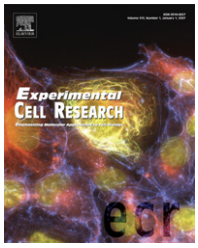
EXPERIMENTAL CELL RESEARCH 313 (2007) 3377–3385

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/yexcr



Review Article

Stem cell niches in mammals

Thimios A. Mitsiadis[a,*], *Ornella Barrandon*[b], *Ariane Rochat*[c], *Yann Barrandon*[c], *Cosimo De Bari*[d,*]

[a]*Department of Orofacial Development and Structure, Institute of Oral Biology, University of Zurich, Plattenstrasse 11, CH 8032 Zurich, Switzerland*
[b]*Wellcome Trust Center for Stem Cell Research, Tennis Court Road, Cambridge CB1 2QR, UK*
[c]*Laboratory of Stem Cell Dynamics, Ecole Polytechnique Federale de Lausanne and Lausanne University Hospital, Lausanne, Switzerland*
[d]*Department of Rheumatology, King's College London, Guy's Hospital, London SE1 9RT, UK*

ARTICLE INFORMATION

Article Chronology:
Received 8 May 2007
Revised version received
23 July 2007
Accepted 24 July 2007
Available online 2 August 2007

Keywords:
Stem cells
Tooth
Incisor
Hair
Bone
Notch signaling
Niches

ABSTRACT

Stem cells safeguard tissue homeostasis and guarantee tissue repair throughout life. The decision between self-renewal and differentiation is influenced by a specialized microenvironment called stem cell niche. Physical and molecular interactions with niche cells and orientation of the cleavage plane during stem cell mitosis control the balance between symmetric and asymmetric division of stem cells. Here we highlight recent progress made on the anatomical and molecular characterization of mammalian stem cell niches, focusing particularly on bone marrow, tooth and hair follicle. The knowledge of the regulation of stem cells within their niches in health and disease will be instrumental to develop novel therapies that target stem cell niches to achieve tissue repair and re-establish tissue homeostasis.

Contents

* *Corresponding authors.* T.A. Mitsiadis is to be contacted at fax: +41 446344310. C. De Bari, fax: +44 2071885883.
E-mail addresses: thimios.mitsiadis@zzmk.uzh.ch (T.A. Mitsiadis), cosimo.debari@kcl.ac.uk (C. De Bari).

0014-4827/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.yexcr.2007.07.027

Introduction

Stem cells are defined by their ability to self-renew and to give rise to mature cell types. Stem cells reside in highly regulated microenvironments called niches, which allow them to maintain a balance of self-renewal and differentiation. These microenvironments are maintained by a constant dialogue between the stem cells and the surrounding niche cells. The niche provides the stem cells shelter from differentiation stimuli, apoptotic stimuli and any other stimuli that might challenge the stem cell stores. The niche must also protect the stem cells from overproduction, which if not properly controlled may lead to cancer [1].

Under homeostatic conditions, stem cells self-renew and produce differentiated progeny. An individual stem cell can give rise to two identical daughter cells (symmetric division) or two non-identical daughter cells, one maintaining the stem-cell identity and the other becoming a differentiated cell (asymmetric division). The orientation of the cleavage plane during mitosis appears to have a crucial role in determining symmetric or asymmetric division, as demonstrated in invertebrate model systems [2–4]. Oriented division may position daughter cells in different microenvironments [2–4], or intrinsic determinants may be segregated into only one daughter cell [5–7]. Evidence for asymmetric cell division in mammalian stem cell systems has been recently provided for the basal cells of the skin epidermis [8] and for the satellite cells of the skeletal muscle [9,10].

Pioneering studies on the gonadal niches in invertebrates [2,11,12] have inspired a great deal of science in mammalian systems with stunning advance in our knowledge in the last few years. In this article, we review recent progress in the anatomical and molecular characterization of mammalian stem cell niches, focusing on three organs: bone marrow, tooth and hair follicle.

The bone marrow niches

The bone marrow contains multiple stem cell types, including the hematopoietic stem cells (HSCs) and the mesenchymal stem cells (MSCs). The HSCs are the best-characterized adult stem cells and have been purified close to homogeneity. Yet, only recent studies have begun to shed some light on their niche(s). In the adult bone marrow, the HSCs are known to reside in two different niches, an “endosteal” niche and a “perivascular” niche.

In the endosteal niche, HSCs are associated with a subset of osteoblasts that line the inner surface of the cavities of trabecular bone. Endosteal osteoblasts are thought to provide a variety of factors that regulate HSC number and function [13,14]. Genetic manipulations in mice that increase osteoblast numbers also result in concomitant proportionate increases in marrow HSCs without changes in committed progenitor populations [13,14]. A possible mechanism by which osteoblasts would regulate the number of HSCs is through secretion of osteopontin. Osteopontin is a bone matrix glycoprotein that appears to maintain HSC quiescence and to negatively regulate HSC proliferation and activity as osteopontin-null mice have increased HSC numbers [15,16]. Osteoblasts are also required for the maintenance of bone marrow HSCs, since their conditional ablation in mice results in a decrease in the number of marrow HSCs [17].

An increasing number of studies point to the existence of a complex paracrine signaling network at the interface between the niche osteoblasts and the adjacent HSCs (Fig. 1). Kit ligand is expressed by osteoblasts and is able to activate Kit on the cell surface of HSCs [18]. Notch signaling plays an important role in cell fate determination in both invertebrates and vertebrates. The Notch ligand Jagged1 is expressed by osteoblasts while Notch1 is activated in HSCs, thus suggesting involvement of the Notch signaling pathway in the regulation of HSC function by osteoblasts [14]. There is evidence that Notch signaling would repress differentiation programs in HSCs and facilitate HSC competence to Wnt signaling with proliferation as a net result [19,20]. Another key interaction is between the ligand angiopoietin-1 at the osteoblast surface with the receptor Tie-2 expressed on HSCs, which has been shown to modulate HSC quiescence [21].

