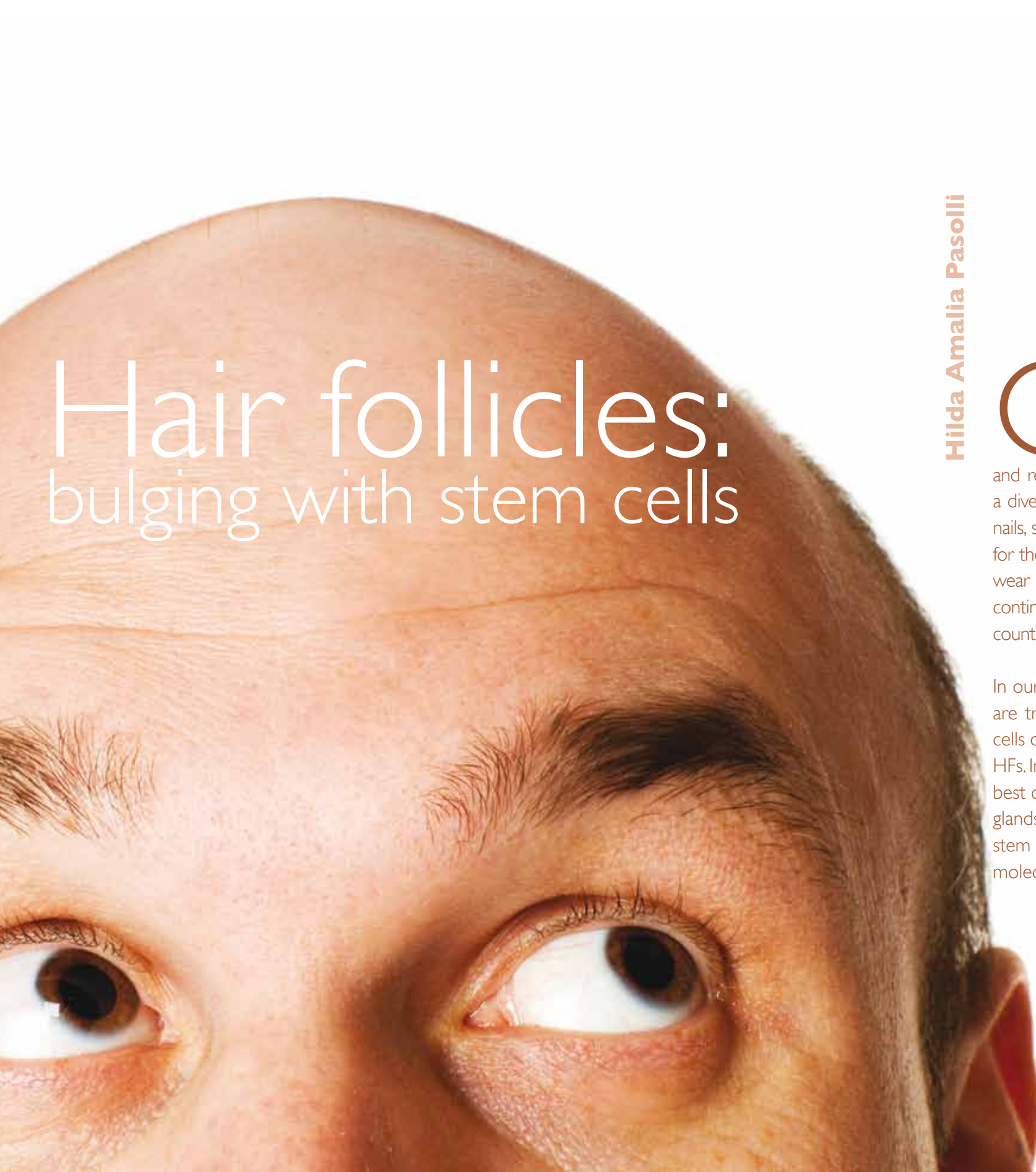




Hair follicles: bulging with stem cells

Hilda Amalia Pasolli

Our bodies are protected by a magnificent cover, the epidermis. Despite being only micrometers thick, it is a formidable seal of our body surface, excluding microbes and retaining body fluids. The epidermis can elaborate a diversity of protective appendages: hair follicles (HFs), nails, sebaceous and sweat glands in mammals. In order for the epidermis and its appendages to survive normal wear and tear as well as injuries, they must undergo a continuous renewal process. For this purpose, the skin counts a reservoir of stem cells.

In our lab, under the direction of Dr. Elaine Fuchs, we are trying to understand how the multipotent stem cells of mammalian skin give rise to the epidermis and HFs. In recent years, it has been unveiled that the three best characterized skin lineages, epidermis, sebaceous glands and HFs, each have their own reservoirs of stem cells. HF stem cells are the best defined in their molecular and cell biology so far.

