

The Sebaceous Gland Stem Cell Niche

Karen Reuter and Catherin Niemann

Abbreviations

AP-1	Activator protein 1
B	Bulge
BCC	Basal cell carcinoma
BLIMP1	B-lymphocyte-induced maturation protein 1
BMP	Bone Morphogenetic Protein
BrdU	5-bromo-2'-desoxyuridine
CD34	Hematopoietic progenitor cell antigen CD34
DAPI	4',6-Diamidin-2-phenylindol
DMBA	Dimethylbenz-[a]-anthracene
EMT	Epithelial-mesenchymal transition
EDAR	Ectodysplasin A Receptor
FGF	Fibroblast growth factors
Hh	Hedgehog
HF	Hair follicle
hr	Hairless
HS	Heparin sulfate
IFE	Interfollicular epidermis
Itga6	α 6-integrin
JZ	Junctional zone
K14	Keratin14
K15	Keratin15
Kras	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
Lef1	Lymphoid enhancer factor 1
Lgr5/6	Leucine-rich repeat-containing G-protein coupled receptor 5/6

K. Reuter · C. Niemann (✉)

Center for Biochemistry, Medical Faculty and Center for Molecular Medicine Cologne,
University of Cologne, Cologne, Germany
e-mail: cnieman1@uni-koeln.de

C. Niemann

Institute for Biochemistry, Center for Molecular Medicine Cologne, University of Cologne,
Robert-Koch-Str. 21, D-50931 Cologne, Germany

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Lrig1	Leucine rich immunoglobuline-like factor 1
Nfatc1	Nuclear factor of activated T-cell c1
NMSC	Nonmelanoma skin cancer
Plet1	Placenta-expressed transcript 1
Ptch1	Patched1
PI	Propidium iodide
Rac1	Ras-related C3 botulinum toxin substrate 1
Ras	Rat sarcoma
SC	Stem cell
SCC	Squamous cell carcinoma
SCD1	Stearoyl-Coenzym A Desaturase 1
SCLT	Sebaceous carcinoma-like tumors
SG	Sebaceous gland
Smad7	Mothers against decapentaplegic homolog 7
Smurf2	SMAD Specific E3 Ubiquitin Protein Ligase 2
Snail	Snail family zinc finger
Sox 9	SRY (sex determining region Y)-box 9
Str	Stroma
T	Tumor
TCF	T-cell factor
Tfam	Transcription factor A, mitochondrial
TPA	12-O-tetradecanoyl-phorbol-13-acetate
UI	Upper isthmus

1 Physiology and Function of the Sebaceous Gland

The skin within its cellular complexity accomplishes many vital functions. Eminently, it forms the protective barrier against harmful insults of the environment and prevents water loss of our body. The essential functions of the skin are assured by the multi-layered epithelium of the interfollicular epidermis (IFE). In addition, over the last years a variety of elegant studies demonstrated an important role of epidermal appendages, including the hair follicle (HF) and sebaceous gland (SG) (Fig. 1) for skin physiology and principal functions of the organ. Although, the SG has not attracted the same intense scientific attention as for instance the HF structure, remarkable progress has been made in our understanding of basic cellular mechanisms that govern SG function and physiology. It is well established that normal development and maintenance of the SG are crucial for homeostasis of mammalian skin [47]. In particular, atrophic SGs and defects in sebaceous lipid production lead to a disturbed barrier function and relevant skin diseases.

The main task of the SGs is to continuously produce mature, differentiated sebocytes and to release sebum to lubricate and waterproof the skin [47, 65, 80].

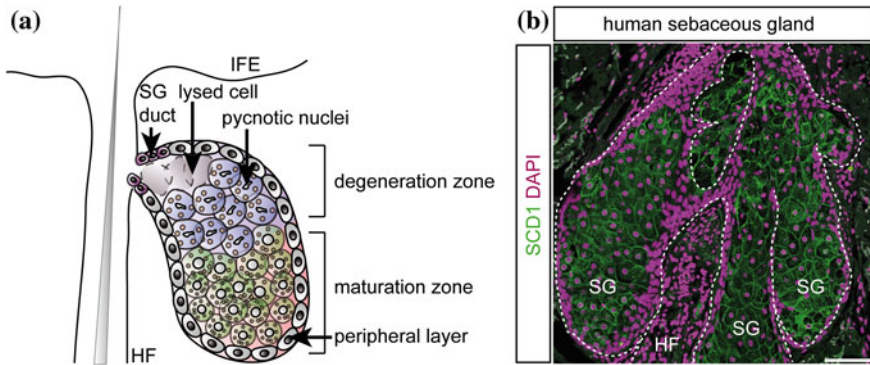


Fig. 1 Morphology and cellular composition of the sebaceous gland. **a** Schematic illustration of the sebaceous gland, presenting the different compartments of sebocyte differentiation in mice. Cells leaving the peripheral layer undergo a defined program of cellular differentiation, including enlargement and production of lipid droplets (maturation zone), followed by progressive maturation and accumulation of lipid droplets until cell lysis of terminal differentiated sebocytes to release sebum (degeneration zone). **b** Staining of human sebaceous glands for the sebocyte marker SCD1 (green) and nuclei stained by DAPI (magenta). IFE, interfollicular epidermis; SG, sebaceous gland; HF, hair follicle; SCD1, stearoyl-Coenzyme A desaturase 1; DAPI, 4',6-Diamidin-2-phenylindol. Scale bar: 50 μ m

