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REVIEW

Home sweet home: skin stem cell niches

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Abstract The epidermis and its appendages, such as the hair follicle (HF), continually regenerate throughout postnatal mammalian life due to the activity of resident epithelial stem cells (SCs). The follicular SC niche, or the bulge, is composed of a heterogeneous population of self-renewing multipotent cells. Multiple intrinsic molecular mechanisms promote the transition of follicular SCs from quiescence to activation. In addition, numerous extrinsic cell types influence the activity and characteristics of bulge cells. Ultimately, the balance between these intrinsic and extrinsic mechanisms influences the function of bulge cells during homeostasis and tissue regeneration and likely contributes to skin tumorigenesis. Here, we review both the intrinsic and extrinsic factors that contribute to the skin SC niche.

Keywords Skin · Hair follicle · Stem cell niche · Cancer

Abbreviations

BCC	Basal cell carcinoma
Bcl2	B-cell CLL/lymphoma 2
Blimp1	B lymphocyte-induced maturation protein 1
BMP	Bone morphogenetic protein
BrdU	Bromodeoxyuridine
Dct	Dopamine tautomerase
DP	Dermal papilla
Ebf1	Early B cell factor
FACS	Fluorescence activated cell sorting
FGF	Fibroblast growth factor
H2B	Histone 2B
HF	Hair follicle
Hh	Hedgehog
IFE	Interfollicular epidermis
Lgr	Leucine-rich repeat containing G protein coupled receptor
Lhx2	LIM homeobox 2
Lrig1	Leucine-rich repeats and immunoglobulin-like domains 1
NFATc1	Nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent 1
ORS	Outer root sheath
Runx1	Runt-related transcription factor 1
Sca-1	Stem cell antigen-1
SCC	Squamous cell carcinoma
SCs	Stem cells
SG	Sebaceous gland
Sox9	Sex determining region Y-box 9
Tcf3	Transcription factor 3
Tcf4	Transcription factor 4
Tgf-β	Transforming growth factor-β

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Introduction

Stem cells (SCs) are a unique class of cells that possess the capability to self-renew and differentiate into specialized cell types. These specialized cells are resident within mature tissues and function to promote tissue homeostasis

and regeneration. Their function is tightly controlled through the local tissue microenvironment or niche that regulates SC activity [60]. Despite extensive characterization of the SC niche within invertebrate systems [8, 12, 38], the components of SC niches in mammalian tissues are not well defined.

Mammalian skin is a particularly useful organ in which to study SC activity because of its extensive capacity for regeneration and its compartmentalization of cell types. As the skin's outermost layer, the interfollicular epidermis (IFE) is a stratified layer of epithelial tissue that functions as a barrier to protect against external pathogens, water loss and physical injury. Cells in the basal layer of the IFE are mitotically active and undergo a terminal differentiation program as they exit the cell cycle and migrate upwards to form the differentiated keratinocyte lineage. This process is continual, as human skin is replaced every 2–4 weeks [1, 52, 59].

Epidermal cells are specified to lineages that form appendages such as the hair follicle (HF) and sebaceous gland (SG), which together with the arrector pili muscle make up the pilosebaceous unit. These individual appendages along with the IFE each contain their own population of SCs that function to renew and repair these micro-organs. In this review, we will focus on recent findings regarding the cells and molecules that comprise the niche for stem cells of the pilosebaceous unit.