A recent study has provided evidence for a new participant in the functional regulation of HSCs at the endosteal niche, the osteoclast [22]. Activation of osteoclasts by RANKL, which is produced by osteoblasts, resulted in mobilization of HSCs into circulation. RANKL altered osteoclast expression of the proteases MMP-9 and cathepsin K, which cleave the membrane-bound Kit ligand. Furthermore, RANKL decreased the abundance of osteoblast Kit ligand and the production of osteopontin, another mediator of HSC function. Conversely, HSCs did not mobilize upon treatment with RANKL in mutant

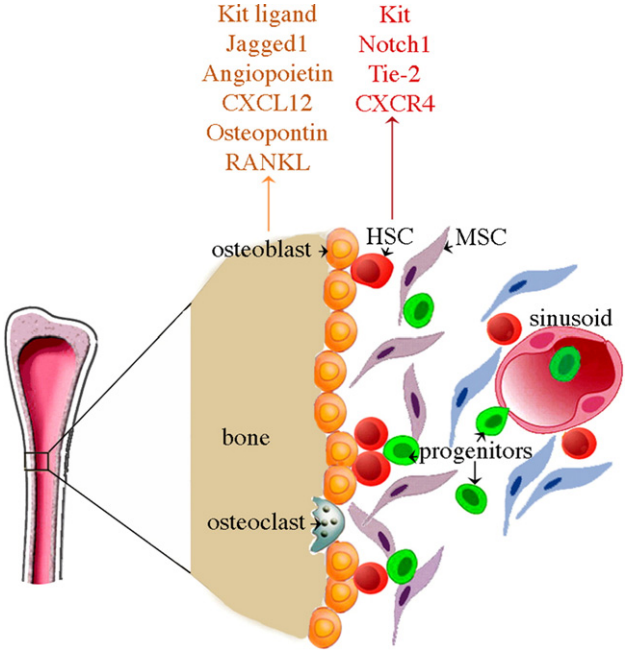


Fig. 1 – Schematic representation of the endosteal and perivascular niches of hematopoietic stem cells (HSCs) within the bone marrow, and signaling molecules involved in their regulation. Stromal cells, possibly including mesenchymal stem cells (MSCs), surround hematopoietic stem and progenitor cells.

mice having dysfunctional osteoclasts [22]. Thus, this study provides a link between bone remodeling and hematopoiesis.

HSCs express a receptor that confers them ability to sense calcium concentrations. HSCs lacking this calcium-sensing receptor show decreased homing to the endosteal niche, suggesting a role of mineral gradients in the location and retention of HSCs [23]. Although the mechanism remains largely known, the poor anatomic localization of HSCs in close proximity to the endosteal surface correlated with defective adhesion to the extracellular matrix protein collagen type I [23].

CXCL12 is highly expressed in bone and is critical for the attraction and retention of HSCs to their niches [24]. Adrenergic signals control G-CSF-induced osteoblast suppression and bone CXCL12 down-regulation, leading to a transfer of HSCs into the circulation [25]. Thus, the sympathetic nervous system regulates the mobility of HSCs to their niche [25].

HSCs can be maintained in extramedullary tissues, such as spleen and liver, which do not contain bone, suggesting that the endosteal niche is only one of the possible niches for HSCs. In this respect, about two thirds of HSCs in the bone marrow are adjacent to sinusoids, thus pointing to the perivascular area of sinusoids as another niche site for HSCs [26]. Marrow sinusoidal endothelial cells express cytokines such as CXCL12 and adhesion molecules such as E-selectin and VCAM1 that are important for HSC mobilization, homing and engraftment [27,28]. The sinusoidal endothelium is fenestrated and allows flow of circulating blood factors across its wall. The connection of HSCs with sinusoids could ensure homeostatic blood cell production and prompt responses to hematological stresses.

It has been shown recently that marrow sinusoids are surrounded by reticular cells that express unusually large amounts of CXCL12 [29]. Previous studies have shown that CXCR4, which is the main receptor for CXCL12, is expressed by HSCs, and that CXCR4–CXCL12 signaling is critical for HSC engraftment [30]. Taken together these findings suggest that reticular cells would be the main source of CXCL12 for HSC perivascular maintenance and niche formation in bone marrow. Intriguingly, HSCs located around sinusoids and at the endosteal site are closely associated with CXCL12-expressing reticular cells, suggesting that reticular cells may serve as a transit pathway for shuttling HSCs between the two niches, which may use some common mechanisms for HSC maintenance [29]. Nonetheless, it has been proposed that these two niches are functionally distinct: the endosteal niche is thought to maintain HSC quiescence over the long term, whereas the perivascular niche is thought to maintain HSCs over a shorter time period, supporting HSC proliferation, favoring myeloid and megakaryocytic lineage differentiation and mediating HSC circulation [31].

Other stem cells present in the bone marrow are the MSCs, which have the ability to self-renew and to differentiate into cartilage, bone and adipose tissue at the single cell level [32]. Their clinical use has been long sought and successfully achieved for cartilage and bone repair [33]. However, the lack of specific cell-surface markers has so far impeded the direct purification of a homogeneous population of MSCs, which would be desirable to obtain clinical grade MSC preparations with consistent and reproducible efficacy [33]. Enrichment of bone marrow MSCs prior to cell culture has been obtained using combinations of markers [34,35]. MSCs have been isolated also from other tissues including periosteum, synovial membrane and synovial fluid [36–39]. Nonetheless, our knowledge on the MSC niches within their native tissues is very poor. It has been suggested that MSCs harbor in perivascular areas in the bone marrow [40], where they could be in close association with HSCs. Indeed, following injection into the bone marrow of immunodeficient mice, human MSCs differentiated into stromal cells, bone-lining osteoblasts and endothelial cells, all functional constituents of the marrow hematopoietic microenvironment [41]. The inhibitory effect of MSCs on cell proliferation in vitro [42] raises the possibility of a role of MSCs in maintaining quiescence of HSCs.

The incisor stem cell niche

The rodent incisor differs from other teeth in that it is a continuously growing organ that erupts throughout the life of the animal. This regenerative property suggests that stem cells are present in the incisor. A highly proliferative area, located in the apical part of the incisor's epithelium (the cervical loop), has been proposed as a stem cell niche [43].

The rodent incisor develops through epithelial–mesenchymal interactions, acquires a cylindrical shape and upon growth occupies the entire part of the bone of the jaws, where is encased in. The incisor is formed by two distinct epithelia, the lingual and labial epithelia, which surround the mesenchymal pulp. The lingual side of the incisor is composed of two epithelial cell layers, the inner and the outer epithelium. Cementum is deposited on this side of the incisor, which provides a secure attachment of the tooth to the alveolar bone. This is why the lingual side of the rodent incisor is known as the root analogue of the molar. The labial side of the incisor is composed of four epithelial cell layers: the inner and outer enamel epithelia that surround the core of stellate reticulum and stratum intermedium. The inner and outer enamel epithelia are in contact with the mesenchyme of the pulp and the dental follicle respectively. The star shaped cells of the stellate reticulum cells create a network, while cells of the stratum intermedium are compressed flattened cuboidal cells in contact with the inner enamel epithelium (Fig. 2). Enamel is deposited on the labial side of the incisor, which is thus analogous to the crown of a molar. The cervical loop is located at the apical end of the epithelium, and consists of a core of undifferentiated cells surrounded by the basal epithelium (i.e. inner and outer enamel epithelia) contacting the dental mesenchyme [44,45]. Cells of the core of this area proliferate and generate the transit amplifying progenitor cells, which then differentiate into all the cells of the incisor including the terminally differentiated ameloblasts (Fig. 2).