Therefore, mature sebocytes need to be replaced by proliferating cells localizing to the basal layer at the peripheral zone of the gland. These basal undifferentiated cells are attached to a basement membrane separating the gland structure from the surrounding dermal tissue. SG cells leaving the basal layer undergo a well-defined program of cellular differentiation (Fig. 1a, b). The underlying molecular and cellular signals steering this important process are not well understood yet but most likely involve intrinsic cellular signaling pathways as well as regulation by hormones, the extracellular matrix and surrounding stromal cells. Adjacent to the single layer of basal cells, sebocytes localize to the maturation zone of the gland. In this compartment, sebocytes enlarge and produce lipid droplets [74]. As sebocytes are squeezed towards the center of the gland they accumulate more lipid droplets and progressively mature. Finally, mature sebocytes reach the necrosis zone of the gland. Pyknotic nuclei are indicative that sebocytes are about to degenerate and to release the lipid-containing sebum into the specialized secretory duct of the gland and the follicular canal to eventually reach the surface of the skin (Fig. 1).

As essential part of the pilosebaceous unit, the SG is associated with the junctional zone of the HF structure (Figs. 1 and 2). Linking the SG to the HF structure, SG duct cells thought to play an important role balancing the crosstalk between HF junctional zone and the SG, which is essential for normal gland homeostasis. In addition, SGs are formed independently from the HF and can be found as specialized glands in distinct regions of mammalian skin, e.g. as Meibomian glands of the eyelid or as Fordyce's spots of the oral epithelium [65].

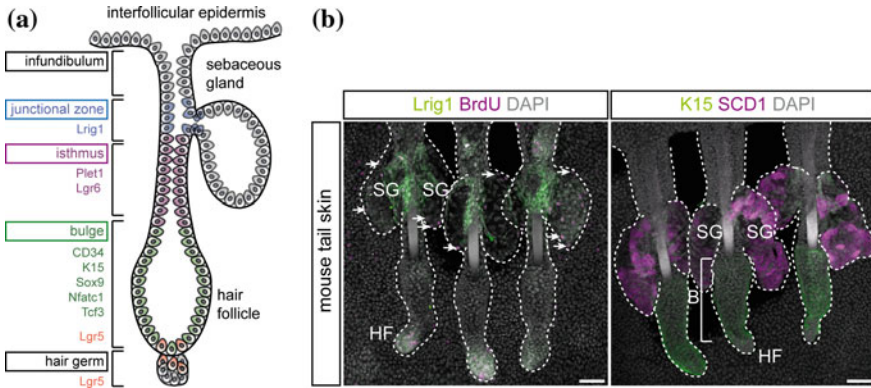


Fig. 2 Stem and progenitor cell populations of the adult hair follicle and the sebaceous gland. **a** Schematic presentation of distinct stem cell compartments localizing to the junctional zone (blue), isthmus (purple), bulge (green) and the hair germ (red). Marker for stem and progenitor cells are listed next to the corresponding compartment. **b** Epidermal whole mounts from mouse tail skin stained for the junctional zone marker (left) Lrig1 (green) and proliferation marker BrdU (magenta). Arrows indicate proliferating cells within the peripheral layer of the sebaceous gland. Staining of bulge stem cell marker (right) Keratin15 (green) and the sebocyte marker SCD1 (magenta). Nuclei were stained with DAPI (grey). SG, sebaceous gland; HF, hair follicle; B, bulge; Lrig1, leucine rich immunoglobuline-like factor 1; BrdU, 5-bromo-2'-desoxyuridine; K15, Keratin15; SCD1, stearoyl-coenzyme A desaturase 1. Scale bar: 50 μ m