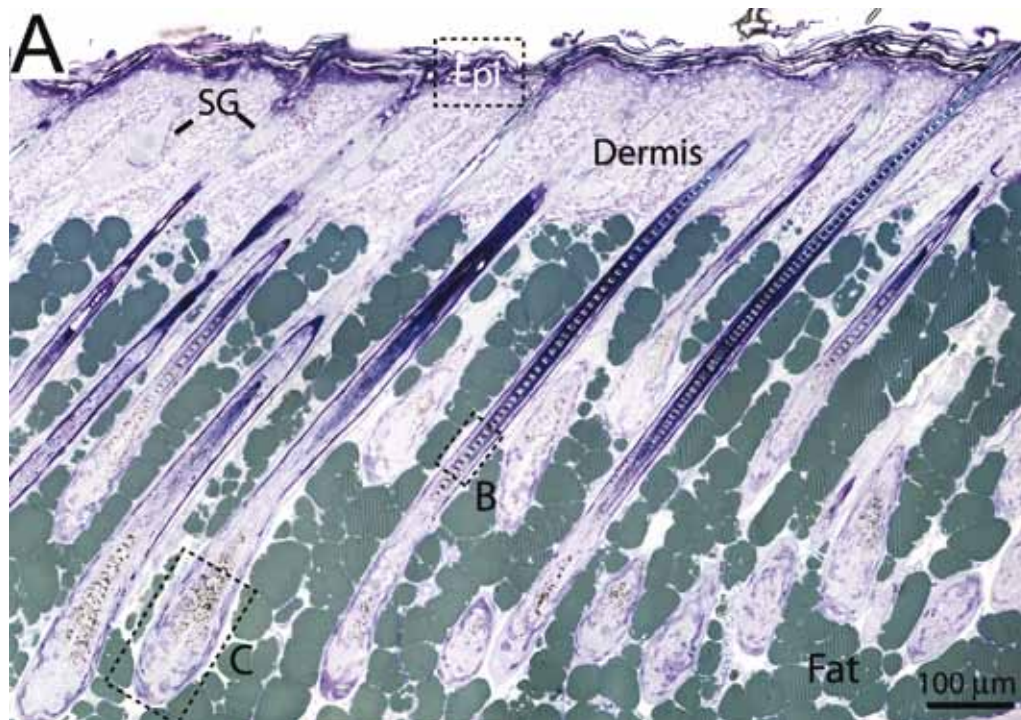


Fig. 1A. Mouse skin: panoramic view. Toluidine blue stained-section displays epidermis, dermis and HFs. Hair shafts emerge outside the epidermis. Subcutaneous fat stains green. SG, sebaceous glands. Boxed areas B and C are shown in the corresponding electron micrographs.

The normal process of skin epithelium development and maintenance implies complex and coordinated changes in cell transcription, polarity, adhesion and cytoskeletal dynamics. By understanding the physiological events that orchestrate skin homeostasis, we can elucidate the steps that go wrong in genetic skin diseases, including cancers (Fuchs, 2007).

The global question we are focusing on is how stem cells become mobilized from their niches to form tissues.

Skin is at the body surface, making it readily accessible and particularly well-suited for mouse and human genetics (Figure 1A). Two pillars of our research are our ability to grow human and mouse epidermal cells (keratinocytes) in the laboratory, and the use of transgenic and knockout technologies in mice. In our research approaches, we utilize a broad

range of techniques encompassing cell, molecular and developmental biology.

We would like to know the attributes of the multipotent skin stem cells that can differentiate to produce either epidermis or HFs. In order to achieve this goal, our lab has developed novel methods to purify these cells from mouse skin and we use microarray technology to establish their global pattern of gene expression (Blanpain et al., 2004; Tumber et al., 2004). Next, we are using this knowledge to investigate how changes in gene expression occur as stem cells respond to various external stimuli, choose a particular lineage and differentiate. We are exploring in detail the molecular coordination of the signalling pathways that operate on these stem cells. We would also like to reveal the mesenchymal-epithelial cross-talk that coaxes stem cells to form the HF in the embryo and then again coerce stem cells to regrow hair from this follicle in the adult. The global question we are focusing on is how stem cells become mobilized from their niches to form tissues.

To tackle this challenging question, it is essential to apply a broad range of expertise and multifaceted research approaches. Ultrastructural analyses by transmission and scanning electron microscopy have proven to be powerful techniques to examine mouse mutants with defects in the epidermis and/or HFs to gain additional insights into the coordinated regulation of their differentiation.

The hair follicle: a fascinating mini-organ

The HF is an amazingly complex structure. Transmission electron microscopy can reveal all the complexity and beauty of HF architecture (Figure 1B). Postnatally, the mature hair shaft is composed of a core, or medulla, cloaked by a concentric ring of cortical cells, which in turn are surrounded by a

