Published in final edited form as:

Stem Cell Rev. 2008 ; 4(2): 113–118. doi:10.1007/s12015-008-9022-4.

The skin: a home to multiple classes of epithelial progenitor cells

Xiaohong Yan¹ and David M. Owens^{2,3,†}

¹Department of Surgery, Columbia University, College of Physicians and Surgeons, New York, NY, USA

²Department of Dermatology, Columbia University, College of Physicians and Surgeons, New York, NY, USA

³Department of Pathology, Columbia University, College of Physicians and Surgeons, New York, NY, USA

Abstract

To maintain homeostasis in the adult skin, epithelial keratinocyte stem cells are thought to divide infrequently giving rise to short-lived (transit amplifying) cells that undergo a limited number of cell divisions and ultimately terminal differentiation. This model for the epidermal stem cell niche has increased in complexity by the multiple putative progenitor keratinocyte populations that have recently been identified in distinct regions of the interfollicular epidermis and hair follicle appendages. Under normal conditions, these progenitor populations are long-lived and able to sustain the cellular input to certain epidermal structures including the interfollicular epidermis and sebaceous gland. Other putative epithelial progenitors derived from the hair follicle possess high *in vitro* proliferative capacity and are able to regenerate skin, hair and sebaceous lineages in transplantation studies. These new findings present the cutaneous epithelium as a highly compartmentalized structure potentially maintained by multiple classes of progenitor cells. In this review, we will discuss the implications of these new putative epithelial progenitor populations and their potential to be influenced by external stimuli for skin homeostasis and carcinogenesis.

Keywords

skin; epidermis; hair follicle; keratinocyte; squamous cell carcinoma

Introduction

Adult mammalian stem cells are distinguished by their high capacity for self-renewal as well as the ability to give rise to progeny that is committed to differentiation (1), properties that are essential to ensure homeostasis in tissues exhibiting relatively high rates of cell turn over such as the skin epithelia, gastrointestinal tract and bone marrow. Research over the past few decades has significantly furthered our understanding of the tissue specific stem cell populations that contribute to the maintenance and repair of adult cutaneous epithelium. Along these lines, the epithelium of mammalian skin is known to contain permanently residing stem cells that are able to maintain multiple differentiated lineages including the interfollicular epidermis (IFE), hair follicle (HF) and sebaceous gland (SG) (2).

[†]Correspondence address: David M. Owens, Ph.D. Columbia University, Herbert Irving Comprehensive Cancer Center, 1130 St. Nicholas Avenue, Room 321A, New York, NY 10032, Telephone: (212) 851-4544, Fax: (212) 851-4540, do2112@columbia.edu.

Early studies identified skin epithelial stem cells as cells able to reconstitute epidermal foci following skin irradiation estimated to be around 10% of the basal cell pool (3-4). Putative epidermal stem cells, as measured by tritiated-thymidine label-retention to mark slow-cycling cells, constituted between 2-10% of the proliferative keratinocyte population (5-6). More recently studies estimate the frequency of epidermal stem cells in adult murine skin measured by transplantation studies to comprise as little as 0.01% of the basal proliferative cell population (7), a level comparable to the hematopoietic stem cell pool. By fluorescence activated cell sorting analysis, IFE stem cells were initially quantified on the basis of high surface levels of $\beta 1$ containing integrins in the range of 10-30% of all basal cells in human skin (8) and in murine skin by high $\alpha 6$ integrin and low CD71 (transferrin receptor) surface levels to constitute 8% of the basal keratinocyte population (9). Finally, the most well characterized population of adult keratinocyte stem cells residing in the bulge region of the HF (10-12) have been quantified in multiple genetic backgrounds based on their surface levels of $\alpha 6$ integrin and CD34 to comprise 7-9% of the basal cell population in adult murine skin (11).