2 Development of the Sebaceous Gland and Establishment of Progenitor Pools

The development of the SG is coupled to HF morphogenesis thereby forming the pilo-sebaceous unit of mammalian skin. HF morphogenesis is initiated during embryogenesis as a result from intensive neuroectodermal-mesodermal interactions and extensive molecular signaling between the different cell types, epithelial and fibroblast cells [16, 41, 67]. Based on defined morphological criteria, the process of HF development has been divided into eight distinct stages. Changes in morphology and progressive maturation results in a complex miniorgan that is the product of a sequence of tightly regulated signaling events, including the Wnt, EDAR, Bmp, Hedgehog and FGF pathways, among others [15, 43]. In the course of formation of the HF structure, keratinocytes start to form a placode (stage 1), a thickening of the epidermis, which is progressing into a hair germ (stage 2) and subsequently a bulbous peg (stage 3 to 5). First sebocytes of the future SG are seen in the upper part of the developing follicular structure at stage 5 (Fig. 3) [19, 56, 64]. As the follicle goes through stages 6 to 8 finally forming a mature HF, emerging sebocytes form a glandular structure that remains associated with the HF via the sebaceous duct. The complex cellular and molecular processes of shaping the SG and defining the correct size and cellular organization (Fig. 1) are not understood yet and require more detailed investigations.

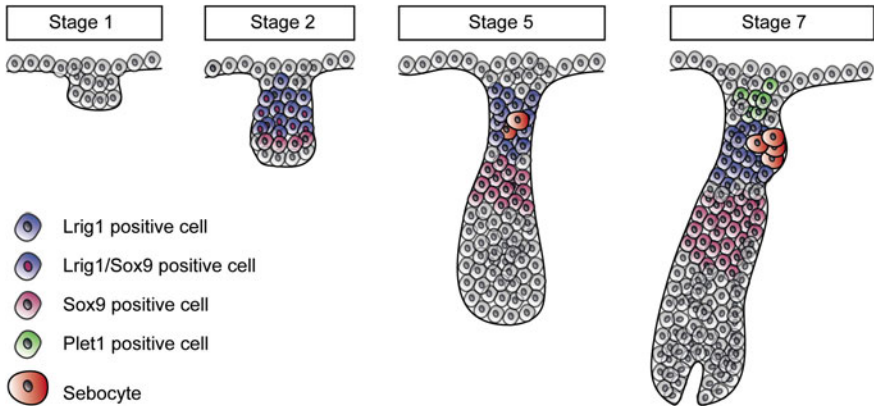


Fig. 3 Establishment of stem cell compartments during morphogenesis of the sebaceous gland. Schematic illustration presenting dynamic pattern of stem cell marker expression during the development of the pilosebaceous unit, starting from placode formation (stage 1), progressing into a hair germ (stage 2), forming the bulbous germ (stage 5) and subsequently bulbous peg (stage 7). Of note Lrig1 and Sox9 positive cells show overlapping localizations at stage 2 and are separating at stage 5, when first sebocytes develop. Lrig1, leucine rich immunoglobuline-like factor 1; Sox9, SRY sex determining region Y-box 9; Plet1, Placenta-expressed transcript 1

Recent studies have been looking into the potential role of epidermal stem and progenitor cells in the process of sebocyte differentiation and SG development. In general, various epidermal SC marker molecules are expressed early during HF formation, including Sox9, Keratin15 and Lrig1 [19, 32, 53]. Initially, Sox9, a marker of the future HF bulge and Lrig1, which is decorating stem cells of the junctional zone in adult skin (Fig. 2) are both expressed by the same progenitor cells contributing to hair germ formation. As HF formation proceeds and lineage specification takes place, Sox9 and Lrig1 expressing cells disperse and ultimately localize to the respective regions within the pilosebaceous unit (Fig. 3) [19]. Sox9-positive SCs that populate the future HF bulge region are involved in SG formation. It has been demonstrated that depletion of Sox9 from embryonic mouse epidermis leads to a block in SG morphogenesis [53]. Thus, Sox9 expression during early stages of HF formation, perhaps by precursor cells that are also positive for Lrig1, is required for proper SG development. Alternatively, Sox9 expression by early bulge SCs could promote differentiation of the sebocyte cell lineage by currently unknown mechanisms.

Recently, it was shown that sebocytes are generated by Lrig1-positive SCs. Detailed analysis of this process revealed that subsequent SG cells are establishing from asymmetric cell fate decision of Lrig1 SCs [19]. Sebocytes emerging during development are enclosed by Lrig1-positive SCs that undergo cell division. In contrast, cells positive for the sebocyte marker SCD1 do not express Lrig1 and do not proliferate. However, the molecular mechanisms regulating the positioning of the Lrig1 precursor pool require further investigations. Furthermore, it is currently

not known how cell fate specification within the *Lrig1* compartment is controlled. Of interest, for pilo-sebaceous units with two prominent SGs it was shown that these emerge from one cluster of sebocytes derived from *Lrig1*-positive cells [19]. Once the sebocyte cell lineage is established, the *Plet1*-positive precursor pool is generated. Therefore, these precursor cells of the HF isthmus seem not to play a decisive role in the process of SG formation (Fig. 3) [19, 52].