Some evidence suggests that the cervical loop is the putative stem cell niche. There is a gradient of differentiation from the apical to incisal direction, and cells of the inner enamel epithelium close to cervical loop region divide more rapidly than cells far away from this area [46,47]. These observations led to believe that the cells responsible for the continual growth of the incisor are located in the cervical loop. Indeed, when the cervical loop is removed and grown in vitro, it is capable of regenerating the rest of the dental epithelium.

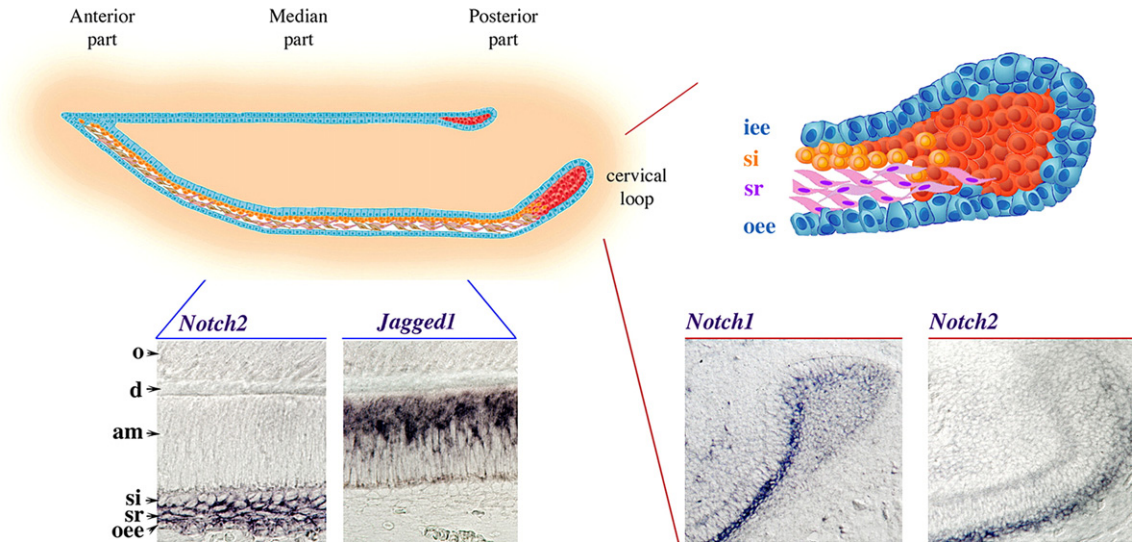


Fig. 2 – Schematic diagram of the stem cell niche within the cervical loop of the rodent incisor (red color compartment of the incisor) and the Notch signaling pathway that mediates proliferation and differentiation of dental epithelial stem cells. Abbreviations: am, ameloblasts; d, dentin; iee, inner enamel epithelium; o, odontoblasts; oee, outer enamel epithelium; si, stratum intermedium; sr, stellate reticulum.

Cell tracking experiments have demonstrated that the cells from the cervical loop are maintained in this area, while others migrate toward the incisal end of the incisor. This migration has been suggested as the movement of the stem cell progeny along their path toward differentiation into the enamel producing cells of the incisor [43].

A characteristic feature of stem cells is their slow cycling nature. BrdU incorporation studies have demonstrated that the cells of the cervical loop region are cycling slowly. Short periods of BrdU incubation have shown that the cells with the most label retention were those in the inner enamel epithelium of the apical end. This demonstrates that cells of the inner enamel epithelium are highly proliferative and cycling very quickly. Other cells of the cervical loop are labeled only very sparsely after a short incubation period, suggesting that these cells are dividing slowly. Longer periods of BrdU incorporation have shown that the number of labeled cells extends to the differentiated ameloblasts. However, cells of the stellate reticulum at the cervical loop were not extensively labeled. Pulse-chase experiments have demonstrated that BrdU labeling still remains in cells located in the internal part of the cervical loop epithelium, but labeling can be also identified in ameloblasts [43]. Cells that are positive for BrdU and have not diluted the dye after the chase period are those cells that divide slowly. This would suggest that the labeled cells of the cervical loop are slow cycling stem cells. These cells remain in the cervical loop and maintain the stem cell population through self-renewal. Cells originated from the cervical loop region have clonal potential as well as the ability to differentiate into cells expressing markers of the inner enamel epithelium and ameloblasts, such as $P75^{NGF}$ and amelogenin [48,49].

The Notch signaling pathway has been also implicated in early tooth morphogenesis and cell differentiation. Notch1 is expressed in the cells of the cervical loop area and in the stratum intermedium, while Notch2 is expressed in cells of the stellate reticulum and outer enamel epithelium (Fig. 2). The general trend of the Notch expression is in accordance with the gradient of cytodifferentiation that exists from the cervical loop to the incisal end of the incisor. Only very few Notch transcripts are expressed in the inner enamel epithelium and the ameloblasts. Notch expression remains notably absent from the epithelium directly contacting the dental mesenchyme and in terminally differentiated ameloblasts [50]. Notch1 and Delta1 (one of the Notch ligands) are expressed in adjacent cell populations: Notch1 is expressed in the stratum intermedium, while Delta1 is expressed in ameloblasts and cells of the inner enamel epithelium [51]. Jagged1 and Jagged2, two other ligands for the Notch receptors, are also expressed in cells of the inner enamel epithelium and ameloblasts (Fig. 2) [43,52]. Notch2 and the Notch signaling modulator, lunatic fringe (Lnf), have been implicated in the rotation of the incisor that determines the lingual/labial asymmetry [53,54]. These patterns of expression suggest that the Notch signaling pathway is involved in the maintenance and determination of the stem cell fate into the ameloblast cell lineage.

