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Keratinocyte Stem Cells: Role in Aging

Tuba Musarrat Ansary, Koji Kamiya and Mamitaro Ohtsuki

Abstract

Stem cells located in the skin are responsible for continual regeneration, wound healing, and differentiation of different cell lineages of the skin. The three main locations of skin stem cells are the epidermis, dermis, and hair follicles. The keratinocyte stem cells are located in the epidermal basal layer (the interfollicular stem cells), hair follicle bulge region (the hair follicle stem cells), and sebaceous glands (the sebaceous gland stem cells) and are responsible for the epidermal proliferation, differentiation, and apoptosis. The interfollicular (IF) stem cells are responsible for epidermis regeneration by proliferating basal cells that attach to the underlying basement membrane and with time they exit from the cell cycle, start terminal differentiation, and move upward to form the spinous, the granular, and the stratum corneum layers. The hair follicle (HF) stem cells are responsible for hair regeneration and these stem cells undergo a cycle consists three stages; growth cycles (anagen), degeneration (catagen), and relative resting phase (telogen). The sebaceous gland (SG) stem cells located in between the hair follicle bulge and the gland and are responsible for producing the entire sebaceous gland which secretes oils to moisture our skin. The role of epidermal stem cells is extremely crucial because they produce enormous numbers of keratinocytes over a lifetime to maintain epidermal homeostasis. However, the age-associated changes in the skin; for example; alopecia, reduced hair density, gray or thin hair, reduced wound healing capacity are related to skin stem cells' decline functionality with age.

Keywords: interfollicular stem cells, hair follicle stem cells, melanocyte stem cells, chronological aging, photoaging

1. Introduction

Skin, the largest organ in the human body gives a protective barrier against the harmful events of the environment, for example, radiation, germs, temperature, and toxic substances. Moreover, the skin also protects our body from excessive dehydration and works as a permeability barrier. To support the above-mentioned roles and repair skin injury and wounds, the skin needs to regenerate and proliferate with the help of skin stem cells. Broadly the skin can be divided into three parts: Epidermis, the outermost layer, is mainly composed of keratinocytes and is known as the squamous stratified epithelium. The dermis, the middle layer, is separated by the basement membrane from the epidermis and is mainly composed of the extracellular matrix of tough collagen fibers, blood vessels, and nerves. The hypodermis, the third layer, mainly consists of fibroblasts, adipose tissues, and connective tissues. Adult skin development involves a multi-stage process that

involved cells from diverse embryonic origins. Following gastrulation, the neuro-ectoderm cells stimulate the formation of the nervous system and skin epidermis. The neural and epidermal fate of these cells is dependent on different signaling pathways, for example, Wnt signaling, fibroblast growth factor (FGF), and bone morphogenetic protein (BMP) signaling, and Notch signaling pathway [1]. During development, the ectoderm-derived cells become the epidermal basal layer and are responsible for all epidermal structures, for example, the hair follicles, sebaceous glands, and sweat glands [2]. A complex and multiple embryonic origins contribute to the dermis formation at different regions of the body. In a broad perspective, the mesoderm-derived cells are responsible for the dermis of the ventral and flank regions of the body and neural-crest-derived cells are responsible for the head dermis [2]. The mesoderm-derived cells are also responsible for the development of the adipose tissues in the hypodermis [3].

In everyday life skin has to perform many functions which are essential for our survival, for example, to protect from physical and mechanical injuries, harmful radiations, and after injury, it needs to form new cells to repair. In this regard, the skin stem cells (SCs) in the epidermis play the most essential roles to maintain skin renewal throughout life and repairing wounds after injury. In this review, we attempt to clarify the 1. Types of stem cells located in the epidermis, 2. The location, function, and markers to identify the epidermal SCs, 3. Role of chronological and photoaging on epidermal stem cells.

2. Epidermal stem cell

The epidermis is mainly consisting of five sub-layers with distinct characteristics although they function together to maintain tissue homeostasis and regeneration (**Figure 1**). The innermost or the deepest layer of the epidermis is the Basal layer, which is a single layer of proliferative basal cells that attach to a basement membrane (BM) by hemidesmosomes. These cells can continually divide and after some period lose attachment from the BM, get pushed by new cells and a program of differentiation has triggered. Above the basal layer, the Squamous cell layer contains the mature basal cells which are now known as squamous cells. This is the thickest layer of the epidermis and spiny projections that are attached to the surrounding cells by desmosomes. The keratinocytes are then got bigger and flatter and push towards two thin layers of the epidermis; the Stratum granulosum and the Stratum lucidum. The stratum corneum is the uppermost layer of the epidermis which contains the dead keratinocytes also referred to as anucleate squamous cells. The skin appendages include the sweat glands, sebaceous gland, nails, hair shafts, and hair follicles, and have both epidermal and dermal components which help the skin to complete its function [4]. The epidermal SCs reside in the basal layer are responsible for the maintenance of the epidermal stratified epithelium by self-renewal, wound repair, and differentiation capabilities. The epidermal proliferative unit (EPU) consists of basal cells that are responsible for the maintenance of the cornified layers by self-renewing and producing stem cells and non-stem cells [5]. There are several techniques available to understand and locate epidermal stem cells, for example, lineage tracing and genetic fate mapping. In the case of lineage tracing, an individual cell is labeled and the location, status, and the number of descendants from that cell can be identified by that label [6]. The genetic fate mapping technique involves marking an individual cell or a group of cells in the embryo and the trace the final position of all descendant cells until the completion of the development [7]. The epidermal SCs are also found in skin appendages, for example, the hair follicle bulge and the sebaceous glands, and have the potency to

