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Chapter 4

Hair Follicle Reconstruction and Stem Cells

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Abstract

De novo hair follicle (HF) formation in embryonic skin and hair growth in postnatal skin are the result of epithelial-mesenchymal interactions between specialized mesenchymal dermal papilla (DP) and epithelial stem cells that give rise to hairs. Adult HF is a valuable source of different lineages of stem cells (SCs) with morphogenetic potential. Epithelial stem cells are residing in the special compartment of HF (the bulge) and can be mobilized to regenerate the new follicle with each hair cycle and to reepithelialize epidermis during wound repair. This review summarizes the current knowledge on key characteristics of HF SC populations in terms of regenerative potential. General biological principles that govern the mesenchymal-epithelial interactions within the HF and the signaling pathways that control HF development are discussed. The main focus is on recent approaches to reconstruct folliculogenesis *in vitro* and perspectives of the tissue engineering in alopecia therapy.

Keywords: epidermis, hair follicle, morphogenesis, stem cells, hair follicle reconstruction, dermal papilla

1. Introduction

Alopecia is a growing health problem in the world, and the age of patients tends to decrease [1]. Dermatologists and trichologists have an increasing list of young patients including women, at the age of 25–30 years or even teenagers. At the same time, there are only few really effective remedies in the field. Achievements in cell biology and biotechnology propose novel products to solve these problems. One of the promising and reasonable ways to develop cell products for hair loss treatment is to obtain trichogenic cells and then to grow small follicle-like structures. To develop effective strategies of hair follicle (HF) reconstruction we need to

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have a deep insight into cellular and molecular mechanisms of HF development and regeneration. The research on HF is a rapidly developing area of skin biology. This mini-organ can be successfully used for a wide range of studies into the mechanisms of morphogenesis, stem cell behavior, cell differentiation, and apoptosis [2–4]. Moreover, as mentioned above, HF investigations can provide invaluable insights into the possible causes of human hair disorders and provide conditions for development of HF restoration technologies.

2. Hair follicle: structure, cycling and stem cells

HF is a skin appendage with very complex structure undergoing lifelong periods of morphogenesis. The major part of HF is produced by the epithelium. Highly proliferative matrix cells in HF bulb gradually move upwards in the course of differentiation. They are progenitors for the inner and outer root sheaths and hair shaft later on. Mesenchymal portion of HF includes dermal papilla (DP) and HF connective tissue sheath. DP is located inside the bulb and is separated from the matrix cells by a basement membrane. In a lower part of the bulb, DP contacts with the dermal sheath that surrounds the entire follicle. This structure is maintained throughout the hair-growth phase – anagen. With time, when HF transits into the destructive phase–catagen–the lower two-thirds of the HF epithelial strand degenerate and the hair shaft production stops. DP also becomes smaller but its losses are much less significant and are mainly caused by reduced content of an extracellular matrix [5] and migration of cells between the DP and the adjacent dermal sheath [6]. During catagen, HF is reduced to a tiny epidermal strand surrounded by a basement membrane. As it retracts, the DP is pulled upward to the upper permanent portion of the HF containing bulge stem cells [7].

Then HF enters the resting phase – telogen. The transition from telogen to anagen is the beginning of a new HF cycle, a process that continues throughout life. In mice, the lengths of anagen and catagen phases are similar from one cycle to the next, while each telogen becomes longer than the previous one. This results in progressive asynchrony in HF cycling with age [8].

Now it is quite clear that the regeneration cycle is maintained by activity of HF stem cells. HF is considered to be a valuable source of adult stem cells (SCs) with morphogenetic potential. SCs may be isolated from epidermal and mesenchymal compartments of HF. Additionally neural crest-derived cells are found in HF, at least in the facial skin [9, 10]. Matrix cells had been thought to be stem cells for a long time as they proliferate very intensively at the beginning of the growth phase. However in experiments with murine HFs, Cotsarelis and co-authors discovered special population of cells at the bottom of a permanent portion of the HF known as the bulge [11]. These cells retained thymidine DNA label after 4 weeks of chase period unlike matrix cells which lost the label as early as 1 week after cessation of labeling. From these pioneering experiments, the bulge has been proved in many studies to be the main reservoir of SCs in HF. It contains morphologically undifferentiated and slow-cycling under the normal conditions of cells. The bulge is a swelling and contiguous part of outer root sheath. As many HFs lack anatomically well-defined bulge region, the term ‘bulge’ is often referred loosely to the permanent region of the follicle below the sebaceous gland [12, 13]. The bulge region is also the point of attachment of the arrector pilorum muscles [11]. SCs of melanocyte lineage