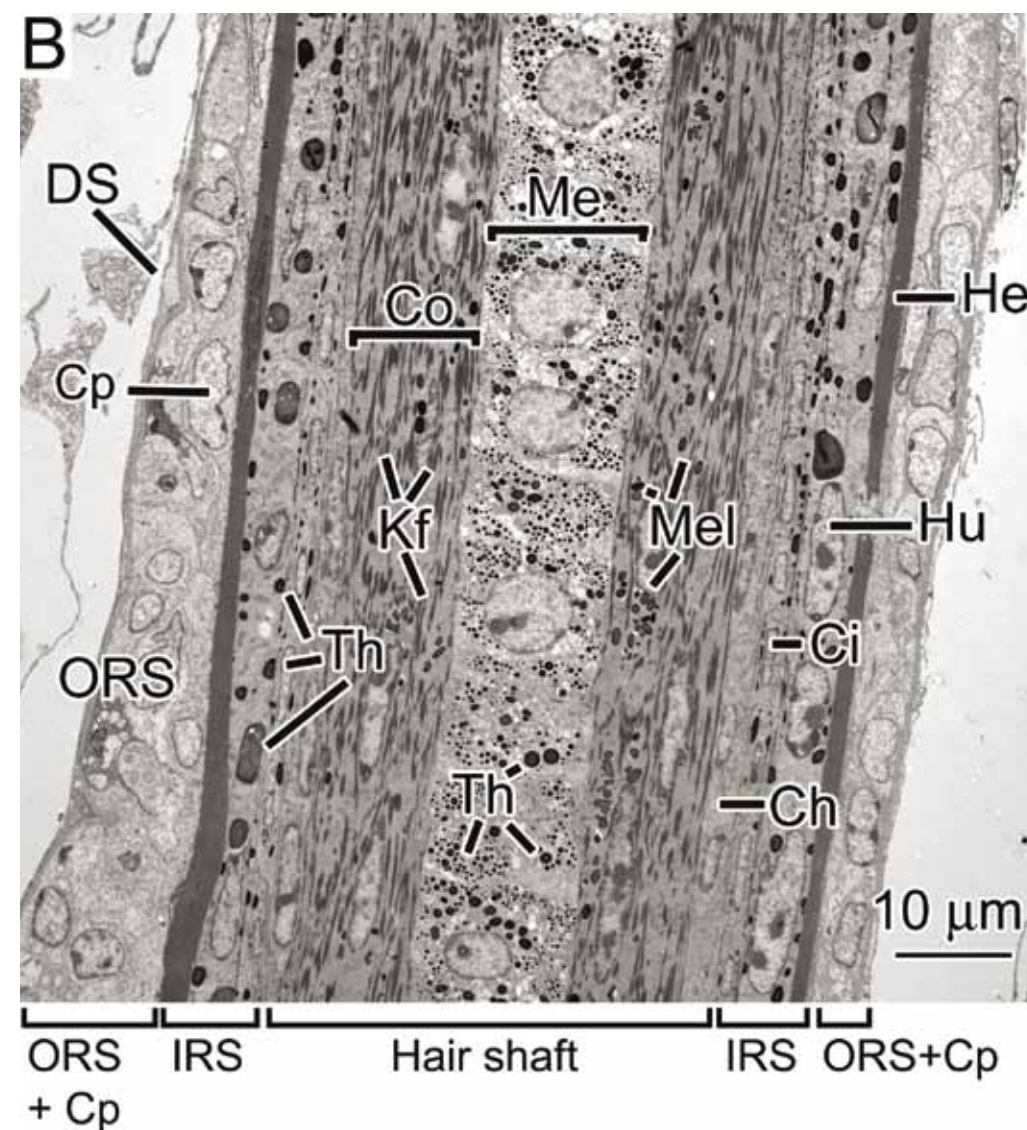


Fig. 1B. Ultrathin section through the mid-segment of an anagen HF. The hair shaft (HS) is composed of three layers: medulla (Me), cortex (Co) and cuticle (Ch). The cortex is rich in keratin filaments (Kf). The hair shaft is surrounded by the inner root sheath (IRS), which comprises three layers: cuticle of the IRS (Ci), Huxley (Hu) and Henle's (He) layers. The Henle layer is encased by the companion layer (Cp) and outer root sheath (ORS) and finally the dermal sheath (DS). Th, trichohyalin granules; Mel, melanin granules.

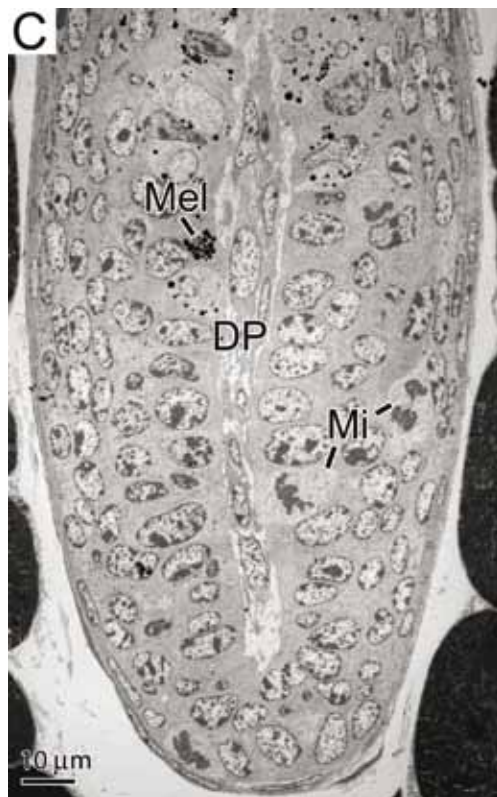


Fig. 1C. Ultrathin section of hair bulb. The vertical layer of cells at the centre corresponds to the dermal papilla (DP). Matrix cells are organized in an onion-skin like fashion. Note the presence of mitoses (Mi) and melanin granules (Mel).

layer of hair shaft cuticle (the hair surface). Beneath the skin surface, the hair is surrounded by an inner root sheath (IRS) composed of a cuticle, Huxley's layer and Henle's layer. The IRS cuticle interlocks with the hair cuticle to guide the hair but, near the skin surface, the IRS degenerates to release the shaft. Above the base (bulb) of the follicle, the Henle's layer is encased by the companion cell layer. The outer layer of cells, called the outer root sheath (ORS), is contiguous with the epidermis and contains a region known as the bulge below the sebaceous gland, at or near the insertion of the arrector pili muscle.