Since incisor growth is under control of epithelium to mesenchyme cross talk, dental mesenchyme may be important for the maintenance of epithelial cell populations within the cervical loop. Mesenchymal signals, such as FGF3 and FGF10, have been suggested to participate in cervical loop homeostasis. FGF10 is expressed in the mesenchyme that surrounds the cervical loop epithelium, as well as in the mesenchyme underlying the inner enamel epithelium. FGF3 expression is restricted to the mesenchyme that underlies the inner enamel epithelium. The receptors of these signaling molecules, Fgfr1β and Fgfr2β, are strongly expressed in the epithelium of the cervical loop, especially in basal epithelial cells and cells of the stratum intermedium [43]. The expression patterns of these molecules indicate that FGFs are important mesenchymal signals involved in the regulation of the development of the cervical loop epithelium.

FGF10 has been found to stimulate epithelial cell proliferation in the cervical loop area. Bead implantation experiments have shown that FGF10 stimulates BrdU uptake in epithelial cells, especially in the cervical loop area as compared to cells of the inner enamel epithelium. Similar experiments have demonstrated that FGF10 can equally stimulate Lnf expression, thereby modulating the Notch signaling of the cervical loop region. Expression of both Lnf and FGF is down-regulated at the transition point where cells of the inner enamel epithelium differentiate into ameloblasts [43]. These findings suggest that interactions between the FGF and Notch signaling pathways would maintain stem cells of the cervical loop in an undifferentiated state.

Experiments using FGF10 null mice indicate that FGF10 is not directly involved in the early morphogenesis of the dental organ, but is involved in the creation of the adult stem cell compartment in the cervical loop region. Incisors from the FGF10 null mice develop normally until E14. Thereafter defects in morphology can be seen: incisors are smaller and the cervical loop is missing. BrdU labeling analysis on the incisors of FGF10 null mice has demonstrated that cell proliferation in epithelium has not decreased in comparison to the epithelium of wild type incisors [55]. It has been thus suggested that the smaller size of the mutant incisor is due to the lack of the stem cell compartment in the severely affected cervical loop, rather than an overall reduction of cell proliferation in the dental organ. Surprisingly enough, there is still a differentiation gradient of enamel producing ameloblasts in incisors of FGF10 null mice. This could be explained by the redundancy between FGF3 and FGF10 during incisor morphogenesis [55].

In vitro loss of function experiments, using an anti-FGF10 neutralizing antibody, suggest that FGF10 prevents apoptosis in the cervical loop and surrounding mesenchyme in incisors. However, the application of recombinant human FGF10 rescued the incisor explants from apoptosis induced by the anti-FGF10 antibody in the epithelium but not in the mesenchyme, indicating that FGF10 is a survival signal for the epithelium. By contrast, the mesenchyme appears to need a separate epithelial-derived survival signal, since the mesenchyme underwent apoptosis when cultured alone, but not when cultured in contact with the cervical loop epithelium [55]. FGF10 has been shown to stimulate cell proliferation in a dose dependent manner and induce differentiation of progenitor cells into cells of the stratum intermedium [56].

The hair follicle stem cell niche

The hair follicle, like the rodent incisor, is a regenerating organ where stem cells allow for this massive large-scale renewal. The hair follicle is composed of an outer root sheath, an inner root sheath, and the hair shaft. The proliferating undifferentiated matrix cells give rise to the inner root sheath and the hair shaft, and are surrounded by a dermal papilla of specialized mesenchymal cells. The dermal papilla instructs the formation of the follicle, but the characteristics of the follicle are acquired by epithelial information. The lower portion of the follicle goes through a growth cycle that involves the phases of anagen (active growth), catagen (destruction) and telogen (quiescence). These different phases last for varying time periods depending on the hair follicle location and function. The matrix cells proliferate rapidly during the anagen phase, migrate upwards then differentiate into the cell types of the inner root sheath and hair shaft. During the catagen phase, the lower follicle undergoes apoptotic death and the dermal papilla moves upwards until it reaches the area beneath the bulge. It remains there during telogen. Once the dermal papilla recruits stem cells from the bulge, anagen begins anew and the follicle can regenerate through proliferation and differentiation [57].

The bulge contains the hair follicle stem cell niche and is located in a protected area near the permanent epithelial portion of the hair follicle (Fig. 3). When the dermal papilla is dissociated and combined with follicle sections containing bulge cells, operational hair follicles can be generated under kidney capsules of athymic mice [58]. Furthermore, when the bulge from a lacZ mouse is transplanted onto a wild type hair follicle deprived of its own bulge, β-gal is found in all cell lineages of the chimeric hair follicles [59]. Stem cells from the hair follicle are multipotent as they can also generate the sebaceous glands and restore the epidermis after wounding [60].

One of the amazing features of the epidermal stem cells is their ability to be grown in culture. Based on the growth potential of epidermal cells grown in culture, three different

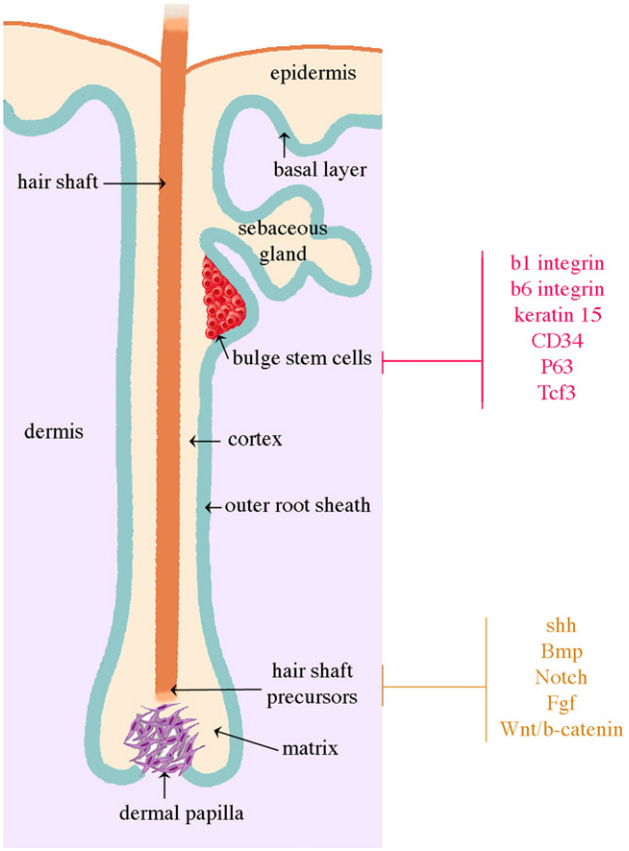


Fig. 3 – Diagram illustrating the stem cell niche in the hair follicle (red color compartment) and the signaling pathways that participate in the regulation of hair follicle stem cells.

types of cells have been identified: holoclones, meroclones and paraclones. Holoclones are those cells with the greatest proliferative potential, which are capable to form proliferative colonies on passaging. Meroclones have less potential to proliferate, and paraclones differentiate after very few passages. It has been suggested that holoclones are stem cells, meroclones are transit-amplifying cells and paraclones are the differentiated cells [61]. Cultures of segments from hair follicles of humans [62] and rodents [63] have shown that the bulge yields the largest holoclone colonies. More recently, it has been shown that EGFP rat cells from the bulge and lower portions of the hair follicle implanted onto the mouse skin contribute to the development and maintenance of hair follicles and other skin appendages, as well as to regenerate the wounded mouse epidermis [64]. Indeed, thymidine incorporation experiments have shown a strong label in cells of the bulge region of the hair follicle, while very few label retaining cells could be found in the basal layer of the epidermis [57].