The variations in the reported frequencies of stem cells in the skin epithelium may be due in part to the differing techniques employed and regions of skin utilized for these analyses. Another plausible explanation for the discrepancies in stem cell quantity between these studies is that these previous analyses may not distinguish between the contributions of stem cells versus putative progenitor cell populations that may possess unipotent and limited self-renewal capacities. The recent identification of multiple putative epithelial progenitor populations discussed in this review suggest that the landscape of adult skin epithelia is highly regionalized and maintained by multiple stem cell populations.

Cutaneous epithelium as a multiple stem and progenitor cell niche system

The capacity of skin epithelial stem cells has been validated based on the adapted criteria developed in the hematopoietic system including infrequent cell division, self-renewal, clonogenicity and multipotency (13). However, multiple lineage studies in skin have shown spatially restricted contributions for most stem cell populations under homeostatic conditions indicating that, unlike the hematopoietic stem cell niche, the normal domain of a particular cutaneous epithelial stem cell and its progeny may be diminutive. Murine keratinocyte stem cells labeled by *in situ* gene transfer give rise to progeny in a spatially-regulated distribution pattern localized to small regions of the IFE, SG or HFs (14). The bulge stem cell reservoir was previously thought to maintain a large range of progenitor cell pools including the HF, SG and IFE (15); however, we now understand that the contributions of bulge stem cells are largely restricted to matrix progenitor cells committed to hair differentiation (14,16) but not the SG (14,17) or IFE (14,16,18). Interestingly, bulge stem cells do contribute to the wounding response in the IFE although bulge-derived cells are not a stable fixture in the IFE after conditions of homeostasis are resumed (18). These findings from lineage tracing studies coupled with the fact that any given stem cell population constitutes a small percentage of the total proliferative epithelial cell population argues that the skin is composed by multiple, regionalized epithelial stem niches that are responsible for maintaining distinct segments of the epidermis and hair follicles under normal conditions (Figure 1).

While there is evidence to suggest that most epithelial cell progenitors originate from a common stem cell population during embryonic development (19), the aforementioned findings from lineage studies present mature cutaneous epithelium as a potentially complicated niche model that is maintained at least in part by an unknown number of progenitor cell populations. In support of this idea, recent studies have begun to shed light on the localization and behavior of epithelial progenitor populations in the IFE and HF. A population of unipotent progenitor cells residing within or adjacent to the SG of murine skin

was identified by their expression of the transcription factor *Blimp1*, which appears to be necessary for homeostasis in the SG (Figure 1) (17). Interestingly, the *Blimp1*⁺ population does not appear to be maintained by stem cells in the HF bulge suggesting that a yet to be identified stem cell population exists within the SG (20) that maintains the *Blimp1*⁺ progenitor pool or that *Blimp1*⁺ cells are sufficient for SG homeostasis. A single progenitor cell population has been identified in adult IFE based on lineage analysis using a *Ahcre*^{ERT}; *R26*^{EYFP} double transgenic mouse model and shown to be sufficient for the maintenance of the IFE under homeostatic conditions (Figure 1) (21). These findings raise questions regarding the stem cell-transit amplifying cell hypothesis (22) and suggest that a similar scenario for progenitor cells may exist for certain HF compartments outside of the bulge region.

As with most tissues, the utilization of antibodies against surface proteins has facilitated the identification and isolation of distinct regions of epithelial cells within the IFE (8-9) and HF (11,23). Bulge stem cells can be distinguished from the upper regions of the HF including the SG and IFE based on their unique co-expression of $\alpha 6$ integrin, a marker of all proliferative epidermal keratinocytes (24), and the hematopoietic stem cell marker CD34 (11). Recently, additional surface markers have been employed revealing phenotypically distinct regions of the murine HF. A distinct compartment of the HF residing below the infundibulum and above the bulge region was identified by the presence of the MTS24 surface marker (Figure 1) (25). The gene recognized by MTS24 has now been identified as *Plet-1*, which encodes a protein of unknown function and may be a marker of progenitor cells in multiple tissues (26). Interestingly, MTS24⁺ HF cells purified by flow cytometry were highly clonogenic *in vitro* and exhibited a transcript profile similar to bulge stem cells suggesting that these cells may represent a progenitor cell population in the HF potentially derived from the bulge (25).