Both hair shaft and IRS form concomitantly through upward terminal differentiation of transiently amplifying progenitor (matrix) cells, which maintain contact with the dermal papilla (DP), the follicular mesenchyme at the core of the hair bulb (Figure

1C). A reservoir of stem cells, the bulge, resides at the base of the noncycling segment of the HF and replenishes matrix cells as they differentiate. It is really a delight to look at the HF using electron microscopy (EM). At the base of the follicle or hair bulb, the matrix cells are arranged like an onion skin and maintain their proliferative state as evident by the frequent mitoses. They keep this state through interaction with this cluster of specialized mesenchymal cells, the dermal papilla, which are separated by the basement membrane.

Hair follicle cycles - from degeneration to regeneration, with a rest in between

HF development is completed by approximately day 14 in the mouse. After this initial period of growth, HFs enter a degenerative phase (catagen) involving massive apoptosis of cells that leads to the loss of the lower two-thirds of the HF (Figure 2). During this process, the DP moves upward and stays connected to the lower part of the bulge by the epithelial strand. Upon full regression, the HF enters a resting stage (telogen) in which the bulge anchors the old hair (club). In telogen, the hair germ becomes a morphologically recognizable structure in close association with the bulge in the upper part and separated from the DP in the lower part by a basement membrane. As a new cycle of hair regeneration (anagen) begins, the hair germ (HG) begins to proliferate and grow downward in a process resembling HF morphogenesis. The cyclic nature of degeneration and regeneration supports the notion that stem cells within the HF exist and maintain this miniorgan.

Electron microscopy: a useful technique to analyze cell lineages in the hair follicle

Transmission and scanning electron microscopy are very instructive techniques for the study of the phenotypes of the different mutant mice in which epidermis and skin appendage formation can be compromised. High resolution analysis by EM can provide useful complementary information to

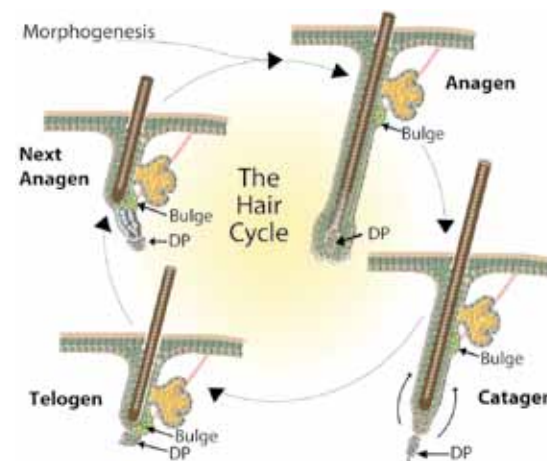


Fig. 2. The hair cycle. HFs undergo periodic cycling from anagen (growing phase) through catagen (regression), and into telogen (resting). At the end of telogen stem cells "wake up" to regenerate the HF. Reprinted from Alonso and Fuchs, 2003 with permission.

understand the participation of different stem cell genes in cell lineage specification in the HF.

We have studied several mouse mutants where ultrastructural analyses have revealed striking abnormalities in HF development. Interesting examples are the electron microscopic analyses of skin of GATA-3-null mice (Figure 3 and Kaufman et al., 2003), of mice with targeted loss of E-cadherin in skin epithelium (Figure 4 and Tinkle et al., 2004; Tinkle et al., 2008) and of mice with loss of microRNAs expression in skin by targeted ablation

Fig. 3. Scanning electron microscopy (SEM) analysis of hair shaft in GATA-3 KO mice. Ablation of transcription factor GATA-3 results in strikingly abnormal HFs due to defects in cell lineage determination. Wild-type follicles displayed a "shingle-like" pattern, characteristic of flat cuticle cells that constitute the outer layer of normal hair shafts. Although flat cuticle cells were present in KO shafts, their organization was highly abnormal (Fig. 5). Additionally, KO hair shafts were short and their diameter was large and irregular compared with their wild-type counterparts. In GATA-3 null hair follicles IRS progenitors failed to differentiate, whereas cortical progenitors differentiated but produced an aberrant hair structure. Reprinted from Kaufman et al., 2003 with permission.



of Dicer 1 or DGCR8 (Yi et al., 2006; Yi et al., 2009) in embryonic skin progenitors.

Slow cycling cells in the bulge

The bulge compartment of the HF was identified initially by its histological appearance. It appears as a thickening of the ORS located just below the sebaceous gland. Based on the principle that stem cells are used sparingly and therefore divide infrequently, researchers have used nucleotide labels in pulse-chase experiments to locate the slow-cycling label-retaining cells (LRCs) within the skin (Cotsarelis et al., 1990). Most of these cells were located in the bulge, which is now the best characterized SC niche in the skin.