SG formation is depending on normal function of mitochondria, particularly the electron transport chain [34]. Ablation of *Tfam*, a key maintenance factor for mtDNA from mouse epidermis and subsequent loss of the electron transport chain leads to a profound defect in SG morphogenesis. Astonishingly, the *Lrig1*-positive SC compartment is generated in *Tfam*-deficient mice demonstrating that the establishment of the *Lrig1* SC compartment is not sufficient to guarantee formation of SGs. Thus, it will be important to identify the additional instructive signals steering SG morphogenesis.

3 Stem Cells in Sebaceous Gland Homeostasis and Renewal

Work by many laboratories has suggested that different SC pools maintain SG homeostasis [47]. As presented in Fig. 4, one can envision different scenarios how SGs are maintained on a cellular level:

(1) Renewal of the gland occurs independent of HF SCs by unipotent progenitor cells localizing to the SG duct or the outermost proliferative cell layer of the gland (Fig. 4e, f). Although such a SG SC has not been identified yet, a previous study investigating retrovirus-mediated gene transfer to genetically mark cutaneous epithelial stem cells in mouse skin revealed that individually labeled cells within the SG seem to at least partially contribute to SG renewal [22]. Furthermore, *Blimp1* (B-lymphocyte-induced nuclear maturation protein1) was described as a marker for sebocyte precursor cells governing SG homeostasis [28]. However, lineage tracing experiments following the fate of genetically marked cells *in vivo* demonstrated that *Blimp1*-positive cells do not give rise to proliferative and differentiating sebocytes [36]. Additionally, several reports have shown that *Blimp1* is expressed by differentiated cells of the IFE, the SG and inner root sheath of HFs [8, 10, 36, 39, 66].

(2) SGs are maintained by progeny of HF SCs repopulating the basal proliferating compartment of the SG (Fig. 4a–d). Indeed, there is evidence that stem and progenitor cells of the HF junctional zone and the isthmus contribute to SG renewal [32, 52]. Lineage tracing of *Lrig1*- and *Lgr6*-positive keratinocytes revealed that these cells are capable to renew SG tissue *in vivo* [54, 68]. In addition, HF bulge SCs can also contribute to SG maintenance *in vivo*. This has been documented by genetic lineage tracing and fate mapping of Keratin15-positive bulge SCs [42, 57, 58]. Interestingly, analyzing progeny of bulge cells expressing Keratin19 revealed that these keratinocytes are not involved in SG maintenance, at least under

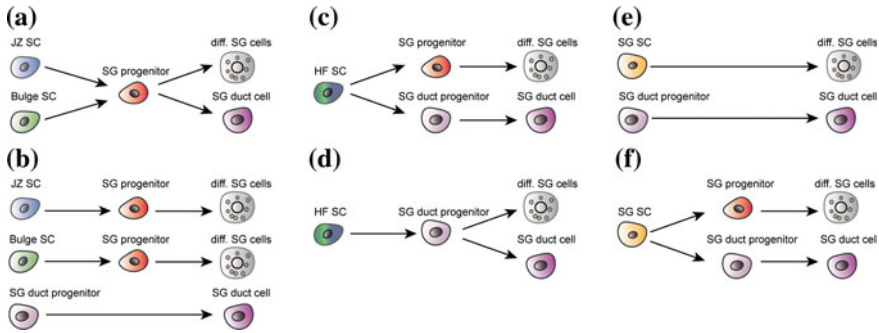


Fig. 4 Potential scenarios of SC contribution to sebaceous gland homeostasis. **a** Junctional zone stem cells and bulge stem cells give rise to one common sebaceous gland progenitor pool. Common sebaceous gland progenitor cells can subsequently differentiate into differentiated sebaceous gland cells and sebaceous gland duct cells. **b** Junctional zone stem cells and bulge stem cells contribute to different sebaceous gland progenitors, which finally differentiate into sebocytes. Sebaceous gland duct progenitor cells differentiate directly into sebocytes. **c** Hair follicle stem cells contribute to sebaceous gland progenitor cells which give rise to differentiated duct cells. Hair follicle stem cells also form sebaceous gland duct progenitor which are precursor cells for sebaceous duct cells. **d** Hair follicle stem cells give rise to sebaceous gland duct progenitors, which then generate both, differentiated sebocytes and sebaceous gland duct cells. **e** Sebaceous gland stem cells and sebaceous gland duct progenitor can differentiate into differentiated sebaceous gland cells and sebaceous gland duct cells respectively. **f** Sebaceous gland stem cells produce sebaceous gland progenitors differentiating into mature gland cells. Sebaceous gland stem cells also generate duct progenitor give rise to sebaceous gland duct cells. The different options of generating a functional sebaceous gland are not mutually exclusive. JZ, junctional zone; SC, stem cell; SG, sebaceous gland