are located in close proximity of the bulge epithelial SCs. Melanocyte proliferation and differentiation is strongly coordinated with the HF cycle. In fact, both types of SCs occupy the same niche or two partially overlapping niches [14, 15]. The arrector pilorum muscle is tightly connected with the bulge region. Epithelial SCs of the outer root sheath deposit nefronectin onto underlying basement membrane and regulate adhesion of mesenchymal cells expressing the receptor to nefronectin. Thus, bulge SC create the niche for smooth muscle cells and participate in regulation of the arrector pilorum muscle [16].

Epithelial and mesenchymal SCs of HF are not only a source of cell mass during HF regrowth phase, but they are also key regulators of hair cycle. Both pools of SCs produced multiple growth factors and cytokines regulating cellular proliferation, differentiation, and HF morphogenesis. Key regulators of hair cycle belong to Wnt, TGFbeta, FGF, and some other signaling pathway families [17, 18].

Bulge cells remain dormant during telogen. The DP plays a pivotal role in initiation of the next cycle of HF formation and hair growth [19–21]. This is associated with bulge cell migration and proliferation in the hair germ to generate the highly proliferative cells at the base of the follicle [7, 22]. Hair germ likely represents a special subpopulation of bulge descendants capable of quick recruitment into intensively proliferating state [7]. The authors suggest that the crosstalk between hair germ and DP via FGF7 signaling contributes significantly to the early steps of hair cycle activation.

3. Dermal papilla cells and their inductive properties

Dermal papilla cells represent mesenchymal cell subpopulation with stem properties. According to their specific features, they may be attributed to classical fibroblast-like cells with special functions. At the same time, DP cells meet stem cell criteria. In a number of works, including those coming from our lab, it was demonstrated that DP cells, according to their characteristics, may be attributed to mesenchymal stem cells along with those derived from bone marrow and adipose tissue [23–26]. These characteristics are widely accepted criteria for mesenchymal stem cells including fibroblastic morphology, ability to adhere and to differentiate into osteogenic, chondrogenic, and adipogenic lineages [24, 27, 28]. It should be mentioned that DP differentiation abilities are often pronounced not to the same extent as those of classical mesenchymal stem cells [23]. As other lineages of differentiation were demonstrated some authors believe DP cells to be multipotent [28]. In laboratory animals, it was demonstrated that this type of cells is able to incorporate into skin structures by grafting [29] and stimulate hair growth and angiogenesis. As it was found in detail during the last 20 years, the ability to induce and regulate HF morphogenesis has been considered to be the main characteristic and core biological function of DP cells. They are indispensable component for embryonic development of HF and postnatal cycling [30]. They serve as the niche for providing signals to matrix progenitors in specifying the size, shape, and pigmentation of hair fiber [5, 31]. Multiple pathways and molecules regulating epithelio-mesenchymal interactions were discovered [32]. Using double reporter Lef1-RFP/K14-H2BGFP mice, Rendl with co-authors discovered detailed genetic signature of isolated mouse DP cells [33].

In ontogenesis, DP first appears as cell condensates on the dermis. As HF develops, epidermal cells proliferate actively and envelope the dermal condensates [34]. Exposed to these new niche conditions, DP cells acquire the expression of BMP-4, its inhibitor noggin, and the surface markers N-CAM and p-75. Additionally, they secret specific extracellular matrix protein versican and show a high level of alkaline phosphatase activity.