Stem cell antigen-1 (Sca-1) is another cell surface protein that labels murine hematopoietic stem cells in addition to other adult stem cell populations (27-29). Sca-1 has been reported to regulate self-renewal (30) and myeloid lineage commitment (31) in hematopoietic stem cells. Using antibodies to detect expression of Sca-1 in conjunction with $\alpha 6$ integrin and CD34 revealed a distinct region of cells residing within the upper isthmus (UI) of the HF just below the sebaceous gland duct, which could be distinguished from all other proliferative epidermal cells by their low $\alpha 6$ integrin surface levels and lack of Sca-1 and CD34 (Figure 1) (32). Purified UI cells were highly clonogenic *in vitro* and exhibited multipotent and self-renewal capabilities in transplantation studies (32). UI cells possess a unique transcript profile compared to cells derived from the bulge and IFE and are not quiescent collectively indicating that UI cells may represent a distinct HF progenitor population (32). Interestingly, expression of Sca-1 in basal epidermal keratinocytes strongly correlated with cells committed to IFE differentiation suggesting that similar to the role of Sca-1 in hematopoietic lineage determination (31), Sca-1 may also direct epidermal lineage fate skewing cells towards squamous differentiation (32). The ability of purified Sca-1⁺ keratinocytes to reconstitute IFE but not HF and SG lineages in transplantation studies supports this idea (32). However, these results do not discount the existence of self-maintaining progenitor cells within the IFE (21), but rather indicate that IFE progenitor cells may have a diminished capacity for hair lineage commitment under certain conditions. Future studies conducting lineage mapping of the cellular progeny derived from MTS24⁺ and UI populations are necessary to substantiate whether these cells may or may not represent long-term progenitor populations. Collectively, these new findings raise the question as to whether certain classic stem cell traits are solely beholden to stem populations or whether changes in the tissue microenvironment can induce stem cell behavior in otherwise committed progenitor cell populations (33).

Epidermal plasticity and the skin microenvironment

Under conditions of skin homeostasis the complex balance between cell proliferation and differentiation is successfully regulated by various types of extracellular and intercellular signals communicated between keratinocytes and other epidermal or dermal cells, collectively termed the skin microenvironment. These signals can be communicated in the form of growth factors, cytokines and adhesion molecules in several ways including: i) paracrine signals such as soluble factors communicated between suprabasal cells in the differentiated compartment and the cells in the basal layer of the IFE; ii) juxtacrine signals mediated between neighboring cells via cell-cell adhesion events; iii) autocrine signals such as soluble factors used by cells to auto-regulate growth and differentiation and iv) autocrine loop signals including soluble factors communicated between epidermal keratinocytes and dermal fibroblasts.

Changes in the microenvironment were postulated to influence epithelial cell plasticity based on the concept that cells committed to differentiation undergo a process of progressive loss of self-renewal capability in which the early stages of this process are reversible (33). Experimental evidence supporting this idea was demonstrated in the conditional ability of early differentiating human keratinocytes to regenerate a stable stratified epidermis when supported by inductive dermal cells and supplemented with extracellular matrix proteins (34). When highly-inductive dermal papilla cells were implanted into split footpad skin in contact with the basement membrane, cultured dermal papilla cells could induce HF morphogenesis and hair growth in adult epidermis (35) suggesting that signals derived from fully inductive dermal papilla cells can re-program most proliferative keratinocyte populations irrespective of their previous lineage commitment. However, IFE basal keratinocytes do not reconstitute HFs in the presence of a heterogeneous dermal fibroblast population, presumably with a collectively weaker inductive capacity compared to purified dermal papilla cells (32); whereas keratinocytes isolated from the bulge (12,36) and upper isthmus (UI) (32) regions of the HF can reconstitute stable, intact pilosebaceous units when co-transplanted with heterogeneous dermal fibroblasts. Therefore, the proven ability of keratinocyte stem cells to regenerate multiple epidermal lineages outside of their normal niche suggests that certain keratinocyte stem cell plasticity traits are common throughout the entire epithelium but that committed progenitor and early differentiating keratinocytes also retain some plastic capacity in response to normally restrictive signals from the microenvironment.