Figure 1.
 The five main layers of epidermis. The basal cells can divide themselves and move upwards. As they move to the next layer they become flatter and start losing nuclei.

differentiate into different lineages that are present in adult skin [8]. The epidermal SCs niche can be classified into three groups according to their location; (1) The interfollicular (IF) stem cell located in the basal layer, (2) The hair follicle (HF) stem cell located in the bulge, and (3) The sebaceous gland (SG) stem cell located in between the bulge and hair shaft (**Figure 2**) [9, 10].

2.1 The interfollicular (IF) stem cell

The IF stem cells are found along with the basement membrane which is a specialized thin layer of extracellular matrices. The IF stem cells help to maintain the epidermis regeneration by self-renewal as well as produce progenitor cells named transit-amplifying (TA) cells which divide a limited number of times and then undergo terminal differentiation and give rise to flattened and dead keratinocytes in the cornified layer [11]. Apart from the multipotency these IF stem cells also show other characteristics, such as plasticity, which means these cells can lose their original identity and differentiate into other lineages [12]. Depending on the proximity from the wound and the specific stem cell niche origin, the epidermal stem cells participate in wound healing and tissue regeneration. By performing genetic fate mapping analysis, one report demonstrated that during initial wound healing there is an abundance of long-lived IF stem cells recruitment which promote re-epithelialization, and as the wound repairing the HF-derived stem cells increased in the wound area [13].

2.1.1 IF stem cell markers

There are several markers that can be used to identify IF stem cells (**Figure 3**). Integrins are the heterodimeric cell-surface receptors that consist of α and β subunits

Figure 2.
Location of epidermal stem cells. The interfollicular (IF) stem cells located in the basal layer of the epidermis. Hair follicle (HF) stem cells located in the bulge area of the hair shaft. Melanocyte stem cells are found in the bulge and also in the hair matrix. The sebaceous gland (SG) stem cell located in the sebaceous gland.

Figure 3.
Markers of epidermal stem cells.

and are responsible for cell adhesion, proliferation, and migration [14]. Adherence of the IF stem cells with the BM and extracellular matrixes is regulated by the integrins [15]. Several types of integrins are expressed in the epidermis; $\alpha 2\beta 1$ (receptor for Collagen), $\alpha 3\beta 1$ (receptor for laminin 5), $\alpha 6\beta 4$ (receptor for laminin), $\alpha 5\beta 1$ (receptor for fibronectin), [16, 17]. Among all integrins, the $\alpha 6$ or CD49f is the most used marker for epidermal stem cells [18]. The well-recognized marker

for IF stem cells are the high $\alpha 6$ and the low transferrin receptor CD71 ($\alpha 6$ -bright/CD71-dim) [19]. As there is a positive correlation between the IF stem cell proliferation and adherence, the proliferative IF stem cells can be distinguished from the low-adhered TA cells with the higher $\beta 1$ integrins expression [20]. During terminal differentiation, the IF stem cells express involucrin, a differentiation marker, and filaggrin, an intermediate filament (IF)-associated protein [21, 22].

2.2 The hair follicle (HF) stem cell

The HF is one of the mini-organs in our body which go through life-long cyclic regeneration and involution [23–25]. The HF is located in attachment with the sebaceous gland and arrector pili muscle and it has two main segments; an epithelium made of keratinocytes and a dermal papilla (DP) made of mesenchymal cells [26, 27]. The cyclic regeneration of HF is mainly consisting of these phases; an active growth phase (anagen), a regression or involution phase (catagen), and a relative rest phase (telogen) and after the hair is shed a new hair cycle begins [28, 29]. The upper HF does not cycle visibly and is mainly divided into 2 segments; the infundibulum and the isthmus and the lower HF which consistently regenerates within the hair cycle divided into the hair bulb and the suprabulbar region [30, 31]. The infundibulum is the uppermost segment of the follicle which is funnel-shaped and begins from the epidermis surface and extends to the sebaceous gland opening [32]. The isthmus is the lower part of the upper HF and is located between the sebaceous gland and the bulge [27]. The bulb is the cyclic portion and the base of the HF which regenerates in every hair cycle and includes dermal papilla and HF matrix [28]. The suprabulbar region includes three parts; outer root sheath, inner root sheath, and the hair shaft and it lies between the hair bulb and the isthmus [33]. Bulge is the region where the HF stem cells are located and which lies between the sebaceous gland and the arrector pili muscle. These quiescent and long-lived stem cells have the potential to generate all epithelial lineages of the skin, including HF and hair [34–36]. The HF stem cells contribute to wound healing by recruiting multipotent SCs and life-long HF regeneration by providing new cells. They are normally known as quiescent, slow-cycling, and label-retaining cells.