Inducing capacity of DP cells, i.e., their ability to induce HF development in embryogenesis and regulate postnatal HF cycling, is the most interesting and intriguing trait of these cells. It is noteworthy that not only DP but also skin dermis on the whole has an ability to regulate differentiation of integumental epithelia. As an example, keratinocytes of the palmoplantar thick skin exclusively express keratin 9 [35]. Recombination of the epidermis from different body sites with palmoplantar dermis caused onset of keratin 9 expression and differentiation of keratinocytes into thick skin [36]. Later it was shown that paleness and thickness of the palmoplantar skin is determined by Wnt signaling. Fibroblasts present in thick skin secrete Wnt inhibitor Dikkopf1, which causes thickening of the epidermis and decreases pigmentation both *in vivo* and *in vitro* [37]. HFs and, thus, DPs are distributed over the entire surface of the mammal body. In spite of different embryological origin of DPs from different sites of the body, their functional properties are quite similar. Analysis of global gene expression using microarrays demonstrated a very high degree of similarity between facial and trunk dermal hair-associated cells indicating phenotypic convergence within HF niche [38].

DP cells have been quite profoundly investigated but their isolation and long-term cultivation is not a trivial task yet. They quickly lose intrinsic biological characteristics, especially hair inductive capacity, with passaging [39–41]. This process correlates with decrease in expression of DP markers including alkaline phosphatase, versican, Wnt5a, and some others [42–45].

A number of studies reported various approaches to maintain innate properties in cultured DP cells. Earlier approach implied cocultivation with keratinocytes or addition of keratinocyte-derived factors [46, 47] based on close interaction of DP cells with keratinocytes in their natural niche. Another group of studies considers specific signaling pathways participating in hair growth activation and epithelial-mesenchymal interactions. Wnt and BMP signaling were shown to play a key role in HF morphogenesis [18, 44, 48, 49]. Wnt proteins demonstrated high effectiveness in respect of DP maintenance [50, 51]. Shimizu and Morgan found that Wnt 3a can maintain the hair-inductive properties of DP cells when they are cultured *in vitro* [49]. The medium containing recombinant Wnt-10b protein promoted the proliferation of DP cells, which successfully maintained their ability to induce HFs up to at least 10 serial passages [52]. Noteworthy, Wnt10b has been shown to be expressed in developing HFs, with the earliest and most marked localization in placodes [53] while Wnt10b-producing cells promoted hair folliculogenesis [54]. Canonical Wnt pathway in cultured DP cells was shown to be modulated by several compounds: ciprofloxacin [55], valproic acid [56, 57], and glycogen synthase kinase (GSK)-3 –inhibitors [43, 58]. Addition of vitamin D3 to culture medium upregulated expression of Wnt10b and TGF-β2 in murine DP cell providing significantly enhanced hair growth in hemivascularized sandwich assay [59].

Members of TGFbeta signaling pathway, Bmp 4 and Bmp 6 were used successfully to maintain specific characteristics of DP cells in culture [44, 48]. EGF and VEGF demonstrated stim-

ulation of DP proliferation [60, 61]. However, these factors failed to maintain specific DP markers (unpublished data). It is not surprising as cell proliferation may necessarily correlate with hair inductive activity. On the other hand, combination of FGF and PDGF-AA promoted DP growth in culture and increased *de novo* HF induction in chamber assay using treated DP cells [62].

Ohyama and co-authors studied molecular signature of freshly dissected human DP cells and found gene expression profiles that distinguish intact human DP from conventionally cultured human DP cells and fibroblasts. Because the bioinformatics analysis performed by the authors implied the involvement of Wnt, BMP, and FGF signaling pathways in the maintenance of specific DP properties they used the mixture of recombinant proteins and small molecules for stimulation of BMP, FGF, and Wnt pathways, respectively. This approach allowed them to maintain or even restore innate DP gene expression profile and trichogenic properties demonstrated in an *in vivo* hair induction assay [43].