It has been proposed that the cells from the bulge migrate to populate the basal layer of the skin epithelium, in a similar manner to that when the stem cells migrate to initiate the next phase of anagen. Nevertheless, the mechanism of how the cells could maintain their stemness during migration has yet to be elucidated. Are the migrating cells committed transit amplifying cells or true stem cells? One possibility is that asymmetrically dividing stem cells may generate transit-amplifying cells that leave the bulge in a manner dependent on their fate and necessity. Another possibility is that symmetrically dividing stem cells remain in the bulge, while some asymmetrically dividing cells are sent out as true multipotent stem cells that will generate committed cells as required and dictated by their environment. Asymmetric cell divisions have not been confirmed by cell kinetic assays of the bulge region [65]. On the other hand, cells from the lower region of the hair follicle are capable of generating epidermis, hair follicles and sebaceous glands when subjected to skin morphogenetic signals [63]. These findings indicate that multipotent stem cells released from the bulge region may maintain their stemness until instructed to adopt a specific fate.

The most stringent way of identifying stem cells is through the analysis of the clonogenenicity, growth potential and regenerative ability of the cells. However, a search for universal epidermal stem cell marker has been raging for some time. In order to maintain their stem phenotype, stem cells may require attachment to the basement membrane. The integrins β1 and β6 have been proposed as markers, since epidermal stem cells express high levels of these two integrins. Nonetheless, neither β1 nor β6 integrins can be considered specific stem cell markers as all proliferating cells utilize integrins in adhesion.

Other molecules such as Keratin15 (K15), CD34 or P63, to mention a few, have been postulated as markers of bulge stem cells (Fig. 3). As of yet, however, stem cells cannot be unambiguously identified using molecular markers. Epidermal stem cells from newborn mouse skin can be sorted by flow cytometry using Hoechst 33,342-dye exclusion. This technique can be used to obtain an almost homogenous population of epidermal stem cells. Nonetheless, the functional characteristics of the cells remain the strongest proof of their stem potential [65].

It has been reported that the canonical Wnt signaling (β-catenin mediated) is involved in the commitment of the stem cells into the hair lineages. Activation of the Wnt pathway leads to β-catenin stabilization and its accumulation in the cytoplasm. Mice with constitutively stabilized β-catenin under the Keratin14 promoter demonstrate de novo hair follicle formation in the interfollicular epidermis. This suggests that β-catenin plays a role in the decision of cells to adopt a hair follicle fate [66]. β-catenin can interact with a variety of partners including E-cadherin and the Lef/Tcf transcription factors. TOPGAL reporter mice, which express β-galactosidase when Wnt signaling activates Lef/Tcf proteins, have been used to show that Wnt signaling is active during hair follicle morphogenesis (Fig. 3). Stem cells residing in the bulge do not usually express Lef1, but they do express Tcf3, which seems to be an important factor for the maintenance of a multipotent cell phenotype [65]. Differentiation of the bulge cells leads to Tcf3 down-regulation and concomitant up-regulation of Lef1 expression. Thus, Wnt mediated activation of Tcf3 or Lef1 appears to be the switch that determines the commitment of epidermal stem cells to either maintain their stemness or enter the hair follicle lineage [66]. Mesenchyme-derived Bmp4 has been also shown to induce Lef1 expression during hair follicle morphogenesis. Mice lacking noggin, an inhibitor of the Bmp signaling, show a loss of hair follicles expression and down-regulation of Lef1 expression. Thus, a balance of Bmp, Bmp antagonists and Wnt signaling governs the properties and fate of the hair follicle stem cells [66].

Sonic hedgehog (Shh) is critical in hair follicle development: Shh mutant mice demonstrate a failure to develop hair follicles because cell proliferation and migration is affected. Fgf4 has also recently been identified as a Wnt target. Fgf4 regulates Notch signaling in the hair follicle placode [66,67]. In the hair follicle, Notch1 expression is restricted in cells that will undergo differentiation into the many cell types of the hair shaft and the inner root sheath. Cells of the bulge do not express Notch1. The absence of Notch1 in the bulge indicates that Notch signaling may not have a role in maintaining the hair follicle stem cell phenotype, but rather in the decision of a transit-amplifying cell to adopt a particular fate [67,68]. Tissue specific ablation of Notch1 under the control of Keratin5 promoter in mice demonstrates that while Notch signaling may not be necessary for embryonic hair formation, postnatal inactivation of Notch1 leads to almost complete hair loss. These results suggest that Notch1 is essential for postnatal hair follicle homeostasis, growth and differentiation [69].

Molecular diversity of stem cell niches

Stem cells offer a unique opportunity to conceive new methods of treatment in the fields of tissue engineering and regenerative medicine. There is an ongoing effort to apply stem cells from various origins in order to repair and/or create tissues and organs such as bone, skin, hair and teeth. Formation or regeneration of organs regulated by epithelial–mesenchymal interactions (e.g. tooth, hair) is more complex, due to an interchange of signaling molecules between the epithelium and mesenchyme that triggers their development. Epithelial and mesenchymal cells from the same organ or from different sources have been recombined in an attempt to

recreate entire organs. However, it is not yet clear if stem cells from different embryonic origins have identical or similar regenerative properties. Therefore, comparative studies are ongoing to assess whether a stem cell population is more effective than others. In this regard, the purification and cloning of stem cells from different sources would be desirable for a better understanding of the repair potential of various stem cell populations.

The relationship between mesenchymal stem cells derived from different embryonic origins as well as their relationship with various epithelial stem cells also warrants investigation. The extent to which co-cultured epithelial and mesenchymal stem cells from two different tissues/organs could recapitulate the developmental events of a third tissue/organ also needs to be determined.