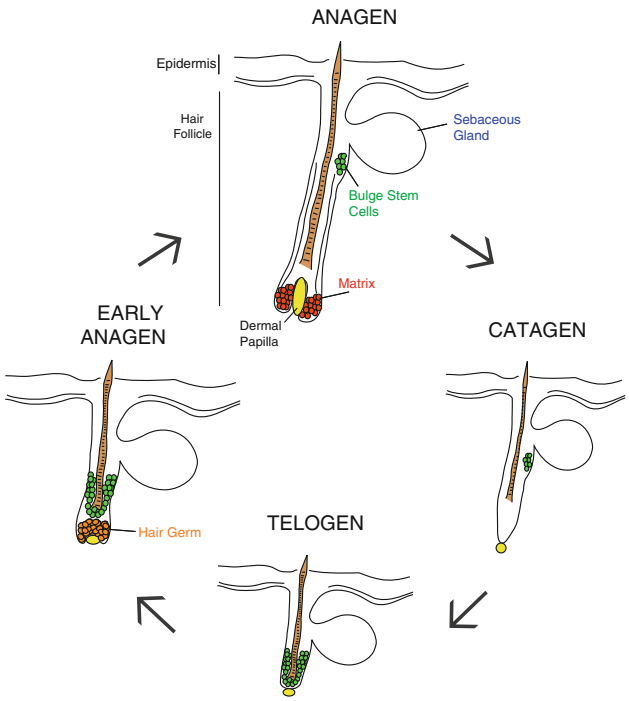

Fig. 1 The hair follicle cycle. After hair follicle morphogenesis (not shown), hair follicles produce external hairs during the anagen growth phase as proliferative matrix cells at the base of the follicle differentiate to form the hair shaft. Eventually, exhaustion of the matrix cells occurs and the follicle regresses in the catagen phase, resulting in a loss of the cycling portion of the follicle. After catagen, the follicle remains in the telogen rest phase until a combination of intrinsic and extrinsic cues initiate the onset of subsequent hair cycles

Identification of HF SCs

The HF undergoes repeated cycles of regeneration throughout the course of postnatal mammalian life, owing to the activity of SCs in the bulge region of the follicle (Fig. 1). The bulge region is located in the upper portion of the follicle and, in contrast to the lower cycling portion, is permanent through the repeated phases of growth (anagen), death (catagen) and rest (telogen) during the hair cycle. HF SCs are required to induce follicular growth, and our understanding of the mechanisms that regulate this process are continually unfolding.

The location of HF SCs was initially suggested through classic pulse–chase experiments using Bromodeoxyuridine (BrdU) and tritiated thymidine to label proliferative cells [10]. Due to their slow cycling nature, a single pulse of these nucleotide analogs is not adequate to label bulge cells. Instead, administration of these nucleotide analogs for several consecutive days in neonatal mice results in the sufficient labeling of all epidermal cells [10]. A subsequent 4-week chase period enables proliferative cells to dilute out the label such that only slow cycling cells remain labeled [67]. Surprisingly, the label-retaining cells of the HF were not located in the cycling portion of the follicle, but rather in the permanent portion of the follicle, the bulge region [10, 67].

The identification of proteins and promoter sequences specifically expressed in the bulge region led to lineage tracing and transplantation experiments that demonstrated that the bulge region contains bone fide stem cells for the follicle. A portion of the keratin 15 promoter, which exhibits preferential expression in the bulge, was used in genetic lineage tracing experiments to follow bulge progeny to the hair follicle lineages [40]. Another powerful marker used for identifying and isolating bulge cells is the hematopoietic SC marker CD34 [5, 35, 72], which coincides with keratin 15 expression and enriches for label-retaining cells [66]. By utilizing CD34 expression to isolate bulge cells, the capacity for bulge cell multipotency has been demonstrated through transplantation experiments of bulge cells onto immunocompromised mice [3, 49], exhibiting that bulge cells have the potential to contribute to lineages of the epidermis, SG and HF [42]. Furthermore, genetic lineage tracing experiments showed that bulge cells do not contribute to the IFE during skin homeostasis [29, 65, 67], yet they can be mobilized to regenerate the epidermis following injury.

Multiple populations of HF SCs

Recent studies throughout the past decade have revealed that the pilosebaceous unit is composed of heterogeneous cell types with multiple SC pools. Leucine-rich repeat containing G protein coupled receptor 5 (Lgr5), a SC marker first identified from its expression in gut SCs [2], is expressed in a subpopulation of HF SCs [30] (Fig. 2). Lgr5 expression partially overlaps with CD34 and keratin 15 in the telogen follicle, spanning from the lower bulge region to the hair germ. Lgr5+ cells actively proliferate during anagen onset and function as SCs by contributing to all regions of the HF.