Progenitor cells and skin carcinogenesis

Historically, stem cells and their properties have long been associated with the neoplastic process in humans. The embryonic rest theory, proposed by Cohnheim in 1875, suggested that cancers were the result of proliferating embryonic stem cells that were maintained in the organs after development (37). Several decades later cancer was classified as a disease of differentiation (38-39) suggesting that tumors lacked the differentiated cells present in normal tissues whose purpose was to positively and negatively regulate the growth of undifferentiated stem cells. This idea was extended by Potter who developed the concept of blocked ontogeny stating that neoplasia resulted from the proliferation of stem cells yielding progenitor cells that had lost the ability to differentiate (40). Potter's concepts embraced the complexity and phenotypic diversity of neoplastic lesions and illustrated how cancer was a disease of proliferation and differentiation, both of these processes we still struggle to understand today.

The inherent slow cycling rate-high growth potential and persistent nature of cutaneous epithelial stem cells indirectly implicates this population in carcinogenesis by serving as the target cell for mutation-inducing environmental assaults. Presumably, as the only long-term

residents in the cutaneous epithelium, stem cells have the highest probability of acquiring the multiple genetic alterations required for tumorigenesis (41) as mutations acquired by committed cells would ultimately be lost through the normal process of differentiation (2). Recently, more direct evidence supporting this concept has been demonstrated in the epidermis of skin by targeting genes that are known to be critical for the development or maintenance of epidermal keratinocyte stem cells. For example, augmented expression of either *c-myc* or a mutant *Lef1* gene in the stem cell compartment leads to *de novo* tumor formation in the epidermis (42-43). Expression of the HMG-box-containing transcription factor Sox9 has been shown to be essential for the development of the HF bulge stem cell compartment (44) and activated Sox9 is constitutively maintained in the epithelial compartment of cutaneous neoplasms thought to be derived from the HF including basal cell carcinomas, trichoepitheliomas and trichilemmomas (45). Cancer stem cells have recently been identified in cutaneous squamous cell carcinoma (SCC) that contain a bulge stem cell phenotype and are dependent on β -catenin signaling for tumor maintenance (46). Similar findings have been observed in parallel studies in other tissues including the role of *Wnt* and *Hedgehog* signaling in regulating the stem cell niche and oncogenesis in the hematopoietic system (47) and the role for *Bmi* in brain development and the pathogenesis of medulloblastoma (48). Overall, these studies highlight the impact of targeting genes unique for stem cell niche maintenance, particularly self-renewal, on tissue homeostasis and tumorigenesis and collectively indicate that genes unique to epidermal stem cells are potentially the most lucrative targets for cutaneous cancer treatment and prevention.

Despite the overwhelming amount of indirect evidence supporting the idea that stem cells are the target cells for cutaneous cancers such as SCC, the originating cell(s) for these lesions has yet to be identified. It is well established that changes in epidermal microenvironment can dramatically influence tumorigenic outcome in the skin (49-50) purportedly by rendering conditions more or less conducive for the clonal expansion of mutant stem cells to found a tumor (2). Even less understood is the potential role of committed epithelial progenitor cell populations in the neoplastic process. While most committed epithelial progenitor cells may exhibit unipotent behavior during homeostasis, the high clonogenic capacity of certain epithelial progenitor cells *in vitro* as well as their performance in transplantation assays suggests that under certain conditions progenitors can adopt stem cell characteristics. While these types of behavior may appear artificial due to the assay conditions and are may not be representative of the activity of a particular epithelial progenitor cell during homeostasis, these types of assays are representative of changes in the cell microenvironment and, as such, may be suggestive of the potential of epithelial progenitors in response to acute or chronic perturbations in skin homeostasis. This raises the possibility that chronic changes in the skin microenvironment that stimulate tumor promotion may also invoke some degree of self-renewal capability in these early neoplastic cells both of which being important for the clonal expansion of mutant epithelial progenitor cells.