homeostatic conditions [54]. The heterogeneous composition of the HF SC bulge, differences within the activation state and the localization of a particular labeled SC within the niche could all impact on the result of individual lineage tracing studies. In fact, expression of multiple bulge SC marker molecules only partially overlap in their expression pattern, including Sox9, Keratin15, CD34, Nfatc1, Keratin19, Lgr5 and Gli1 [29, 59, 71]. HF bulge SCs present a heterogeneous population comprising a quiescent SC pool and SCs that are rapidly activated for HF regeneration and wound response [69, 76, 77]. Moreover, there is functional evidence that bulge SCs exist in different states of activation and are differentially prone to respond to homeostatic clues, e.g. regulation by the circadian molecular clock mechanisms [30]. In the future, innovative techniques like the intravital live cell imaging will allow visualizing individual labeled SCs and following their responses and lineage contribution within their native environment [6].

Clearly, there is intense cross-regulation between bulge and sebaceous gland [59]. The intimate relationship between the HF bulge SCs and the SG has been observed in the Rhino mutant mouse where the bulge SC compartment is impaired. In this mutant, the *hairless* gene activity is lost leading to the disintegration of bulge SCs and defects in hair growth. Remarkably, shortly after hair loss the SGs

disappear. In contrast, another mutant mice with recessive mutation of the *hairless* locus (*hr*), HFs also disintegrate but retain some bulge cells that can be activated and proliferate. Consequently, *hr* mice exhibit well-differentiated SGs, thus indicating that the presence of the bulge SC compartment is required for proper SG maintenance [55].

Next, there is good evidence that SGs have significant impact on the HF structure and HF SCs. Loss of SGs and sebocyte function can lead to scarring alopecia demonstrating the dependence of HFs on SGs [5, 70]. However, until now it is not known how the crosstalk between SG tissue and the HF bulge SCs is controlled on a molecular level and further studies are needed to dissect the potential contribution of individual HF and SG SCs and the cellular environment.

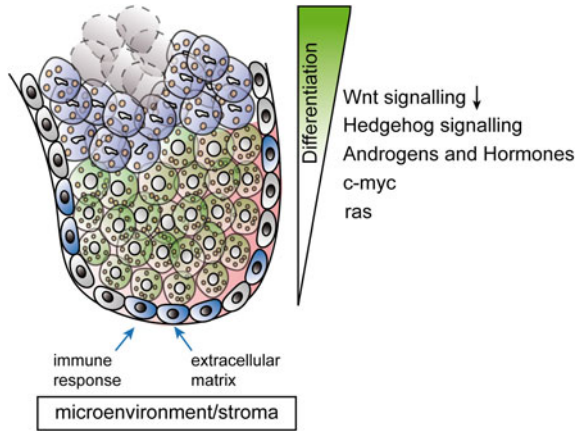
Until now, little is known about the cellular origin and maintenance of the sebaceous duct connecting SG and hair canal (Fig. 4e, f). Previous results analyzing expression of marker molecules suggest that SG duct cells are different from SG cells. Particularly, *Lrig1* is detected within sebaceous duct cells but not in differentiating sebocytes [36, 54]. Furthermore, activation of the Hedgehog signaling pathway stimulates enlargement of specifically the SG duct cell lineage in *Gli2* transgenic mice [24]. Obviously, more research is required to unravel if the SG duct is maintained by its own pool of progenitors and if such progenitor cells contribute to the homeostasis and regeneration of the SG.

4 Stem Cell Regulatory Mechanisms

Over the last years, important work by many laboratories has demonstrated that a variety of different factors can modulate SG morphogenesis and SG function, among them hormones, cytokines, signaling pathways as well as cell-cell and cell-matrix interactions [47, 65, 73, 75]. However, much less is known about molecular mechanisms operating directly on stem and progenitor cells of the SG.

One pathway that is essential in directing cell fate decisions in HF bulge SCs is canonical Wnt/ β -catenin signaling [9, 51]. It is well established that transcription factors of the TCF/Lef1 family, which are mediating canonical Wnt/ β -catenin activity, control bulge SC activation for cyclic HF regeneration and HF differentiation [25, 38]. In addition, previous data demonstrated that blocking TCF/Lef1 activity promotes SG lineage selection by HF stem and progenitor cells [40, 48]. Importantly, inhibition of TCF/Lef1 signaling in bulge SCs results in expansion of the *Lrig1* SC pool and induces de novo SG formation [57]. In contrast, expression of TCF3 in mouse epidermis leads to a block in sebocyte specification and the lack of SG development [45]. One important mechanism of repressing canonical Wnt/ β -catenin signaling in sebocytes involves Smad7 activity. It has been shown that Smad7 directly binds to β -catenin and recruits Smurf2, an ubiquitin E3 ligase that leads to the degradation of cytoplasmic β -catenin [26]. Taken together, these results reveal that suppression of β -catenin/TCF/Lef1 activity in epidermal stem and progenitor cells is driving SG cell specification and proper SG differentiation (Fig. 5).