The bone marrow stem cell niches clearly differ from tooth and hair follicle stem cell niches. However, there is a great similarity in the molecular programs that operate in stem cell niches of different tissues/organs. For example, Wnt signaling plays a crucial role in regulating bone marrow HSC niches and epidermal stem cell niches [19,20,66,67,70]. By contrast, FGF signaling regulates the epithelial stem cell niche in rodent incisors [43,55], but its role in the bone marrow niches remains to be elucidated.

A very recent study has shown that the regulatory control of the stem cell niche in the incisor implies a complex network consisting of activin, follistatin, BMP and FGF molecules [71]. While Wnt signaling has not been studied in detail in incisors, a recent study has demonstrated that activated canonical Wnt signaling induces continuous tooth generation in mouse [72], suggesting that Wnt signaling may be part of the molecular network regulating dental epithelial stem cells.

In spite of the diversity of stem cell niches, the key molecules appear to be the same across different systems and organs. Nonetheless, these molecules play distinct and often diverse roles according to the embryonic origin and specific functions of the tissues.

Conclusion

The elucidation of the stem cell niche biology in health and disease has become a pressing issue in basic science and medicine. Understanding how niche cells and extracellular matrix control stem cell fate outcomes will provide new tools with which to endorse differentiation of stem cells into particular cell types. This knowledge is likely to instruct development of novel therapies in the near future. The increasing availability of small molecules with the ability to target specific signaling pathways and the development of controlled delivery systems make the modulation of stem cell niches an attractive approach for tissue/organ regeneration and repair.

Acknowledgments

Thimios Mitsiadis is supported by grants of the University of Zurich; Cosimo De Bari is supported by the UK Medical Research Council.

REFERENCES

[1] K.A. Moore, I.R. Lemischka, Stem cells and their niches, Science 311 (2006) 1880–1885.
[2] A. Spradling, D. Drummond-Barbosa, T. Kai, Stem cells find their niche, Nature 414 (2001) 98–104.
[3] Y.M. Yamashita, D.L. Jones, M.T. Fuller, Orientation of asymmetric stem cell division by the APC tumor suppressor and centrosome, Science 301 (2003) 1547–1550.
[4] Y.M. Yamashita, M.T. Fuller, D.L. Jones, Signaling in stem cell niches: lessons from the *Drosophila* germline, J. Cell Sci. 118 (2005) 665–672.
[5] J. Betschinger, J.A. Knoblich, Dare to be different: asymmetric cell division in *Drosophila*, *C. elegans* and vertebrates, Curr. Biol. 14 (2004) R674–R685.
[6] J. Betschinger, K. Mechtler, J.A. Knoblich, Asymmetric segregation of the tumor suppressor brat regulates self-renewal In *Drosophila* neural stem cells, Cell 124 (2006) 1241–1253.
[7] G. Emery, A. Hutterer, D. Berdnik, B. Mayer, F. Wirtz-Peitz, M.G. Gaitan, J.A. Knoblich, Asymmetric Rab 11 endosomes regulate delta recycling and specify cell fate in the *Drosophila* nervous system, Cell 122 (2005) 763–773.
[8] T. Lechler, E. Fuchs, Asymmetric cell divisions promote stratification and differentiation of mammalian skin, Nature 437 (2005) 275–280.
[9] V. Shinin, B. Gayraud-Morel, D. Gomes, S. Tajbakhsh, Asymmetric division and cosegregation of template DNA strands in adult muscle satellite cells, Nat. Cell Biol. 8 (2006) 677–687.
[10] S. Kuang, K. Kuroda, G.F. Le, M.A. Rudnicki, Asymmetric self-renewal and commitment of satellite stem cells in muscle, Cell 129 (2007) 999–1010.
[11] A.A. Kiger, H. White-Cooper, M.T. Fuller, Somatic support cells restrict germline stem cell self-renewal and promote differentiation, Nature 407 (2000) 750–754.
[12] T. Xie, A.C. Spradling, A niche maintaining germ line stem cells in the *Drosophila* ovary, Science 290 (2000) 328–330.
[13] J. Zhang, C. Niu, L. Ye, H. Huang, X. He, W.G. Tong, J. Ross, J. Haug, T. Johnson, J.Q. Feng, S. Harris, L.M. Wiedemann, Y. Mishina, L. Li, Identification of the haematopoietic stem cell niche and control of the niche size, Nature 425 (2003) 836–841.
[14] L.M. Calvi, G.B. Adams, K.W. Weibrecht, J.M. Weber, D.P. Olson, M.C. Knight, R.P. Martin, E. Schipani, P. Divieti, F.R. Bringhurst, L.A. Milner, H.M. Kronenberg, D.T. Scadden, Osteoblastic cells regulate the haematopoietic stem cell niche, Nature 425 (2003) 841–846.
[15] S. Stier, Y. Ko, R. Forkert, C. Lutz, T. Neuhaus, E. Grunewald, T. Cheng, D. Dombkowski, L.M. Calvi, S.R. Rittling, D.T. Scadden, Osteopontin is a hematopoietic stem cell niche component that negatively regulates stem cell pool size, J. Exp. Med. 201 (2005) 1781–1791.
[16] S.K. Nilsson, H.M. Johnston, G.A. Whitty, B. Williams, R.J. Webb, D.T. Denhardt, I. Bertoncello, L.J. Bendall, P.J. Simmons, D.N. Haylock, Osteopontin, a key component of the hematopoietic stem cell niche and regulator of primitive hematopoietic progenitor cells, Blood 106 (2005) 1232–1239.
[17] D. Visnjic, Z. Kalajzic, D.W. Rowe, V. Katavic, J. Lorenzo, H.L. Aguila, Hematopoiesis is severely altered in mice with an induced osteoblast deficiency, Blood 103 (2004) 3258–3264.
[18] K. Miyazawa, D.A. Williams, A. Gotoh, J. Nishimaki, H.E. Broxmeyer, K. Toyama, Membrane-bound steel factor induces more persistent tyrosine kinase activation and longer life span of c-kit gene-encoded protein than its soluble form, Blood 85 (1995) 641–649.
[19] A.W. Duncan, F.M. Rattis, L.N. Dimascio, K.L. Congdon, G. Pazianos, C. Zhao, K. Yoon, J.M. Cook, K. Willert, N. Gaiano, T. Reya, Integration of Notch and Wnt signaling in

