G. and Birchmeier, W. (2001). beta-Catenin controls hair follicle morphogenesis and stem cell differentiation in the skin. *Cell* **105**, 533-545.

Jahoda, C. A., Horne, K. A. and Oliver, R. F. (1984). Induction of hair growth by implantation of cultured dermal papilla cells. *Nature* **311**, 560-562.

Kishimoto, J., Burgeson, R. E. and Morgan, B. A. (2000). Wnt signaling maintains the hair-inducing activity of the dermal papilla. *Genes Dev.* **14**, 1181-1185.

Kulessa, H., Turk, G. and Hogan, B. L. (2000). Inhibition of Bmp signaling affects growth and differentiation in the anagen hair follicle. *EMBO J.* **19**, 6664-6674.

Lavker, R. M., Sun, T. T., Oshima, H., Barrandon, Y., Akiyama, M., Ferraris, C., Chevalier, G., Favier, B., Jahoda, C. A., Dhouailly, D. et al. (2003). Hair follicle stem cells. *J. Invest. Dermatol. Symp. Proc.* **8**, 28-38.

Lindner, G., Botchkarev, V. A., Botchkareva, N. V., Ling, G., van der Veen, C. and Paus, R. (1997). Analysis of apoptosis during hair follicle regression (catagen). *Am. J. Pathol.* **151**, 1601-1617.

Lo Celso, C., Prowse, D. M. and Watt, F. M. (2004). Transient activation of beta-catenin signalling in adult mouse epidermis is sufficient to induce new hair follicles but continuous activation is required to maintain hair follicle tumours. *Development* **131**, 1787-1799.

Lowry, W. E., Blanpain, C., Nowak, J. A., Guasch, G., Lewis, L. and Fuchs, E. (2005). Defining the impact of beta-catenin/Tcf transactivation on epithelial stem cells. *Genes Dev.* **19**, 1596-1611.

Ma, L., Liu, J., Wu, T., Plikus, M., Jiang, T. X., Bi, Q., Liu, Y. H., Muller-Rover, S., Peters, H., Sundberg, J. P. et al. (2003). 'Cyclic alopecia' in Msx2 mutants: defects in hair cycling and hair shaft differentiation. *Development* **130**, 379-389.

Mill, P., Mo, R., Fu, H., Grachtchouk, M., Kim, P. C., Dlugosz, A. A. and Hui, C. C. (2003). Sonic hedgehog-dependent activation of Gli2 is essential for embryonic hair follicle development. *Genes Dev.* **17**, 282-294.

Millar, S. E. (2002). Molecular mechanisms regulating hair follicle development. *J. Invest. Dermatol.* **118**, 216-225.

Muller-Rover, S., Handjiski, B., van der Veen, C., Eichmuller, S., Foitzik, K., McKay, I. A., Stenn, K. S. and Paus, R. (2001). A comprehensive guide for the accurate classification of murine hair follicles in distinct hair cycle stages. *J. Invest. Dermatol.* **117**, 3-15.

Oshima, H., Rochat, A., Kedzia, C., Kobayashi, K. and Barrandon, Y. (2001). Morphogenesis and renewal of hair follicles from adult multipotent stem cells. *Cell* **104**, 233-245.

Schmidt-Ullrich, R. and Paus, R. (2005). Molecular principles of hair follicle induction and morphogenesis. *BioEssays* **27**, 247-261.

St-Jacques, B., Dassule, H. R., Karavanova, I., Botchkarev, V. A., Li, J., Danielian, P. S., McMahon, J. A., Lewis, P. M., Paus, R. and McMahon, A. P. (1998). Sonic hedgehog signaling is essential for hair development. *Curr. Biol.* **8**, 1058-1068.

Taylor, G., Lehrer, M. S., Jensen, P. J., Sun, T. T. and Lavker, R. M. (2000). Involvement of follicular stem cells in forming not only the follicle but also the epidermis. *Cell* **102**, 451-461.

Tumbar, T., Guasch, G., Greco, V., Blanpain, C., Lowry, W. E., Rendl, M. and Fuchs, E. (2004). Defining the epithelial stem cell niche in skin. *Science* **303**, 359-363.

Van Mater, D., Kolligs, F. T., Dlugosz, A. A. and Fearon, E. R. (2003). Transient activation of beta-catenin signaling in cutaneous keratinocytes is sufficient to trigger the active growth phase of the hair cycle in mice. *Genes Dev.* **17**, 1219-1224.

Cell Science at a Glance on the Web

Electronic copies of the poster insert are available in the online version of this article at jcs.biologists.org. The JPEG images can be downloaded for printing or used as slides.