Fig. 5 Regulators of sebaceous gland homeostasis. Sebaceous gland cell proliferation (*blue arrows*) and differentiation are influenced by different signaling pathways, hormones, signal molecules and the microenvironment



Another pathway governing sebocyte proliferation and differentiation is Hedgehog signaling. The binding of the hedgehog ligand to its receptor patched-1 leads to activation of the co-receptor smoothened thereby initiating a sequence of intracellular signaling events. Subsequently, a cascade of signaling reactions in primary cilia is induced culminating in the Gli transcription factor activation and hedgehog target gene transcription [61]. There is good evidence that stimulating Hedgehog signaling activity promotes SG differentiation whereas inhibition of the canonical Hedgehog pathway by overexpressing a dominant-negative Gli mutant blocks sebocyte differentiation (Fig. 5) [2, 24]. Additionally, it has been shown that Indian hedgehog expression can increase sebocyte proliferation and maturation in vitro and drives differentiation of sebaceous gland tumors in vivo [33, 50]. However, more detailed studies are required to identify the underlying molecular and cellular mechanisms and to demonstrate which stem and progenitor cell is mediating these effects.

Recently, it was shown that increasing KRas signaling by expressing an oncogenic constitutive active mutant KRas G12D in bulge SCs, promotes SG cell fate and leads to enlarged SGs (Fig. 5) [37]. This highlights again that modulating the HF bulge SC compartment can induce tremendous responses of the SG tissue indicating an intimate crosstalk between the different cellular compartments.

Epithelial-mesenchymal interactions trigger the development of the pilosebaceous unit and cyclic renewal of the HF [67]. This important cellular interrelationship is controlled by the composition of the extracellular matrix that can also modulate SC function and activation [78]. There is strong evidence that the extracellular matrix and cellular environment impact on SG morphology and function (Fig. 5). A recent study unraveled an important role of heparin sulfate (HS), a proteoglycan found in the extracellular matrix and on the cell surface for HF and SG physiology. In particular, HF ablation from mouse epidermis results in an

increase in the number of HFs and SGs and induced SG hyperplasia with excessive sebum production [11]. Based on the observation that HFs and SGs are strongly affected, HS is suggested to regulate SC compartments involved in HF and SG maintenance and regeneration. However, the underlying molecular mechanisms and the type of SC pool involved have not been discovered yet.

Cyclic HF regeneration and HF SC activation is modulated by other cell types that most likely also affect SG physiology and SCs maintaining SG homeostasis [23]. These include adipocytes and neurons that provide important signaling molecules, including hedgehog ligands and BMP2 [7, 18]. Furthermore, inflammatory and immune cells impact on epidermal SC function as demonstrated by the regulation of hair loss and wound repair [17, 35, 62]. In the future, it will be important to study their role in normal function of sebocytes as well as their involvement in defective SG tissue, including the formation and progression of sebaceous tumors.

It is well established that hormones regulate SG activity [73, 75]. In particular, androgens can modulate sebocyte proliferation *in vitro* and *in vivo* [1, 13, 79]. Interestingly, the androgen receptor has been identified as a Myc target gene in mouse epidermis [44] suggesting that Myc activity on SG function is mediated by androgen signaling [10]. However it is not known if androgens directly affect SC pools that are driving SG maintenance.

5 Stem Cells and Sebaceous Gland Pathologies

The SG is implicated in the pathogenesis of relevant skin diseases including forms of severe acne and some skin tumors. Several different types of sebaceous tumors are found in patients, ranging from benign well-differentiated sebaceous adenoma to malignant and aggressive sebaceous carcinoma (Fig. 6a, b) [47].

In recent years, some important studies have shed light on molecular mechanisms involved in the generation of sebaceous lesions. Although there is a constant increase in the number of mutant mice strains displaying defective SG morphology as well as abnormal sebocyte function, only a few genetic mouse models have been described displaying sebaceous tumors [47].

Transgenic mice overexpressing *c-myc*, an oncogene that has been revealed to affect epidermal SCs, show an increase in number and size of SGs and generate sebaceous adenomas in response to a two-step carcinogenesis protocol involving topical application of the carcinogen DMBA and a tumor-promoting agent TPA [3, 27]. Generally, DMBA/TPA treatment of mouse skin results in benign squamous papilloma with the ability to progress into malignant squamous skin carcinoma (SCC) [14] demonstrating that *c-myc* is specifically promoting a program of sebocyte differentiation in nonmelanoma skin cancer (NMSC).