Label retaining cells in the hair follicle are purified and characterized

The identification of LRCs in the bulge raised a challenging question: can these cells indeed function as stem cells? To verify this hypothesis scientists needed to show that HF LRCs have the ability to self renew and to generate all the skin epithelial cell lineages. First it was necessary to develop a method to isolate and characterize LRCs, especially since that could eventually allow their handling for potential stem cell derived therapies. A few years ago, two research groups, led by Elaine Fuchs and George Cotsarelis respectively, accomplished this task (So and Epstein, 2004). They engineered transgenic mice carrying specific labels on bulge cells which were then purified using fluorescence activated cell-sorting (FACS) based on these specific labels. The strategy of the Fuchs lab was to induce for a limited time the expression of a keratin 14 (K14) promoter-driven transgene, encoding a long-lived histone tagged with green fluorescent protein (GFP) (Tumbar et al., 2004). Keratin 14 is specifically expressed in the basal cells of epidermis and ORS cells, which includes bulge cells, therefore all cycling keratin 14 expressing cells became GFP-positive. By administering a drug to the mice, the expression of the transgene can be turned off and

the GFP label from actively dividing cells will 'wash out' after several months. They found, as predicted, those GFP-label-retaining cells were located in the hair bulge. Then standard FACS could be used to isolate and characterize the cells expressing high levels of GFP.

The Morris and Cotsarelis group based their approach on the expression of the intermediate filament protein keratin 15 (K15). They showed that K15 was specifically expressed in the bulge region while sparse in other skin epithelial cells (Morris *et al.*, 2004). They engineered mice in which the K15 promoter drives the expression of GFP, thus also allowing FACS-based sorting of cells into those expressing high levels of GFP. Later, the purification of bulge stem cells has been accomplished in our lab by FACS based on the expression of bulge surface markers such as $\alpha 6$ integrin and CD34 coupled with K14-GFP expression (Blanpain *et al.*, 2004).

Label-retaining cells are multipotent and can self renew

The isolation of HF bulge cells allowed researchers to verify self-renewal and pluripotency of these cells, the two crucial features of stem cells, by performing clonal analyses and engraftment. Bulge cells were cultured and grafted together with dermal cells onto the back of Nude mice (a mice strain which lacks hair due to a genetic defect). Nude mice developed tufts of hair at grafted sites. Microscopic analysis revealed that bulge cells were able to regenerate epidermis, HFs and sebaceous glands showing their multipotency (Blanpain *et al.*, 2004). The Cotsarelis group showed that the K15 bulge cells could produce all the epithelial components of the anagen follicle (Morris *et al.*, 2004).

These methods have allowed researchers to not only identify and image bulge LRCs, but also to

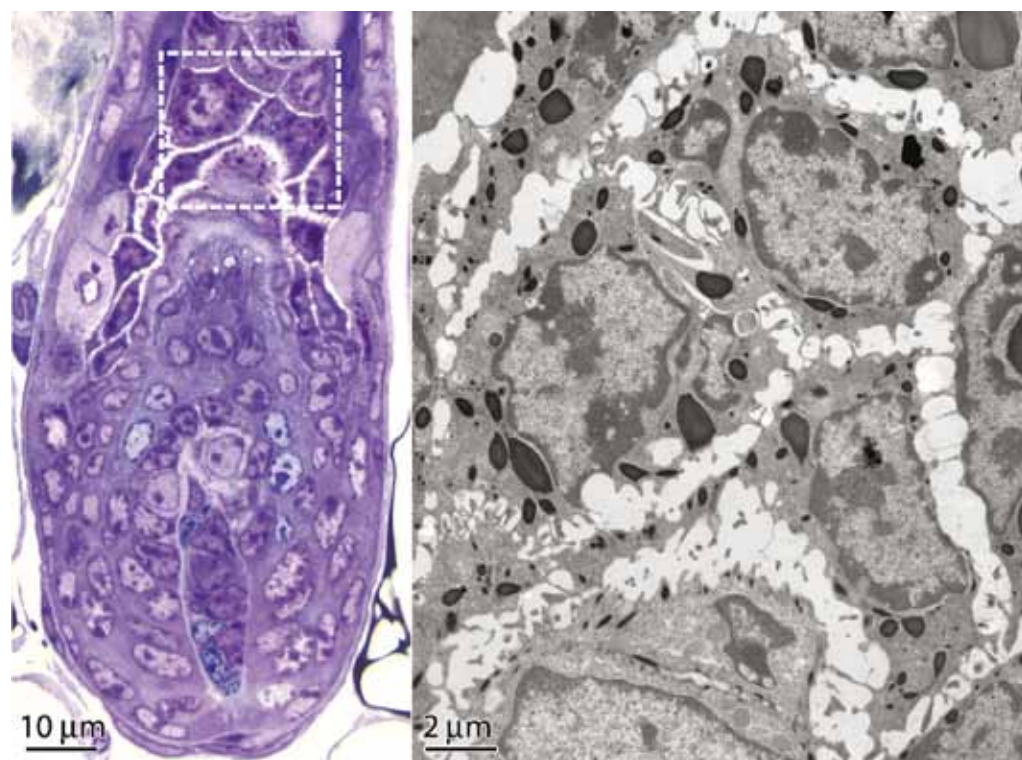


Fig. 4. HF bulb from mouse lacking E-cadherin in the skin epithelium. HFs lost the integrity of several layers, especially the inner root sheath layers. Ultrastructure of the boxed area shows Huxley's layer cells, with frequent intercellular gaps due to the loss of adhesion.