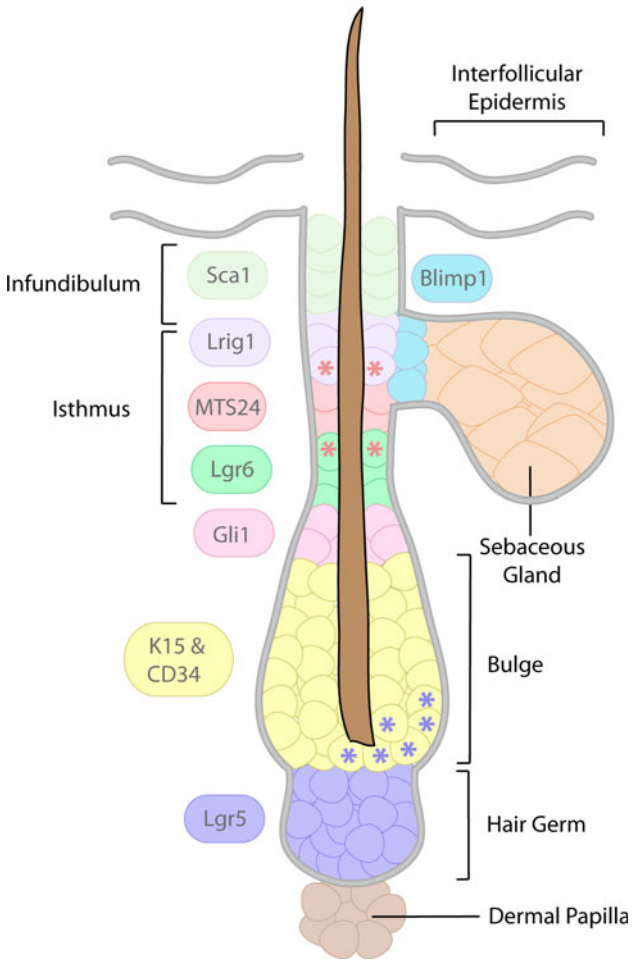

Fig. 2 Multiple populations of cells reside in the pilosebaceous unit. Schematic depicts stem cell populations in the adult murine hair follicle. Cells in the infundibulum express Sca1 (*olive*). Blimp1 expressing cells (*blue*) reside at the mouth of the sebaceous gland. The isthmus consists of cells expressing Lrig1 (*lilac*), MTS 24 (*salmon*) and Lgr6 (*green*). The upper bulge is positive for Gli1 reporter activity (*rose*), while the main bulge co-expresses K15 and CD34 (*yellow*). Lgr5 expression (*indigo*) has been identified in the hair germ and lower bulge region. *Salmon-colored asterisks* represent MTS24 expression overlap, and *indigo-colored asterisks* represent Lgr5 overlap

Several distinct SC subpopulations have also been identified above the CD34+ bulge region near the SG and in the isthmus or junctional zone. Directly above the bulge lies a population of cells in the central isthmus expressing Lgr6 [62]. During postnatal tissue homeostasis, lineage tracing of *Lgr6* expressing cells reveals that these cells give rise to the IFE and SG with infrequent contribution to the HF. In the upper portion of the isthmus lies a collection of basal cells expressing α6 integrin and keratin 14 that also express MTS24 [45]. Bulge cell markers keratin 15 and CD34 are absent from these cells and BrdU pulse–chase experiments show occasional label retention in this region, yet far less than in the bulge. In vitro clonogenicity studies of MTS24+ cells highlight their capacity for self-renewal and their potential as a SC pool. Additionally, B lymphocyte-induced maturation protein 1, or Blimp1, marks a population of unipotent progenitor cells at the SG bud site [24].

Spanning the upper isthmus and the junctional zone is a domain of cells expressing Leucine-rich repeats and immunoglobulin-like domains 1 (Lrig1) [31, 32]. Skin reconstitution assays have demonstrated that Lrig1+ cells contribute to all epidermal lineages, and lineage tracing reveals their contribution to the HF and SG during homeostasis [32]. Loss of Lrig1 expression throughout the animal results in increased levels of epidermal proliferation, suggesting Lrig1 plays a role in maintaining SC quiescence within the epidermis. Additionally, stem cell antigen-1 (Sca-1) marks a cell population in the upper infundibulum that can regenerate the IFE, but not the HF [33].

With ever more molecularly distinct populations of SCs being discovered throughout the HF, we are beginning to understand the complex cellular heterogeneity that exists within this structure. However, it remains unclear if the SC compartment functions as one general SC pool or if it consists of several independently functioning subpopulations. Lineage tracing experiments have begun to address this question to test if cells expressing one molecular marker can ultimately give rise to a cell expressing a different molecular marker with which it is not usually co-expressed. For example, lineage tracing experiments for Lgr5 expressing cells reveal that descendents of these cells localize to the MTS24-expressing isthmus region [30]. Although most molecular marker expression has been characterized throughout the hair cycle stages, future experiments should analyze molecular marker expression patterns at various stages of the cell cycle that could particularly play a role in SC activation. Furthermore, SC ablation experiments that eliminate a specific subpopulation of the SC compartment can test if other SC subpopulations can regenerate the eliminated population. These experiments may also reveal a SC hierarchy in the

hair follicle that dictates which SCs are capable of regenerating additional SC pools. By better understanding how these sub-populations function in the skin, we will enhance our understanding of developing directed targets specific for distinct SC populations in the HF.