Recently it was shown that systemically administered pharmacological inhibitors of Janus kinase (JAK) family of protein tyrosine kinases, as downstream effectors of the IFN-γ and γc cytokine receptors, prevented the development of alopecia areata in a mouse model reducing the accumulation of effector T cells in the skin [63]. During the course of the study, the authors noticed unexpected regrowth of HFs after topical treatment with JAK-STAT inhibitors. They checked it in a separate study and were able to demonstrate direct stimulation of HFs growth both in mice, and the human xenografts and HF organ culture model [64]. Moreover, treatment of human DP spheres with the inhibitor of JAK1/3 signaling tofacitinib enhanced inductivity of human DP cells grown in spheres significantly which resulted in larger and significantly greater numbers of HFs obtained in the patch assay.

Another way to get closer to native DPs is to cultivate DP cells in spheres. It has been noticed long ago that DP cells demonstrate aggregative behavior in culture [65]. This may be readily used for creation of three-dimensional (3D) environment by hanging drop or non-adherent biomaterial culture systems. This approach can partially recover expression of core markers in human DP cultures [66]. Cells in spheres stop to proliferate and establish multiple cell-cell contacts that may enhance Wnt signaling. They returned to a more native state judged by alpha-smooth muscle actin expression. It is noteworthy that not all strains demonstrated this behavior indicating large differences between cultures derived from different donors. Nevertheless, many studies with DP cells have been conducted recently using 3D cultivation [3131, 64, 67, 68]. They showed prolongation of specific markers expression and enhancement of hair inductive capacity after preliminary DP cell aggregation [42, 43, 66].

Taking into account complex natural HF niche it seems quite reasonable to introduce elements of this niche into DP culture systems. Huang with co-authors [68] combined DP with SCs derived from the adipose tissue (ASC) which normally surrounds HF and is shown to influence HF cycling presumably via PDGF signaling [69]. It was found that core-shell patterning of combined spheres with DP cells inside and ASC outside had a beneficial effect on DP markers expression (Hey 1 and Versican) and the rate of hair formation in *in vivo* patch assay. Mature adipocytes incorporated into the same type of spheres had no impact on these processes. A simple mixture of cells within spheres without the formation of core-shell

structures yielded much worse results [68]. The authors assume that the mixture of ASCs and DPs in simple mixed spheres interrupted the direct cell-cell interactions and association in DP cells or diluted the signals from ASCs to the DP sphere. It was reported that extracts and conditioned medium from neural stem cells were able to stimulate keratinocyte growth and enhanced hair growth compared to minoxidil [70].

Further search for suitable factors and conditions for effective cultivation and propagation of DP cells will allow one to elucidate mechanism of their self-maintenance and develop large-scale culture technologies.

4. Hair follicle reconstruction

Regeneration ability of organs and even tissues is significantly limited in humans. At the same time, loss of teeth, hair, and even mammary glands due to different reasons is quite abundant. These organs are comparable by their ontogenetic epithelial-mesenchymal origin i.e., like almost all organs in the body, they arise from organ germs which undergo subsequent stages of reciprocal epithelial-mesenchymal crosstalk and close interactions. In adult human body, reproduction of these interactions in the right order and availability of germ-initiating cells to regenerate the entire architecture of multicomponent tissues and organs seems to be impossible or at least dramatically impeded. Development of novel technologies proposes a new hope for people. Tissue engineering is a promising approach to replace the lost tissues and organs. However, the problem how to obtain complex structures which can imitate an organ or develop the organ after grafting is far from solution. In many cases, practical technologies imply transplantation of specialized cells in suspension or sheets. More complicated structures are much more difficult to grow.

Reconstruction of folliculogenesis *in vitro* has been in the minds of scientists for a long period of time taking into account vast knowledge and impressive progress in skin biology beginning from the pioneering works on cultivation of epidermal cells [71] and the epidermis being one of the first tissues that has been reconstructed using tissue engineering [72]. Skin comprises epithelial and mesenchymal components which form body coverage and multiple skin appendages like HF and different types of glands. Since it became possible to reconstruct and reconstitute damaged skin, the problem of HF and gland reconstruction emerged for proper functioning of skin grafts as well as for fundamental studies. It has become especially attractive because a new direction of tissue engineering and regenerative medicine has been developed which utilized the ability of pluripotent cells to self-organize in culture into organ-like structures reproducing functional activity of the corresponding organ [73]. However postnatal cells represent quite a different story.