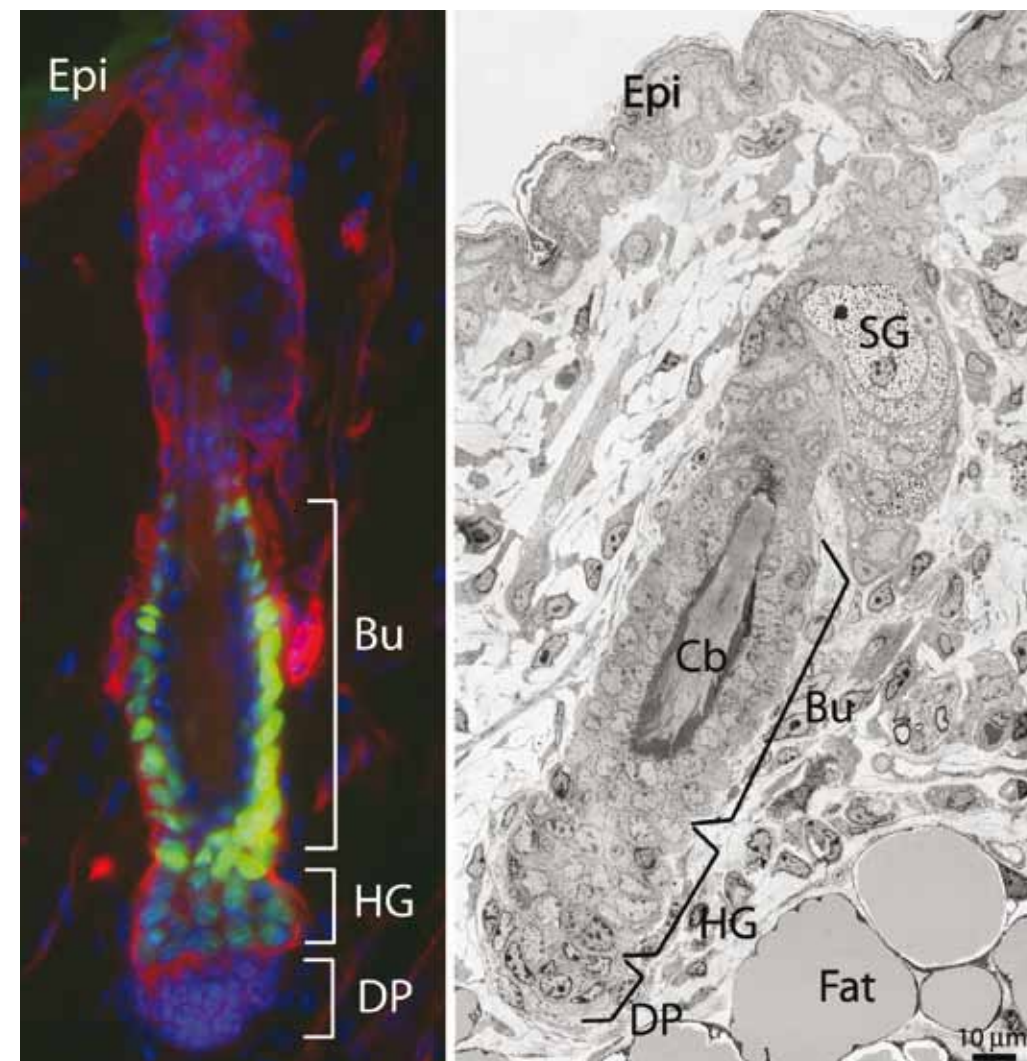


Fig. 5. HF in telogen. Slow cycling cells (marked by histone H2-GFP) are located in the bulge. The basement membrane is delineated in red by indirect immunofluorescence using an antibody against $\beta 4$ integrin. At the right ultrastructure of a telogen follicle, showing bulge (Bu) cells separated from the dermal papilla (DP) by a morphologically distinct structure, the hair germ (HG). Cb, club hair; Epi, epidermis; SG, sebaceous glands.

characterize their gene expression by performing microarray analyses. Approximately 150 genes are preferentially expressed in the bulge relative to the proliferating basal cells of the epidermis. Although each of the procedures developed by the Cotsarelis and Fuchs groups purifies slightly different cell populations, the array data are in quite good agreement, allowing researchers to take advantage of this information to gain more knowledge about HF stem cells. As a result of these studies, researchers have identified further markers of stem cells such as Tcf3, Lhx2, NFATc1, Sox9 and Lgr5, (Horsley *et al.*, 2008; Jaks *et al.*, 2008; Merrill

et al., 2001; Nguyen *et al.*, 2009; Nowak *et al.*, 2008; Rhee *et al.*, 2006) and are on the way to elucidate how these transcription factors act to maintain the bulge stem cell niche.