Bulge cells during HF SC activation

The stimulatory mechanisms by which SCs become activated and mobilized are essential for maintaining follicular homeostasis. In the HF, single cell lineage tracing experiments have suggested that bulge cells migrate to the hair germ prior to proliferating [74]. In response to this migration, neighboring bulge cells self-renew to fill the gaps from their departed neighbors. Additionally, BrdU labeling experiments have demonstrated that cells in the hair germ compartment are activated prior to bulge proliferation during the telogen to anagen transition [21, 28]. While the sequence of these events remains elusive, these data implicate the cells of the hair germ as a compartment containing activated progeny from bulge SCs.

Single-cell labeling experiments have attempted to identify the point at which HF SCs lose their "stemness" along the path from bulge cell to differentiated cell during HF regrowth. Using a Histone 2B (H2B)-GFP pulse–chase technique [67], Fuchs and colleagues mapped the fates of bulge cell progeny throughout the hair cycle [26], revealing that the progeny of bulge SCs retain their cycling kinetics relative to their distance from the bulge. Cells that retain a high level of GFP label and have proliferated infrequently in the outer root sheath (ORS) are capable of returning to the bulge in the subsequent telogen follicle. Cells that have partially diluted out the GFP label due to a few cell cycle progressions reside in the middle portion of the ORS and get recycled to the new hair germ, but not to the new bulge. Actively cycling SC progeny in the ORS with low GFP retention are spared from apoptosis during catagen and form an inner layer of keratin 6+ bulge cells that function to anchor the hair in place. This layer of keratin 6+ bulge cells may serve as a signaling center for regulating HF SC activity, because ablation of this cell layer results in anagen induction [26].

Intrinsic regulation of HF SCs

With the ability to isolate bulge cells based on specific genetic tools, molecular characterization of bulge cells led to the identification of the intrinsic mechanisms that control the activity and characteristics of stem cells in the hair follicle. Tumbar et al. [67] devised a strategy to label and isolate slow cycling cells by expressing a doxycycline-regulated H2B-GFP under control of the keratin 5 promoter. In addition, expression of GFP under the keratin 15 promoter allowed molecular characterization of bulge cells [42].

Gene expression profiling of bulge SCs has revealed the upregulation of several molecular markers relative to those of their progeny in the basal layer [3, 42, 67]. In particular, the CD34-expressing domain in the bulge is grouped into two regions based on the level of α6 integrin expression and attachment to the basal lamina [3] (Fig. 2). These two populations have different gene expression profiles, yet both were shown to generate all lineages of the HF. Consistent with their slow-cycling nature, bulge cells express more cell cycle inhibitory genes and fewer cell cycle promoting genes than their progeny [42, 67].

Transcription factors have been shown to play important intrinsic roles in the functional regulation of HF SC activity (Fig. 3). In particular, bulge cells upregulate sex-determining region Y-box 9 (Sox9), which functions in the proper formation of the SC compartment and promotion of hair differentiation [48, 69]. Additionally, LIM homeobox 2 (Lhx2) has been shown to promote both bulge cell maintenance and quiescence [58]. Bulge cell label retention is regulated in part by expression of the transcription factors Nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent 1 (NFATc1) and Runt-related transcription factor 1 (Runx1) [25, 50, 67]. NFATc1 is expressed in the nuclei of a subpopulation of bulge cells throughout all stages of the HF cycle [25]. Epithelial-specific knockout of NFATc1 results in a loss of HF SC quiescence and precocious entry into anagen. Runx1, which is expressed in an increasing gradient from the bulge to the hair germ, is also required for bulge cell activation [50].

In addition to transcriptional regulation, the bulge is exposed to various signaling factors that play a role in regulating its activity (Fig. 3). In particular, bone morphogenetic protein (BMP) signaling has been shown to repress bulge cell proliferation, and the loss of this signaling results in premature bulge cell activation [3, 25, 34]. Plikus et al. [53] revealed a periodic expression pattern of *BMP2* mRNA in subdermal adipocytes throughout the hair cycle, implicating adipocytes as potential regulators of HF SC quiescence. Interestingly, the wave of *BMP2* expression is out of sync with the Wnt/β-catenin cycle, the latter of which functions to promote HF SC activation. Ultimately, the balance between BMP and Wnt signaling is functionally important in regulating the transition from quiescence to activation.