Importantly, mutations within the N-terminus of the transcription factor Lef1 have been identified in human sebaceous adenoma and eyelid sebaceous carcinoma [31, 72]. These mutations prevent the binding of Lef1 to β -catenin and result in a block of β -catenin-dependent transcription of Wnt target genes. Transgenic mice

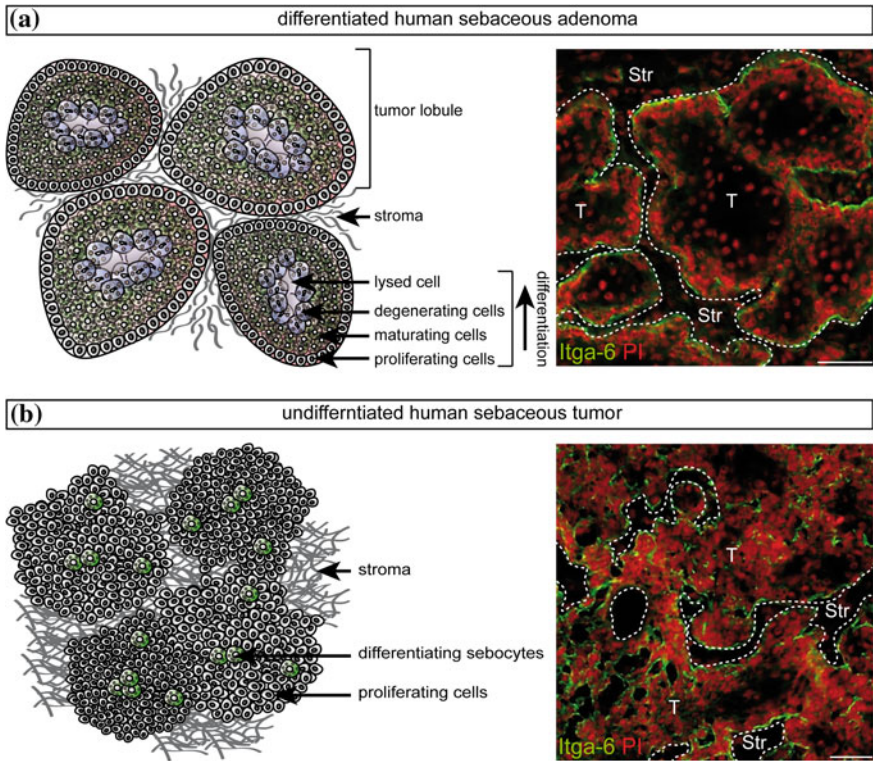


Fig. 6 Morphology of different types of sebaceous tumors. **a** Illustration depicting the morphology of well-differentiated sebaceous adenoma (*left*). Note the lobular architecture of sebaceous adenomas and the presence of mature sebocytes in the center of tumor lobules. Proliferating cells leaving the peripheral layer undergo a defined program of sebocyte maturation. Immunofluorescence staining of Itga-6 (*green*) labeling the periphery of tumor lobules in differentiated human sebaceous adenoma. Nuclei were stained using PI (*red*). **b** Schematic presentation of undifferentiated human sebaceous tumors/carcinomas, illustrating the loss of well-defined tumor architecture and a decrease of sebocyte differentiation (*left*). Arrows indicate proliferating cells (*grey*) and differentiated sebocytes (*green*). Itga-6 staining in undifferentiated human sebaceous tumors throughout the tumor mass. Itga-6, $\alpha 6$ -Integrin; PI, propidium iodide; T, tumor tissue; Str, stroma. Scale bar: 100 μ m

expressing a similar mutant form of Lef1 under control of the Keratin14 promoter (K14 Δ NLef1 mice) display enlarged and de novo SGs and develop spontaneous sebaceous tumors [48]. This demonstrates that mutant Lef1 activity indeed is a highly relevant mechanism driving sebaceous tumor formation in mammalian skin. In addition, treatment of K14 Δ NLef1 mice with the carcinogen DMBA results in sebaceous tumors in high frequency within a short period of time [49].

Another example how sebaceous gland differentiation is regulated in the process of skin tumourigenesis came from studies manipulating the AP-1 transcription factor. In particular, the typical response to chemical carcinogenesis was changed

from squamous tumors towards sebaceous adenomas following blocking AP-1 activity in mice [21]. It was further shown that inhibition of AP-1 induced a block in β -catenin/TCF/Lef1 function thereby promoting sebocyte differentiation within the skin tumors. Thus, repression of Wnt/ β -catenin signaling is a common feature within the different mouse models of sebaceous tumor formation [46].

Interestingly, expression of mutant Lef1 specifically in HF bulge SCs (K15 Δ NLef1 mice) also lead to spontaneous sebaceous skin tumors. Skin tumor formation is accelerated following treatment with a single dose of DMBA [60]. Astonishingly, sebaceous lesions forming in K15 Δ NLef1 mice display a more aggressive and malignant phenotype when compared to sebaceous tumors of K14 Δ NLef1 mice. Thus, mice expressing mutant Lef1 in different epidermal compartments produce a variety of different sebaceous skin lesions demonstrating that the cell population, e.g. SC versus SC progeny has a tremendous impact on the phenotype and grade of malignancy of tumors [60].