Stem cell activation during hair regeneration: role of the hair germ

Telogen, the dormancy period of HFs, ends when the follicle starts the rapid cell proliferation that characterizes anagen. This cyclic process of degeneration, rest and regeneration lasts for the whole life of the animal. Anagen and catagen phases

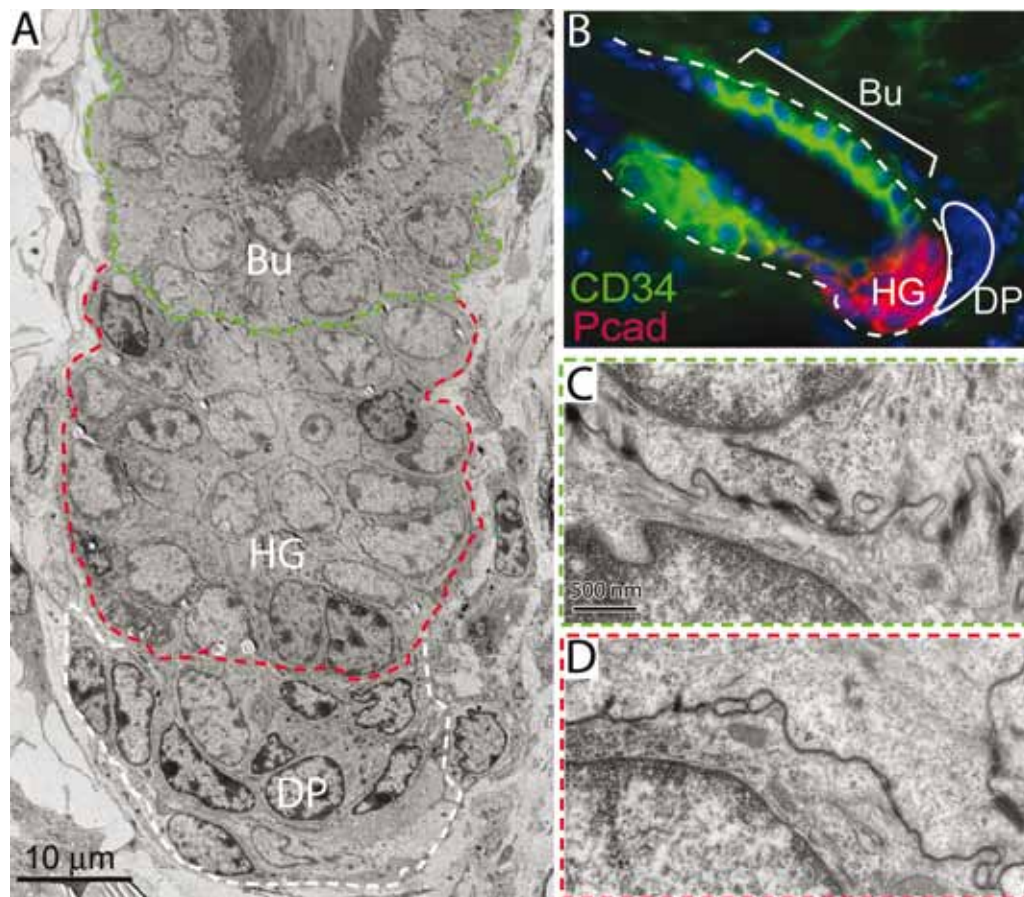


Fig. 6. Hair germ and bulge cells are biochemically and ultrastructurally distinct. A. Higher magnification of the lower part of a telogen follicle. Dotted green line encases the bulge area; dotted red line surrounds the hair germ and dotted white line the dermal papilla. HG cells display heterogeneity in chromatin condensation. B. Bulge cells express the marker CD34 (green) and while hair germ cells are negative for CD34 and express P-cadherin (red). Reprinted from Greco et al., 2009, with permission from Elsevier. C. and D. Ultrastructural analyses reveal morphological distinctions in hair germ and bulge cells intercellular junctions. C. The boundary between two bulge cells is rich in desmosomes. D. Hair germ cells possess fewer desmosomes in their intercellular junction.

remain constant in duration from one cycle to the next. In contrast, each telogen becomes increasingly longer than the previous one. During the second telogen, the DP and the lower part of the HF are in contact for nearly 4 weeks and the third telogen is even longer (Muller-Rover et al., 2001).

Two signalling pathways have been implicated in the HF transition from telogen to anagen: Wnt and BMP signalling. The roles of these two pathways in stem cell activation and quiescence have been unveiled in recent years (for a review see Fuchs and Nowak, 2008 and references therein).

However, the mystery about how stem cells become activated at the start of a new hair cycle is still unravelling. Several questions remain unanswered: how do HFs suddenly 'wake up' and start growing after sometimes long periods of dormancy? How does the follicle avoid using up its SC reservoir during the transition to anagen? Do other pathways in addition to Wnt signalling and BMP inhibition take part in triggering this transition to growth?

To answer these questions, our lab has focused on the extended second telogen phase of the hair cycle and dissected the earliest steps involved in SC activation and HF regeneration. There are two

distinct epithelial cell compartments in the lower follicle that exist throughout telogen (Figure 6): the slow-cycling bulge cells that express CD34 and the (secondary) hair germ (HG), a small group of P-cadherin-enriched cells that originate at the end of catagen. The hair germ is in direct contact with bulge cells and it is separated from the dermal papilla by a basement membrane (Lyle et al., 1999; Muller-Rover et al., 1999; Panteleyev et al., 2001). These two populations are also ultrastructurally different. Bulge cells display strong attachment to neighbouring cells companion layer cells through abundant desmosomes. On the contrary, hair germ cells have scant number of desmosomes.