Conclusions

Recent studies indicate that although the skin is composed of a continuous epithelium it is highly compartmentalized by multiple phenotypically distinct progenitor cell populations. Whether certain classic stem cell traits such as multipotency and unlimited self-renewal are solely beholden to cutaneous stem cell populations or whether changes in the tissue microenvironment can induce stem cell behavior in otherwise committed unilineage epithelial progenitor or transit amplifying cell populations is an important question for cutaneous research. The clonogenic and multipotent capacity of putative epithelial progenitor cells in response to perturbations in the skin microenvironment may also have important implications for therapeutic strategies against epithelial tumors that strictly focus

on eradicating neoplastic stem cells. Future lineage analysis of these populations will provide great insight into the role of these cells during homeostasis, wound regeneration and carcinogenesis.

Acknowledgments

We wish to thank Drs. Angela Christiano, Colin Jahoda and Soosan Ghazizadeh for their helpful advice. This work was supported by a Florence Irving Research Career Award and National Institutes of Health R01CA114014 and R03AR054071 research grants.

References

1. Lajtha LG. Stem cell concepts. Differentiation. 1979; 14:23–34. [PubMed: 383561]
2. Owens DM, Watt FM. Contribution of stem cells and differentiated cells to epidermal tumours. Nat Rev Cancer. 2003; 3:444–451. [PubMed: 12778134]
3. Withers HR. Recovery and repopulation in vivo by mouse skin epithelial cells during fractionated irradiation. Radiat Res. 1967; 32:227–239. [PubMed: 6051472]
4. Potten CS, Hendry JH. Letter: clonogenic cells and stem cells in epidermis. Int J Radiat Biol. 1973; 24:537–540.
5. Mackenzie IC, Bickenbach JR. Label-retaining keratinocytes and Langerhans cells in mouse epithelia. Cell Tissue Res. 1985; 242:551–556. [PubMed: 2416451]
6. Morris RJ, Fischer SM, Slaga TJ. Evidence that the centrally and peripherally located cells in the murine epidermal proliferative unit are two distinctive cell populations. J Invest Dermatol. 1985; 84:277–281. [PubMed: 3981041]
7. Schneider TE, Barland C, Alex AM, et al. Measuring stem cell frequency in epidermis: a quantitative in vivo functional assay for long-term repopulating cells. Proc Natl Acad Sci USA. 2003; 100:11412–11417. [PubMed: 13679571]
8. Jones PH, Watt FM. Separation of human epidermal stem cells from transit amplifying cells on the basis of differences in integrin function and expression. Cell. 1993; 73:713–724. [PubMed: 8500165]
9. Tani H, Morris RJ, Kaur P. Enrichment for murine keratinocyte stem cells based on cell surface phenotype. Proc Natl Acad Sci USA. 2000; 97:10960–10965. [PubMed: 11005869]
10. Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. Cell. 1990; 61:1329–1337. [PubMed: 2364430]
11. Trempus CS, Morris RJ, Bortner CD, et al. Enrichment for living murine keratinocytes from the hair follicle bulge with the cell surface marker CD34. J Invest Dermatol. 2003; 120:501–511. [PubMed: 12648211]
12. Blanpain C, Lowry WE, Geoghegan A, Polak L, Fuchs E. Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. Cell. 2004; 118:635–648. [PubMed: 15339667]
13. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001; 414:105–111. [PubMed: 11689955]
14. Ghazizadeh S, Taichman LB. Multiple classes of stem cells in cutaneous epithelium: a lineage analysis of adult mouse skin. EMBO J. 2001; 20:1215–1222. [PubMed: 11250888]
15. Taylor G, Lehrer MS, Jensen PJ, Sun TT, Lavker RM. Involvement of follicular stem cells in forming not only the follicle but also the epidermis. Cell. 2000; 102:451–461. [PubMed: 10966107]
16. Levy V, Lindon C, Harfe BD, Morgan BA. Distinct stem cell populations regenerate the follicle and interfollicular epidermis. Dev Cell. 2005; 9:855–861. [PubMed: 16326396]
17. Horsley V, O'Carroll D, Tooze R, et al. Blimp1 defines a progenitor population that governs cellular input to the sebaceous gland. Cell. 2006; 126:597–609. [PubMed: 16901790]
18. Ito M, Liu Y, Yang Z, et al. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. Nat Med. 2005; 11:1351–1354. [PubMed: 16288281]