Although the Wnt signaling cascade is not active in bulge cells [11], these cells do express Frizzled receptors and transcriptional partners of β-catenin which enable them

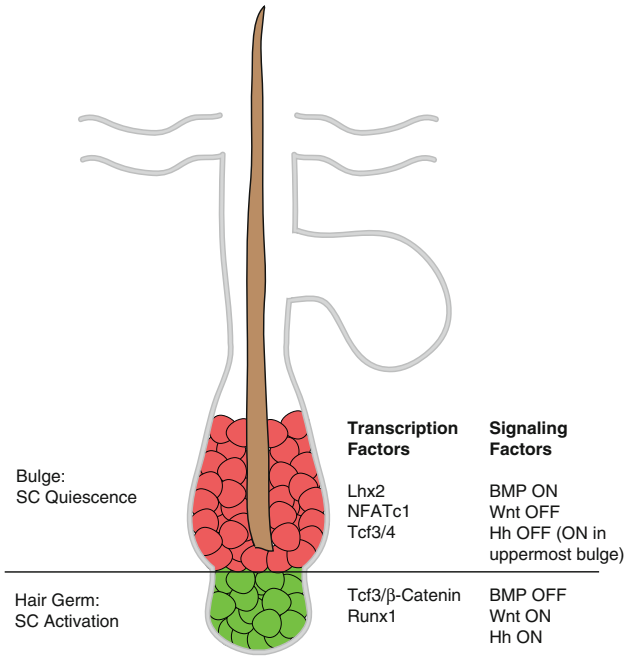

Fig. 3 Intrinsic factors and signaling pathways involved in HF SC activity. The schematic summarizes the transcription and signaling factors involved in balancing HF SC quiescence and activation. In the bulge, BMP signaling, Lhx2 and NFATc1 promote SC quiescence, while Tcf3/4 promote stem cell fate. Runx1 expression and activation of β-catenin following Wnt signaling occurs in an increasing gradient from the lower bulge to the hair germ, where they function to promote SC activation. Hedgehog signaling is active in the uppermost portion of the HF bulge and the hair germ compartment

to receive and process Wnt signals [43, 44, 67]. In the quiescent bulge, the β-catenin transcriptional coactivator Transcription factor 3 (Tcf3) promotes SC quiescence and inhibits differentiation in the absence of Wnt ligand [43]. Additionally, Tcf3 and Tcf4 function to promote self-renewal of epidermal SCs [44]. Expression of a stabilized β-catenin in telogen HFs induces premature hair growth [37, 39, 68], suggesting its role in bulge cell activation. Elevation of β-catenin levels in the bulge also results in the upregulation of cell cycle promoting genes and the activation of HF SCs [39].

Extrinsic regulators of HF SCs

The intrinsic factors that regulate bulge cell function are controlled by extrinsic signaling molecules produced by surrounding cell types. Several non-epithelial cell types including blood vessels, nerves, adipocytes and mesenchymal cells establish the dermal environment that surrounds the HFs. Recent data have implicated a number of these cell types in the regulation of HF SC activity. Below, we review the data supporting a role for different cell types as niche cells for the HF SCs (Fig. 4).

Dermal papilla

The dermal papilla (DP) is a collection of mesenchymal cells that forms prior to HF development and remains in close contact with the base of the HF throughout hair regeneration (Fig. 1). During embryonic skin development, epidermal cells form a placode, or region of thickening, that will generate a future HF. Underlying this thickening, the DP forms as a condensate of dermal fibroblasts that convenes beneath the specified epithelium. Bidirectional signaling between the epithelium and dermal condensate induces the proliferation and formation of a developing HF [14, 23, 41]. Mature DP cells have been isolated using fluorescence-activated cell sorting (FACS) and characterized molecularly in order to determine their gene expression profile [13, 56]. These analyses have revealed that the DP is a source of multiple signaling molecules that can aid HF regeneration, including Wnts, BMPs, noggin and fibroblast growth factors (FGFs) [4, 16, 21, 56, 57].

Various experiments have suggested that the DP acts as a niche for regulating HF SC activation. Mice with the *hairless* mutation lose the attachment of the DP to the HF during the first catagen, and these mice are unable to reactivate hair growth during subsequent hair cycles [51]. Additionally, DP-specific ablation of β-Catenin results in the inability for HFs to regenerate during the hair cycle, suggesting the importance of Wnt signaling and/or adhesion in DP cells during bulge SC activation [16]. Furthermore, DP cells have been suggested to control melanocyte activity [15, 17, 27]. In particular, the DP-specific gene *Corin* has been shown to regulate the agouti pathway to determine coat color. Future studies using DP specific gene deletion should determine the function of the DP during HF regeneration.