Where does the HG come from? Different theories have tried to explain its origin. One hypothesis proposes that the HG originates from the lateral disc, a small pocket of Sonic hedgehog (Shh) - expressing cells in the matrix at the base of the anagen HF (Panteleyev et al., 2001). According to this theory, the bulge and the HG represent different populations of stem cells kept in separate niches at all stages of the hair cycle.

An alternative explanation is that the HG derives from CD34(+) label-retaining cells (LRCs) in the bulge. This could happen either directly by migration

of lower bulge stem cells at the end of catagen as proposed by (Ito et al., 2004), or indirectly through preservation of unused stem cells that may have exited the bulge at the end of anagen but persisted within the epithelial strand during catagen (Panteleyev et al., 2001).

Our lab has recently shown that the HG maintains its size, shape and morphology throughout telogen, where it persists as an morphologically distinct entity (Greco et al., 2009). By genetic lineage tracing we showed that while Shh-expressing cells give rise to the IRS lineage, they undergo apoptotic death during catagen and therefore could not generate the HG. By performing BrdU pulse-chase our studies support the conclusion that the bulge is the precursor of the HG. HG forms at the catagen to telogen transition. While HGs proliferate by late telogen, bulge cells stay dormant well into anagen. We uncovered that stem cell activation during hair regeneration is a two-step process: HG cells proliferate several days before bulge cells and are the major contributors to the first stage in HF regeneration. *In vitro*, HG cells also initiate colonies more rapidly than bulge cells but display reduced long term growth potential relative to bulge cells.

Finally, we have characterized the transcriptional profile of bulge, HG and DP populations by performing microarray assays on purified cell populations at telogen. We found that during the resting phase, both HG and DP are transcriptionally more dynamic than bulge cells and that key signalling proteins required for the telogen to anagen transition accumulate in these compartments in late telogen. Using a combination of *in vitro* and *in vivo* strategies, we demonstrated that FGF signalling contributes to the telogen to anagen transition, adding new insights into the process of stem cell activation (Greco et al., 2009).

HF stem cell characterization triggers a never ending cycle of exciting questions: could they be used for therapeutic purposes, such as correcting

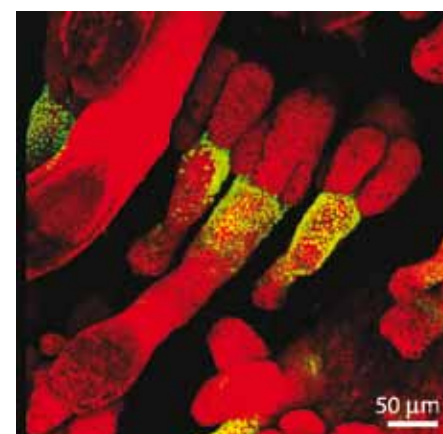


Fig. 7. HFs of mutant mice expressing histone H2-GFP to mark label retaining cells (green) in the bulge. A red fluorescent dye stains cellular membranes. Above the bulge are the sebaceous glands. A hair bulb is located at the lower left corner of the picture. Reprinted from Fuchs et al., 2004 with permission from Elsevier.

skin disorders or repairing wounds? Could they be the coveted solution for baldness? Could hair stem cells have the plasticity to become a non-skin cell type? Our knowledge about hair stem cells has experienced an active process of growth in the last few years. Will it come to a resting period? With so many challenges ahead, the active phase is prompted to continue.

Acknowledgments

My thanks go to Elaine Fuchs, for her continuous encouragement and support of my work. To the Fuchs Lab members, for providing me with such exciting material to work with. I am grateful to my colleagues, Ellen Ezratty for critical reading of the manuscript and Valentina Greco and Jonathan Nowak for providing immunofluorescence pictures.

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As a member of the Laboratory of Mammalian Cell Biology and Development at the Rockefeller University, Hilda Amalia Pasolli uses her electron microscopy expertise to gain insights on how skin cells proliferate, differentiate and regenerate. She employs ultrastructural analysis to visualize normal and aberrant skin cell structures after key signalling molecules in the skin have been deleted or disrupted. The lab, directed by Elaine Fuchs, uses a broad repertoire of approaches to study how stem cells located within the skin give rise to the skin's top layer, the epidermis and to skin appendages such as HFs and sebaceous glands. Hilda Amalia Pasolli received her Ph.D. in Chemical Sciences in 1993 for her thesis work at the Centre for Electron Microscopy at Cordoba National University in Argentina. She conducted postdoctoral research in the Department of Neurobiology at Heidelberg University in Germany from 1994 until 1998. She then returned to Cordoba as Assistant Professor and Researcher at the Centre for Electron Microscopy. She joined the Fuchs lab at Rockefeller as a Research Assistant Professor in 2002 and was promoted to Research Associate Professor in 2008. Hilda Amalia Pasolli was the recipient of the Diatome Award for her work on electron microscopy of skin in 2005 and 2009.