hematopoietic stem cell maintenance, Nat. Immunol. 6 (2005) 314–322.
[20] T. Reya, A.W. Duncan, L. Ailles, J. Domen, D.C. Scherer, K. Willert, L. Hintz, R. Nusse, I.L. Weissman, A role for Wnt signalling in self-renewal of haematopoietic stem cells, Nature 423 (2003) 409–414.
[21] F. Arai, A. Hirao, M. Ohmura, H. Sato, S. Matsuoka, K. Takubo, K. Ito, G.Y. Koh, T. Suda, Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche, Cell 118 (2004) 149–161.
[22] O. Kollet, A. Dar, S. Shivtiel, A. Kalinkovich, K. Lapid, Y. Sztainberg, M. Tesio, R.M. Samstein, P. Goichberg, A. Spiegel, A. Elson, T. Lapidot, Osteoclasts degrade endosteal components and promote mobilization of hematopoietic progenitor cells, Nat. Med. 12 (2006) 657–664.
[23] G.B. Adams, K.T. Chabner, I.R. Alley, D.P. Olson, Z.M. Szczepiorkowski, M.C. Poznansky, C.H. Kos, M.R. Pollak, E.M. Brown, D.T. Scadden, Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor, Nature 439 (2006) 599–603.
[24] C.L. Semerad, M.J. Christopher, F. Liu, B. Short, P.J. Simmons, I. Winkler, J.P. Levesque, J. Chappel, F.P. Ross, D.C. Link, G-CSF potently inhibits osteoblast activity and CXCL12 MRNA expression in the bone marrow, Blood 106 (2005) 3020–3027.
[25] Y. Katayama, M. Battista, W.M. Kao, A. Hidalgo, A.J. Peired, S.A. Thomas, P.S. Frenette, Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow, Cell 124 (2006) 407–421.
[26] M.J. Kiel, O.H. Yilmaz, T. Iwashita, O.H. Yilmaz, C. Terhorst, S.J. Morrison, SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells, Cell 121 (2005) 1109–1121.
[27] D.A. Sipkins, X. Wei, J.W. Wu, J.M. Runnels, D. Cote, T.K. Means, A.D. Luster, D.T. Scadden, C.P. Lin, In vivo imaging of specialized bone marrow endothelial microdomains for tumour engraftment, Nature 435 (2005) 969–973.
[28] A. Wilson, A. Trumpp, Bone-marrow haematopoietic-stem-cell niches, Nat. Rev., Immunol. 6 (2006) 93–106.
[29] T. Sugiyama, H. Kohara, M. Noda, T. Nagasawa, Maintenance of the hematopoietic stem cell pool by CXCL12–CXCR4 chemokine signaling in bone marrow stromal cell niches, Immunity 25 (2006) 977–988.
[30] A. Peled, I. Petit, O. Kollet, M. Magid, T. Ponomaryov, T. Byk, A. Nagler, H. Ben-Hur, A. Many, L. Shultz, O. Lider, R. Alon, D. Zipori, T. Lapidot, Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4, Science 283 (1999) 845–848.
[31] J.M. Perry, L. Li, Disrupting the stem cell niche: good seeds in bad soil, Cell 129 (2007) 1045–1047.
[32] M.F. Pittenger, A.M. Mackay, S.C. Beck, R.K. Jaiswal, R. Douglas, J.D. Mosca, M.A. Moorman, D.W. Simonetti, S. Craig, D.R. Marshak, Multilineage potential of adult human mesenchymal stem cells, Science 284 (1999) 143–147.
[33] C. De Bari, C. Pitzalis, F. Dell'Accio, Reparative medicine: from tissue engineering to joint surface regeneration, Regen. Med. 1 (2006) 59–69.
[34] S. Gronthos, A.C. Zannettino, S.J. Hay, S. Shi, S.E. Graves, A. Kortesidis, P.J. Simmons, Molecular and cellular characterisation of highly purified stromal stem cells derived from human bone marrow, J. Cell Sci. 116 (2003) 1827–1835.
[35] E.A. Jones, S.E. Kinsey, A. English, R.A. Jones, L. Straszynski, D.M. Meredith, A.F. Markham, A. Jack, P. Emery, D. Mcgonagle, Isolation and characterization of bone marrow multipotential mesenchymal progenitor cells, Arthritis Rheum. 46 (2002) 3349–3360.
[36] C. De Bari, F. Dell'Accio, P. Tylzanowski, F.P. Luyten, Multipotent mesenchymal stem cells from adult human synovial membrane, Arthritis Rheum. 44 (2001) 1928–1942.
[37] C. De Bari, F. Dell'Accio, F. Vandenabeele, J.R. Vermeesch, J.M. Raymackers, F.P. Luyten, Skeletal muscle repair by adult human mesenchymal stem cells from synovial membrane, J. Cell Biol. 160 (2003) 909–918.
[38] C. De Bari, F. Dell'Accio, J. Vanlauwe, J. Eyckmans, I.M. Khan, C.W. Archer, E.A. Jones, D. Mcgonagle, T.A. Mitsiadis, C. Pitzalis, F.P. Luyten, Mesenchymal multipotency of adult human periosteal cells demonstrated by single-cell lineage analysis, Arthritis Rheum. 54 (2006) 1209–1221.
[39] E.A. Jones, A. English, K. Henshaw, S.E. Kinsey, A.F. Markham, P. Emery, D. Mcgonagle, Enumeration and phenotypic characterization of synovial fluid multipotential mesenchymal progenitor cells in inflammatory and degenerative arthritis, Arthritis Rheum. 50 (2004) 817–827.
[40] S. Shi, S. Gronthos, Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp, J. Bone Miner. Res. 18 (2003) 696–704.
[41] Y. Muguruma, T. Yahata, H. Miyatake, T. Sato, T. Uno, J. Itoh, S. Kato, M. Ito, T. Hotta, K. Ando, Reconstitution of the functional human hematopoietic microenvironment derived from human mesenchymal stem cells in the murine bone marrow compartment, Blood 107 (2006) 1878–1887.
[42] S. Glennie, I. Soeiro, P.J. Dyson, E.W. Lam, F. Dazzi, Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells, Blood 105 (2005) 2821–2827.
[43] H. Harada, P. Kettunen, H.S. Jung, T. Mustonen, Y.A. Wang, I. Thesleff, Localization of putative stem cells in dental epithelium and their association with notch and FGF signaling, J. Cell Biol. 147 (1999) 105–120.
[44] T.A. Mitsiadis, P. Couble, E. Dicou, B.B. Rudkin, H. Magloire, Patterns of nerve growth factor (NGF), ProNGF, and P75 NGF receptor expression in the rat incisor: comparison with expression in the molar, Differentiation 54 (1993) 161–175.
[45] H. Ohshima, N. Nakasone, E. Hashimoto, H. Sakai, K. Nakakura-Ohshima, H. Harada, The eternal tooth germ is formed at the apical end of continuously growing teeth, Arch. Oral Biol. 50 (2005) 153–157.
[46] C.E. Smith, H. Warshawsky, Cellular renewal in the enamel organ and the odontoblast layer of the rat incisor as followed by radioautography using 3H-thymidine, Anat. Rec. 183 (1975) 523–561.
[47] C.E. Smith, H. Warshawsky, Quantitative analysis of cell turnover in the enamel organ of the rat incisor. Evidence for ameloblast death immediately after enamel matrix secretion, Anat. Rec. 187 (1977) 63–98.
[48] S. Kawano, M. Saito, K. Handa, T. Morotomi, T. Toyono, Y. Seta, N. Nakamura, T. Uchida, K. Toyoshima, M. Ohishi, H. Harada, Characterization of dental epithelial progenitor cells derived from cervical-loop epithelium in a rat lower incisor, J. Dent. Res. 83 (2004) 129–133.
[49] K. Abe, K. Miyoshi, T. Muto, I. Ruspita, T. Horiguchi, T. Nagata, T. Noma, Establishment and characterization of rat dental epithelial derived ameloblast-lineage clones, J. Biosci. Bioeng. 103 (2007) 479–485.
[50] T.A. Mitsiadis, M. Lardelli, U. Lendahl, I. Thesleff, Expression of Notch 1, 2 And 3 is regulated by epithelial–mesenchymal interactions and retinoic acid in the developing mouse tooth and associated with determination of ameloblast cell fate, J. Cell Biol. 130 (1995) 407–418.
[51] T.A. Mitsiadis, E. Hirsinger, U. Lendahl, C. Goridis, Delta-Notch signaling in odontogenesis: correlation with cytodifferentiation and evidence for feedback regulation, Dev. Biol. 204 (1998) 420–431.
[52] T.A. Mitsiadis, D. Henrique, I. Thesleff, U. Lendahl, Mouse Serrate-1 (Jagged-1): expression in the developing tooth is regulated by epithelial–mesenchymal interactions and fibroblast growth factor-4, Development 124 (1997) 1473–1483.
[53] M.L. Mucchielli, T.A. Mitsiadis, Correlation of asymmetric Notch2 expression and mouse incisor rotation, Mech. Dev. 91 (2000) 379–382.