Neurons

A recent study has implicated neurons as niche cells for the HF. Researchers investigating the role of hedgehog (Hh) signaling in the skin identified sensory nerves surrounding the bulge as a source of sonic hedgehog signals that regulate HF SC activity [6]. Mice expressing a genetic reporter under the control of the *Gli1* promoter reveal that Hh signaling is activated in the lower bulge/hair germ and in a unique compartment above the CD34+ bulge yet beneath the MTS24+ and Lrig1+ regions of the upper follicle. Interestingly, the upper Gli1+ domain in the follicle corresponds to a contact site for sensory neurons, and denervation results in a loss of Gli1 reporter activity in this region. While denervation does not alter follicular regeneration, the contribution of the upper follicle cells to wound healing and SG homeostasis may implicate Shh signals in these processes [6].

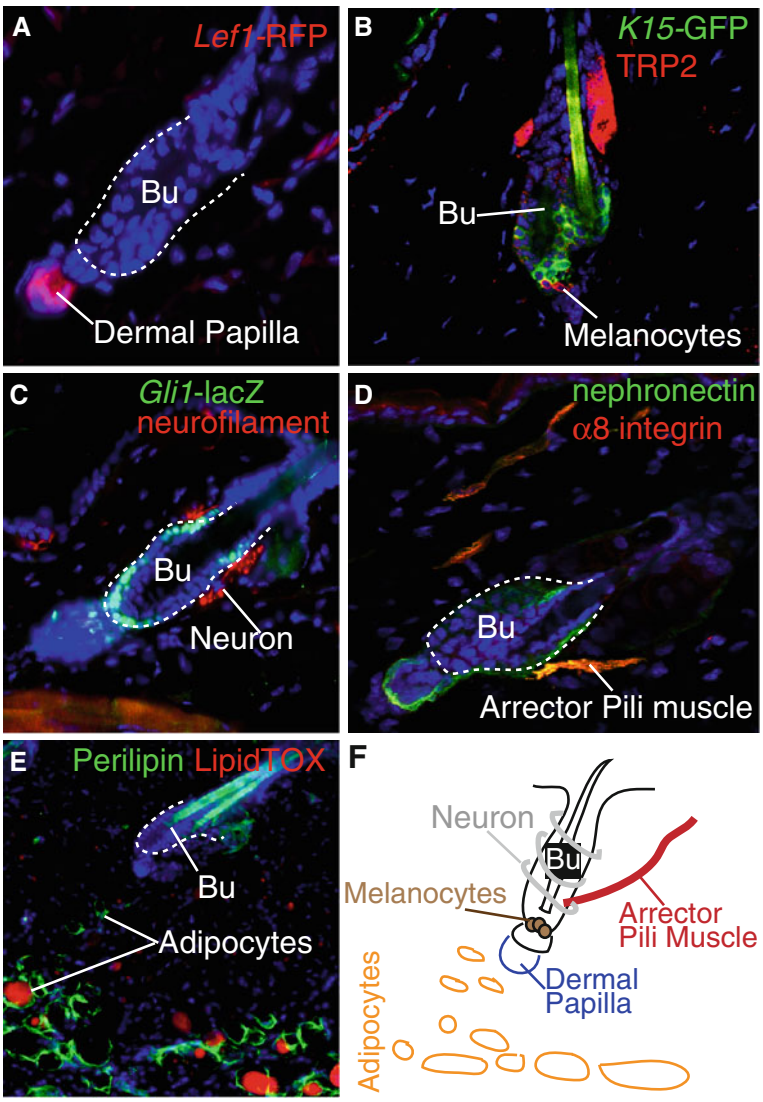

Fig. 4 Non-epithelial cell types compose the stem cell niche. Fluorescent reporters and immunostaining reveal the proximity of non-epithelial cell types to the hair follicle bulge (Bu). **a**, **b** The dermal papilla (*Lef1*-RFP) and melanocytes (TRP2) reside below the bulge. In contrast, the arrector pili muscle (α8 integrin) (**c**) and peripheral neurons (neurofilament) (**d**) attach to the side of the bulge cells. The adipocytes (**e**) underlie the follicular structure in the dermis. **f** Schematic illustrating the niche cells in the skin. Images courtesy of Michael Rendl (*Lef1*-RFP), Hironobu Fujiwara and Fiona Watt (nephronectin; α8 integrin), Isaac Brownell and Alex Joyner (Gli1-lacZ; neurofilament), and Mayumi Ito (K15-GFP; TRP2)

Adipocytes

Adipocytes occupy a large portion of the skin below the fibroblast and extracellular matrix rich reticular dermis. Interestingly, the size of the intradermal adipocyte layer was shown to dramatically change in parallel with the hair cycle [7, 9, 18, 22]. However, the role of these cells in the skin was unknown. Two recent studies have shed light on the potential function of these cells in the control of HF growth.