19. Fuchs E. Scratching the surface of skin development. *Nature*. 2007; 445:834–842. [PubMed: 17314969]
20. Niemann C, Owens DM, Hulsken J, Birchmeier W, Watt FM. Expression of Δ NLef1 in mouse epidermis results in differentiation of hair follicles into squamous epidermal cysts and formation of skin tumours. *Development*. 2002; 129:95–109. [PubMed: 11782404]
21. Clayton E, Doupe DP, Klein AM, Winton DJ, Simons BD, Jones PH. A single type of progenitor cell maintains normal epidermis. *Nature*. 2007; 446:185–189. [PubMed: 17330052]
22. Jones PH, Simons BD, Watt FM. Sic Transit Gloria: farewell to the epidermal transit amplifying cell? *Cell Stem Cell*. 2007; 1:371–381. [PubMed: 18371376]
23. Ohyama M, Terunuma A, Tock CL, et al. Characterization and isolation of stem cell-enriched human hair follicle bulge cells. *J Clin Invest*. 2006; 116:249–260. [PubMed: 16395407]
24. Watt FM. Role of integrins in regulating epidermal adhesion, growth and differentiation. *EMBO J*. 2002; 21:3919–3926. [PubMed: 12145193]
25. Nijhof JG, Braun KM, Giangreco A, et al. The cell-surface marker MTS24 identifies a novel population of follicular keratinocytes with characteristics of progenitor cells. *Development*. 2006; 133:3027–3037. [PubMed: 16818453]
26. Depreter MGL, Blair NF, Gaskell TL, et al. Identification of Plet-1 as a specific marker of early thymic epithelial progenitor cells. *Proc Natl Acad Sci USA*. 2008; 105:961–966. [PubMed: 18195351]
27. Spangrude GJ, Heimfeld S, Weissman IL. Purification and characterization of mouse hematopoietic stem cells. *Science*. 1988; 241:58–62. [PubMed: 2898810]
28. Welm BE, Tepera SB, Venezia T, Graubert TA, Rosen JM, Goodell MA. Sca-1(+) cells in the mouse mammary gland represent an enriched progenitor cell population. *Dev Biol*. 2002; 245:42–56. [PubMed: 11969254]
29. Oh H, Bradfute SB, Gallardo TD, et al. Cardiac progenitor cells from adult myocardium: homing, differentiation, and fusion after infarction. *Proc Natl Acad Sci USA*. 2003; 100:12313–1218. [PubMed: 14530411]
30. Ito CY, Li CY, Bernstein A, Dick JE, Stanford WL. Hematopoietic stem cell and progenitor defects in Sca-1/Ly-6A-null mice. *Blood*. 2003; 101:517–523. [PubMed: 12393491]
31. Bradfute SB, Graubert TA, Goodell MA. Roles of Sca-1 in hematopoietic stem/progenitor cell function. *Exp Hematol*. 2005; 33:836–843. [PubMed: 15963860]
32. Jensen UB, Yan X, Triel C, Woo SH, Christensen R, Owens DM. A distinct population of clonogenic and multipotent murine follicular keratinocytes residing in the upper isthmus. *J Cell Sci*. 2008; 121:609–617. [PubMed: 18252795]
33. Potten CS, Loeffler M. Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the Crypt. *Development*. 1990; 110:1001–1020. [PubMed: 2100251]
34. Li A, Pouliot N, Redvers R, Kaur P. Extensive tissue-regenerative capacity of neonatal human keratinocyte stem cells and their progeny. *J Clin Invest*. 2004; 113:390–400. [PubMed: 14755336]
35. Reynolds AJ, Jahoda CAB. Cultured dermal papilla cells induce follicle formation and hair growth by transdifferentiation of an adult epidermis. *Development*. 1992; 115:587–593. [PubMed: 1425341]
36. Morris RJ, Liu Y, Marles L, et al. Capturing and profiling adult hair follicle stem cells. *Nat Biotech*. 2004; 22:411–417.
37. Cohnheim J. Congenitales, quergestreiftes Muskelsarkom der Nieren. *Virchows Arch*. 1875; 65:64., see Cohnheim J. *Lectures on General Pathology*. 1889; II:789. New Sydenham Society London
38. Osgood EE. A unifying concept of the etiology of the leukemias, lymphomas, and cancers. *J Natl Cancer Inst*. 1957; 18:155–166. [PubMed: 13406538]
39. Markert CL. Neoplasia: a disease of cell differentiation. *Cancer Res*. 1968; 28:1908–1914. [PubMed: 5676741]
40. Potter VR. Phenotypic diversity in experimental hepatomas: the concept of blocked ontogeny. The 10th Walter Hubert Lecture. *Br J Cancer*. 1978; 38:1–23. [PubMed: 356869]
41. Hahn WC, Weinberg RA. Rules for making human tumor cells. *N Engl J Med*. 2002; 347:1593–1603. [PubMed: 12432047]