During recent decades, HF biology was profoundly studied. As mentioned above, HF in mammals is the only organ which in normal physiological condition undergoes degeneration (catagen) to small aggregates of resting cells (telogen) with subsequent full regeneration leading to complete restoration of multicellular organ generating corneal shaft (anagen). Multiple mechanisms regulating organogenesis and physiological regeneration of HFs are found, the

cellular structure of HF is studied in detail, properties and functions of cell subpopulations are elucidated [74-78].

Numerous studies utilized the ability of epithelial and mesenchymal cells of different organs to produce mutual influence even in culture conditions in attempts to reproduce morphogenetic processes. After both compartments were determined in HF, this approach was applied to reconstruct folliculogenesis *in vitro*. It was proved that DP cells affect interfollicular keratinocytes in many aspects. Coculturing of keratinocytes and DP cells in Transwell system stimulated expression of follicular markers in keratinocytes [79]. Direct contact between cells of different types enhances this interaction [80].

Due to specific inducing properties of DP cells morphogenesis of HF may be reproduced in culture. While keratinocytes possess intrinsic ability to form structures resembling different stages of HF morphogenesis, HF mesenchyme regulates and intensifies this process. DP-conditioned medium stimulates morphogenesis in keratinocyte culture demonstrating high rate of tube formation in the collagen gel [81]. However, production of fully functional HFs from postnatal cells is still challenging.

Scientists tried to improve effectiveness of HF morphogenesis using more potent cells including keratinocytes from HFs or embryonic cells. As it can be predicted, embryonic tissues demonstrate higher potential to develop organs after inoculation into culture. Significant portion of studies were performed using embryonic tissues in order to avoid roadblocks of postnatal conditions. Mouse embryonic skin explants may successfully develop HFs in culture [82]. Dissociated cells from embryonic tissues aggregate and form the organ germs which can develop into mature primordium and then into a functioning organ. Such results were demonstrated for tooth and hair germs. Buds from dissociated skin of murine embryos developed into mature HFs in culture or after transplantation to immunocompromised animals [83-85]. However, it is quite difficult to reproduce this type of experiments using postnatal HF cells. Long-term cultivation of HFs from postnatal skin is usually completed with gradual degradation of the structure and degeneration of HF. Even in optimized conditions, HFs begin to degenerate after 20 days in culture, on average, while apoptotic cells appear approximately on day 5 [86]. HFs maintained *in vitro* are unable to keep cycling [87, 88]. In the study on rat HFs cultured on gelfoam supports, Philpott and Kealey were able to demonstrate signs of cycling but all follicles appeared to remain blocked in pro-anagen [89]. Non-follicular keratinocytes failed to reconstruct HFs in combination with DP cells but the latter improved significantly the quality of engineered skin grafts applied onto acute skin defects in nude mice [90]. Human DP cells used in skin equivalent together with epidermal cells enriched with HF keratinocytes could generate HF bud 14 days after transplantation into nude mice but further development was impeded [91]. Interestingly, the authors also noticed a quality improvement in composite skin substitutes containing DP cells as compared to dermal fibroblasts, these substitutes more accurately mimicked a well-ordered epithelium. More impressive results in terms of folliculogenesis were reported in xenogenic equivalents combining human foreskin keratinocytes and murine dermal cells [92, 93]. Six weeks after grafting, the authors recorded bulbous pegs and HFs, which however lacked sebaceous glands and were not able to erupt through the epidermal surface. These experiments declare the development of skin

substitutes with a high degree of homology to native skin as a long-term objective. At the same time, such an approach may be a useful tool to elaborate an effective technique for HF production. To overcome problems with HF eruption through the epithelial sheet and prevent epithelial cyst formation, a nylon thread was used as a guide for the infundibulum direction via insertion into the bioengineered germ [94]. This method showed perfect results in terms of the shaft formation after transplantation onto nude mice. Both mouse and human HF germs were reconstructed in the study. Human bioengineered HF germ was composed of the bulge region-derived epithelial cells and scalp HF-derived intact DPs of an androgenetic alopecia patient. These germs developed pigmented hair shafts within 21 days after intracutaneous transplantation into the back skin of nude mice [94].