Recently, a number of elaborate and elegant *in vivo* studies have unraveled that many different types of NMSC arise from multipotent epidermal SCs [4]. Our own experiments have shown that HF bulge SCs constitute one cell of origin for mutantLef1-driven sebaceous tumors. More specifically, lineage tracing experiments of bulge SCs show clonal expansion of individual labeled Keratin15-positive cells and their contribution to sebaceous adenoma formation in K14 Δ NLef1 transgenic mice [60]. However, sebaceous tumors are not monoclonal derived suggesting that non-labeled cells (other SCs or non-SCs) could contribute to tumors. In the future, it will be important to investigate the potential role of SCs of the upper isthmus and junctional zone as well as cells of the sebaceous duct in the process of sebaceous tumor development. Of note, Lrig1-positive SCs of the junctional zone do not constitute a cell of origin for squamous skin tumors [54] but have the potential to contribute to the initiation of basal cell carcinoma (BCC) following inactivation of the hedgehog co-receptor ptch1 [60].

Analyzing the underlying molecular mechanism of sebaceous tumorigenesis revealed that mutant Lef1 interferes with SC-specific surveillance mechanisms of the HF bulge, including the control of DNA damage response and proliferation [60]. These data support the observation that bulge SCs are important for the SG lineage in normal skin and in epidermal tumors.

It has been shown that markers of different HF SC compartments are expressed in sebaceous tumors, including bulge SC marker Keratin15, CD34 and Sox9 (Fig. 7) [60, 63]. Remarkably, the expression level of SC marker for the junctional zone and upper isthmus, Lrig1 and Plet1 respectively, correlate with the malignant progression of sebaceous skin tumors [60]. Here, the SC-regulatory small GTPase Rac1 was shown to promote Lrig1 production by tumor cells and to induce progression of benign sebaceous adenoma to malignant sebaceous carcinoma-like tumors (SCLT) [20]. It was also shown that epidermis-specific overexpression of the EMT-inducing transcription factor Snail induces various types of skin carcinoma, including SG carcinoma [12]. This was accompanied by an increase in

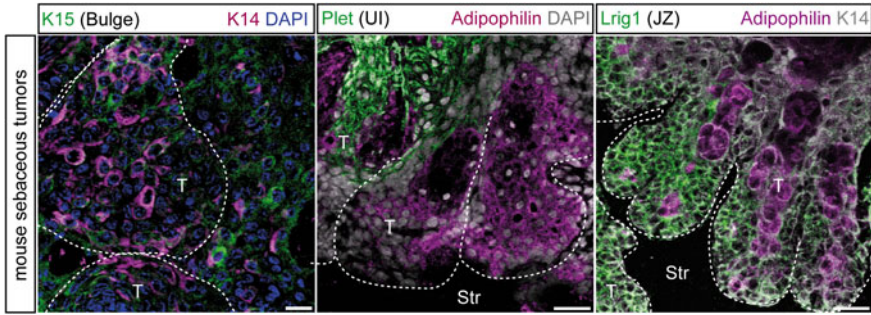


Fig. 7 Stem cell marker expression in mouse sebaceous tumors. Immunofluorescence staining of the bulge stem cell marker Keratin15 (green) together with Keratin14 (magenta) (left), the upper isthmus marker Plet1 (green) stained with Adipophilin (magenta) (middle) and the junctional zone marker Lrig1 (green) together with Adipophilin (red) and Keratin14 (grey). Nuclei were stained using DAPI. K15, Keratin15; K14, Keratin14; Lrig1, leucine rich immunoglobuline-like factor 1; Plet1, Placenta-expressed transcript 1. Scale bar: 25 μ m

progenitor cells of the upper isthmus expressing Plet1. However, the specific role of different types HF SCs in sebaceous carcinomas needs to be investigated in more detail.

Taken together, work of recent years has just begun to unravel the molecular and cellular mechanisms driving the process of SG disease, particularly the formation of sebaceous tumors in vivo. Further studies are needed to better understand how the individual pathways are interconnected and which SC is targeted and drives the disease in patients.

6 Concluding Remarks

Over the last years several distinct stem cell compartment have been identified within mammalian epidermis contributing to SG morphogenesis and maintenance of its normal function. Good progress has been made to develop elaborate in vivo mouse models, which allow deciphering the molecular mechanisms steering SG differentiation and we have begun to understand that interfering with normal SC function impacts on SG physiology. Clearly, more research is required to unravel the complexity and the specific contribution of diverse SC pools to SG homeostasis and patho-physiologies of the gland. In addition, more detailed studies will lead to the identification of cellular and molecular signals determining the SG cell fate.

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