42. Arnold I, Watt FM. c-Myc activation in transgenic mouse epidermis results in mobilization of stem cells and differentiation of their progeny. *Curr Biol.* 2001; 11:558–568. [PubMed: 11369200]
43. Niemann C, Watt FM. Designer skin: lineage commitment in postnatal epidermis. *Trends Cell Biol.* 2002; 12:185–192. [PubMed: 11978538]
44. Vidal VP, Chaboissier MC, Lutzkendorf S, et al. Sox9 is essential for outer root sheath differentiation and the formation of the hair stem compartment. *Curr Biol.* 2005; 15:1340–1351. [PubMed: 16085486]
45. Vidal VP, Ortonne N, Schedl A. SOX9 expression is a general marker of basal cell carcinoma and adnexal-related neoplasms. *J Cutan Pathol.* 2008; 35:373–379. [PubMed: 18333897]
46. Malanchi I, Peinado H, Kassen D, et al. Cutaneous cancer stem cell maintenance is dependent on β -catenin signalling. *Nature.* 2008; 452:650–654. [PubMed: 18385740]
47. Taipale J, Beach PA. The Hedgehog and Wnt signaling pathways in cancer. *Nature.* 2001; 411:349–354. [PubMed: 11357142]
48. Leung C, Lingbeek M, Shakhnova O, et al. Bmi is essential for cerebellar development and is overexpressed in human medulloblastomas. *Nature.* 2004; 428:337–341. [PubMed: 15029199]
49. Moore RJ, Owens DM, Stamp G, et al. Mice deficient in tumor necrosis factor- α are resistant to skin carcinogenesis. *Nat Med.* 1999; 5:828–831. [PubMed: 10395330]
50. Owens DM, Romero MR, Gardner C, Watt FM. Suprabasal $\alpha 6 \beta 4$ integrin expression in epidermis results in enhanced tumorigenesis and disruption of TGF β signalling. *J Cell Sci.* 2003; 116:3783–3791. [PubMed: 12902406]

Figure 1. Landscape of adult murine epidermis showing the multiple compartments of stem and putative progenitor populations

IFE progenitors maintain the proliferative and differentiative compartments of the epidermis. *Blimp1*⁺ progenitors in the SG maintain the sebocyte pool, and bulge stem cells maintain matrix progenitor cell populations that are committed to hair differentiation. Putative progenitor populations identified as MTS24⁺ cells (between double-dashed lines) or the UI region (between single-dashed lines) reside in the HF above the bulge region. Arrows designate known or unknown (?) progeny derived from each population. Abbreviations: IFE, interfollicular epidermis; SG, sebaceous gland; UI, upper isthmus.