Inamatsu with colleagues compared the process of neofolliculogenesis after intracutaneous transplantation of postnatal DP cells and embryonic dermal condensate in mice [95]. They showed that the dermal condensate-triggered development of HFs is similar to that in embryogenesis. Postnatal DP induced formation of new follicles by a different way, it induces the onset of the anagen-like stage without embryonic-like development.

Nevertheless, a number of studies have demonstrated successful reconstruction of follicle-like structures from cells cultivated *in vitro*. They are focused on development of these structures into HF after transplantation as it was discussed above. This is achieved by two ways: skin equivalents with cells capable of hair follicle induction or aggregates made of keratinocytes and trichogenic mesenchyme with subsequent transplantation. Zheng and co-authors [96, 97] used DP and keratinocyte suspension to inject into mice. It was shown that keratinocytes aggregated first, DP cells stimulated their proliferation enlarging hair follicle primordium and then the shaft began to grow into the cavity which had been formed in the aggregate. It was found that the way of cell combination affects epithelio-mesenchymal interactions. In mixed culture, aggregates were smaller; keratinocytes proliferated better and escaped apoptosis [98]. In the study by Havlickova with co-authors, human keratinocytes of the outer root sheath and DP were placed into specially constructed pseudodermis comprising collagen matrix and dermal fibroblasts. The authors found that cells preserved viability, expressed specific markers, and supported proliferation. They were also able to produce specific reaction on substances stimulating or inhibiting hair growth [99]. However, the appropriate architecture of hair follicle bud was lost. Thus, authors supposed to use the model for drug testing. They think such model should (1) imitate at least one typical feature of the human HF; (2) manifest the predicted reaction to the known modulators of HF cycle and development; and (3) exhibit the reactions which are reproducible *in vivo* [99]. Scientists from Technical University in Berlin reported the production of microfollicles *in vitro* by mixing DP aggregates with the basement membrane components and the outer root sheath keratinocytes [100]. They found expression of HF markers such as vimentin, cytokeratins, trichohyalin, and chondroitin sulfate. Remarkably, they observed hair-like fibers sprouting from the nascent microfollicles. Different types of free aggregates present another modification of culture conditions. Cells may be placed on partially-adhesive substrates [101]. Being seeded on poly(ethylene-co-vinyl alcohol), DP cells first aggregate in this model and then are

covered with keratinocytes. The authors found keratinocytes expressed keratin 6 and, thus, underwent differentiation.

Another way to closely reproduce HF morphogenesis *in vitro* may involve specialized HF cells derived from the pluripotent cells. For example, the derivation of functional DP-like cells from human embryonic stem cells was recently reported [102]. Derivation of multipotent progenitors of the epithelial lineage [103, 104] gives an opportunity to combine trichogenic cells at their early stages of commitment with hopefully better results.

Using the advantage of induced pluripotency Yang with colleagues [105] obtained follicu-logenic CD200+/ITGA6+ epidermal stem cells from human fibroblast-derived induced pluripotent cells. Patch *in vivo* assay demonstrated the ability of these cells to generate all HF lineages including the hair shaft, and the inner and outer root sheaths. The regenerated HFs possessed a stem cell population and produced hair shafts expressing hair specific keratins. The ability of pluripotent cells to self-organize and spontaneously differentiate into all cell lineages was used by Takagi and colleagues [106] who carefully selected conditions that enabled direct derivation of HFs from induced pluripotent cells through embryoid bodies using the clustering-dependent embryoid body transplantation method.

Currently, there are a number of ongoing clinical trials using cultured cells to treat alopecia [107]. It is noteworthy that interfollicular unspecialized cells are used in many cases, put it simply, dermal fibroblasts and epidermal keratinocytes. Therapeutic mechanisms of such preparations are unclear and positive effect depends on patient's remaining HFs. However, the latter are absent in many cases. Therefore, modern approaches to HF restoration are badly needed for severe cases of hair loss or alopecia. Taking into account great progress in skin and HF biology, biotechnology, and tissue engineering we hope to meet highly effective methods of HF production in the nearest future.

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