[54] L. Pouyet, T.A. Mitsiadis, Dynamic lunatic fringe expression is correlated with boundaries formation in developing mouse teeth, Mech. Dev. 91 (2000) 399–402.
[55] H. Harada, T. Toyono, K. Toyoshima, M. Yamasaki, N. Itoh, S. Kato, K. Sekine, H. Ohuchi, FGF10 maintains stem cell compartment in developing mouse incisors, Development 129 (2002) 1533–1541.
[56] T. Morotomi, S. Kawano, T. Toyono, C. Kitamura, M. Terashita, T. Uchida, K. Toyoshima, H. Harada, In vitro differentiation of dental epithelial progenitor cells through epithelial–mesenchymal interactions, Arch. Oral Biol. 50 (2005) 695–705.
[57] L. Alonso, E. Fuchs, Stem cells of the skin epithelium, Proc. Natl. Acad. Sci.U. S. A. 100 (Suppl 1) (2003) 11830–11835.
[58] K. Kobayashi, E. Nishimura, Ectopic growth of mouse whiskers from implanted lengths of plucked vibrissa follicles, J. Invest. Dermatol. 92 (1989) 278–282.
[59] H. Oshima, A. Rochat, C. Kedzia, K. Kobayashi, Y. Barrandon, Morphogenesis and renewal of hair follicles from adult multipotent stem cells, Cell 104 (2001) 233–245.
[60] G. Taylor, M.S. Lehrer, P.J. Jensen, T.T. Sun, R.M. Lavker, Involvement of follicular stem cells in forming not only the follicle but also the epidermis, Cell 102 (2000) 451–461.
[61] Y. Barrandon, H. Green, Cell migration is essential for sustained growth of keratinocyte colonies: the roles of transforming growth factor-alpha and epidermal growth factor, Cell 50 (1987) 1131–1137.
[62] A. Rochat, K. Kobayashi, Y. Barrandon, Location of stem cells of human hair follicles by clonal analysis, Cell 76 (1994) 1063–1073.
[63] K. Kobayashi, A. Rochat, Y. Barrandon, Segregation of keratinocyte colony-forming cells in the bulge of the rat vibrissa, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 7391–7395.
[64] S. Claudinot, M. Nicolas, H. Oshima, A. Rochat, Y. Barrandon, Long-term renewal of hair follicles from clonogenic multipotent stem cells, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 14677–14682.
[65] L. Gambardella, Y. Barrandon, The multifaceted adult epidermal stem cell, Curr. Opin. Cell Biol. 15 (2003) 771–777.
[66] L. Alonso, E. Fuchs, Stem cells in the skin: waste not, Wnt not, Genes Dev. 17 (2003) 1189–1200.
[67] C. Blanpain, E. Fuchs, Epidermal stem cells of the skin, Annu. Rev. Cell Dev. Biol. 22 (2006) 339–373.
[68] R. Kopan, H. Weintraub, Mouse Notch: expression in hair follicles correlates with cell fate determination, J. Cell Biol. 121 (1993) 631–641.
[69] S. Vauclair, M. Nicolas, Y. Barrandon, F. Radtke, Notch1 is essential for postnatal hair follicle development and homeostasis, Dev. Biol. 284 (2005) 184–193.
[70] W.E. Lowry, C. Blanpain, J.A. Nowak, G. Guasch, L. Lewis, E. Fuchs, Defining the impact of beta-catenin/Tcf transactivation on epithelial stem cells, Genes Dev. 19 (2005) 1596–1611.
[71] X.P. Wang, M. Suomalainen, S. Felszeghy, L.C. Zelarayan, M.T. Alonso, M.V. Plikus, R.L. Maas, C.M. Chuong, T. Schimmang, I. Thesleff, An integrated gene regulatory network controls stem cell proliferation in teeth, Plos. Biol. 5 (2007) E159.
[72] E. Jarvinen, I. Salazar-Ciudad, W. Birchmeier, M.M. Taketo, J. Jernvall, I. Thesleff, Continuous tooth generation in mouse is induced by activated epithelial Wnt/Beta-catenin signaling, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 18627–18632.