By exploring the mechanisms by which the intradermal adipocyte depot increases during HF growth, we have recently demonstrated a functional role for adipocytes as extrinsic regulators of HF SC activity [18]. BrdU pulse–chase experiments demonstrate that a dynamic process of adipogenesis parallels the murine HF cycle to increase the size of the adipocyte layer during follicular growth. By analyzing hair regeneration in mouse models that lack immature and mature adipocytes, the role of immature adipocytes in the activation of hair regrowth was revealed. These data reveal that immature subcutaneous adipocytes induce new follicular growth. A role for mature adipocytes in hair cycling was also suggested based on the expression of BMP2 mRNA in these cells during the hair cycle [53]. Interestingly, BMP2 expression in adipocytes corresponds to the stages of telogen that were refractory to anagen induction, suggesting that mature adipocytes may control telogen duration. Additional studies using adipocyte-specific gene deletion are required to fully investigate the molecular events controlled by intradermal adipocytes in the skin.

Besides their role in energy storage, adipocytes can play an important role in thermal regulation and as a mechanical cushion for tissues. The coordinated regulation of adipogenesis and hair follicle cycling may have some adaptive benefits for an organism. If intradermal adipocyte stores are

depleted, this coordination may allow energy conservation by not generating a new hair follicle. Furthermore, the interplay between adipogenesis and hair cycling may be involved in seasonal changes in hair growth among mammals. For instance, the stimulation of adipogenesis and adipocyte growth during months of food abundance may promote hair growth to protect and warm the animal during winter months. Further investigation of the interplay between intradermal adipocytes and the hair follicle should reveal whether these roles can influence hair biology.

Arrector pili muscle

The bulge cells also interact with the arrector pili muscle, which erects the hair to form "goosebumps" during stimulation by the sympathetic nervous system in response to stress such as cold, fear, etc. Fujiwara and colleagues recently showed that the interaction between the bulge and the arrector pili muscle occurs through the expression of the extracellular matrix protein nephronectin by bulge cells and its receptor, $\alpha 8/\beta 1$ integrin, which is expressed on the arrector pili muscle [19]. Arrector pili muscles are unable to physically attach to the bulge in *nephronectin* knockout mice and instead attach to a region of the upper bulge that expresses another extracellular matrix molecule, EGF-like-domain, multiple 6 (EGFL6). Similarly, when $\alpha 8$ integrin expression is ablated in mice, the arrector pili muscle adopts a random attachment to the EGFL6 region or the nephronectin-expressing bulge region. Therefore, correct arrector pili muscle attachment is dependent on the proper basement membrane deposition of the bulge. Whether the attachment location alters hair erection upon neuronal stimulation is unknown.

Proper adherence of the arrector pili muscle to the hair follicle bulge is an essential feature in promoting survival of an organism. For example, hair erection plays a role in mammalian thermal regulation by trapping air close to the skin to insulate the animal when cold. Piloerection also causes an animal to appear larger in size, which serves as a useful defense mechanism to intimidate predators. Functional experiments are needed to test the structure–function relationship of the arrector pili muscle in hair erection for these purposes.

Melanocyte SCs

The bulge cells also interact with the neural crest-derived melanocyte SCs in the HF, which supply pigment to the follicular keratinocytes [55]. Melanocytes regenerate in parallel with the hair cycle, and melanocyte SCs are responsible for generating melanocytes throughout postnatal mammalian life [61]. Melanocyte stem cells reside in the bulge and express the early melanocyte marker dopamine tautomerase (Dct), also known as Trp2 [46]. The interaction of the bulge and melanocytes requires the production of the ECM protein Col17a1, and mice deficient for *Col17a1* lose both HF and melanocyte SCs [64]. Overexpression of *Col17a1* rescues this defect, demonstrating that the bulge serves as a functional niche for proper melanocyte SC maintenance.

Transforming growth factor β (Tgf-β) and Wnt signaling also play a role in regulating melanocyte SC maintenance and activation, respectively. Conditional ablation of Tgf-β receptor 2 in melanocytes results in premature hair graying due to melanocyte depletion, suggesting that Tgf-β signaling is involved in melanocyte SC maintenance [47]. Additionally, in vitro experiments suggest that Tgf-β signaling promotes quiescence in melanocyte SCs. Since Tgf-β signaling is active in the HF bulge, it may serve as a source for this important niche signal to maintain quiescence in melanocyte SCs [67].

Recently, Wnt signaling has been shown to regulate the coordinated activity of epithelial and melanocyte SCs in the HF [54]. Conditional stabilization of β-catenin in melanocyte SCs drives their premature differentiation, whereas melanocyte specific ablation of β-catenin inhibits their differentiation. Additionally, epithelial specific stabilization of β-catenin using mouse models expressing inducible forms of Cre recombinase under the control of the *keratin 15* promoter, which drives expression in the bulge, results in the expansion of Dct+ melanocyte cells throughout the upper HF and epidermis. Thus, elevation of Wnt signaling during follicular growth promotes the activation of melanocyte SCs to induce pigmentation in newly forming HFs.

Recent findings on the interplay between the bulge and diverse cell populations in the skin continue to shed light on the vital role of the bulge as a regulator of skin homeostasis. In addition to serving as a niche for HF SCs, the bulge likely regulates the activity of multiple cell types in the skin as indicated by the interplay between melanocytes and bulge cells [54]. For example, reciprocal signaling between the activated SCs of the follicle and the DP have been identified [56]. In addition, the dynamic process of adipogenesis that parallels the hair cycle [18] may be dependent on signaling from bulge cells to initiate this process. Further research on the interaction of the bulge with non-epithelial cell types in the skin may elucidate its role as an extrinsic regulator in the skin.

Contribution of bulge cells to skin tumors

By better understanding the mechanisms that control HF SC function during normal development and tissue homeostasis, we can attempt to reverse the processes that

make skin SC function go awry, as in skin tumors. Epithelial skin cancers, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are very common. It is well known that UV irradiation induces DNA damage that must be repaired to maintain genomic integrity. Keratinocytes are exposed to multiple environmental stimuli that can induce DNA damage, particularly UV exposure from the sun. Interestingly, bulge cells in the HF appear to have extra armor in the battle against DNA damage than their basal layer counterparts, since they express higher levels of B-cell CLL/lymphoma 2 (Bcl2) protein, an anti-apoptotic protein that stimulates their resistance to programmed cell death [63]. Additionally, a downregulation of p53 in bulge cells empowers these cells to resist DNA damage.

Bulge cells were initially thought to give rise to skin tumors based on morphological criteria. Recently, two groups experimentally established bulge cells as a cell of origin for SCC by targeting a constitutively active Kras mutant to distinct epithelial cell populations in the skin using genetic recombination experiments [36, 71]. Upon removal of p53, SCCs arose when Kras was expressed in bulge cells but not their transiently amplifying progeny of the HF. Although the HF progeny are short-lived and may account for their lack of tumor production, these studies demonstrate that HF SCs are capable of generating SCCs when oncogenes are expressed and tumor suppressors are downregulated.

In addition to SCC, BCC can also be derived from HF bulge cells. After treatment with ultraviolet irradiation, mice heterozygous for the patched receptor generate BCCs that are derived from bulge cells, as shown by lineage tracing experiments [70]. Furthermore, targeting activated Gli2, the primary transcriptional effector of Hh signaling, to bulge cells via an inducible genetic system results in BCC formation [20]. Other genetic systems expressing an activated smoothened receptor in bulge cells have suggested that Hh mutations in the IFE induce BCC formation [73]. Together, these studies suggest that different cell populations are capable of BCC formation depending on the amount of activated Hh signaling. Lineage tracing of bulge cells following different tumor-promoting stimuli may elucidate the early mechanisms by which bulge cells give rise to tumors. In addition, the recent identification of the influence of skin niche cells on bulge cell activity suggests that niche cells may also control the initiation and promotion of skin tumors.

Concluding thoughts

Recent advances in our understanding of the cellular and molecular mechanisms that control skin homeostasis have revealed that a multitude of cell types in the skin interact to generate a complex and multifaceted niche for epithelial stem cells. In the future, examining how the skin niche cells and the signals that they generate go awry during skin diseases and cancers will shed light on how the niche is regulated during disease states. To this end, it will be crucial to develop specific tools to genetically target non-epithelial cell types. These tools will aid in our understanding of skin niche cells as well as how these cell types contribute to niches in other tissues, illuminating the components of mammalian tissue SC niches.

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