Another type of stem cell that resides in the bulge of the HF is the long-lived neural-crest cell-derived melanocyte stem cell, which performs a crucial role in hair pigmentation maintenance [37]. Generally, melanoblasts, the immature progenitors of melanocytes, proliferate and differentiate into melanocytes in the epidermis and migrate to the hair follicle and divided into two categories; the hair matrix melanocytes responsible for pigmenting the original hair and the bulge melanocyte stem cells which are responsible for the following hair cycle pigmentation [38]. The regeneration of the follicular Melanocyte stem cells is synchronized with the HF cycle. During the anagen phase, the melanogenically active Melanocyte stem cells reside in the hair matrix proliferate and differentiate into Melanocyte progenitors to produce melanin and transfer to the neighboring keratinocytes and serve as a reservoir of the pigmentary unit for eye, hair, and skin [39]. In the catagen phase, the differentiated Melanocyte stem cells die because of the high apoptosis rate [40]. Melanin not only gives the essential pigmentation but also protects our skin from harmful UV radiation as the melanin granules work like a UV absorbent. To identify the lineage of the Melanocyte stem cell, a transgenic mouse model has been developed. The undifferentiated Melanocyte stem cells reside in the bulge express Dopachrome tautomerase (DCT) and tyrosinase-related proteins 1 (TRP-1) and serve as an early marker of Melanocyte stem cell. Nishimura et al. developed a transgenic mouse by using a lacZ reporter manipulated by the DCT promoter and which enables people to find out the DCT positive melanoblasts [37]. However, both

progenitor and mature melanocyte stem cells express DCT, so it cannot be regarded as a specific marker for the Melanocyte stem cell [41]. The CD34 can also be used to identify the Melanocyte stem cells, for example, one paper reported that CD34 negative Melanocyte expressed high DCT, KIT (KIT Proto-Oncogene, Receptor Tyrosine Kinase), Tyr (tyrosinase), Tyrp1, Pmel17 (premelanosome protein), and MITF (Melanocyte Inducing Transcription Factor) [42]. Sox10 (Sry-related high-mobility-group box 10) can also be used as a marker for Melanocyte stem cells as this transcription factor plays an important role during the differentiation of the neural crest cell to Melanocyte stem cell [43, 44].

2.2.1 Location

There are some differences of opinion regarding the location of the stem cells and between the species. Some reports demonstrated that the germinative cells located in the lower area of the bulb are the HF stem cells as they have the differentiation ability [45, 46], however, several reports have challenged this idea and showed that HF stem cells are located in the bulge which is the upper and permanent portion of the HF. Several lines of experiments using pulse-chase experiment, in-vitro analysis, lineage analysis, seminal experiments, and BrdU- labeling experiments have proven the HF stem cells residing in the bulge [35, 46–51]. The in-vitro clonal analysis has shown that 95% of multipotent stem cells reside in the bulge and the rest of 5% are in the bulb, which is known as matrix cells or transit-amplifying (TA) cells [2, 52, 53].

2.2.2 Major functions

The HF stem cells located in the HF bulge area are label-retaining slow-cycling cells that perform several functions; for example, hair regeneration, reepithelization after a wound. HF stem cells play an important role in the generation of all layers of HF and hair regeneration by fueling the hair cycle [46, 48, 49, 54]. In general, when an anagen phase starts, the HF stem cells become activated and an HF will grow and regenerate and push the club hair above. During the anagen phase, the stem cells from the bulge area and the hair germ cells are activated by the mesenchymal cells from the DP, start proliferating in descending order, move to the bulb area, and create an outer root sheath (ORS) [55]. Throughout the anagen, the matrix or transit-amplifying (TA) cells originated from the bulge stem cells, move upward, and start to differentiate into follicle cells [49, 56]. By performing lineage tracing and double pulse-chase experiments one report confirmed that these TA cells then return to the bulge niche and lose the stemness property [55]. The catagen phase started when the matrix TA cells are exhausted and undergo apoptosis [47]. During catagen, apoptosis causes a huge decline in TA cell number, regression of approximately two-thirds of the hair follicles and only long-lived stem cells survive [57, 58]. After catagen, the resting phase or telogen phase will start. The telogen phase includes quiescent HF stem cells and shedding of the old HFs and this phase becomes longer progressively throughout life [57, 58]. In response to the signals from the DP, a new anagen phase started after the telogen phase and a new hair cycle begins [30, 59].

In addition to hair regeneration, the HF stem cells also play an important role in wound healing and re-epithelization. HF stem cells have the potential to differentiate into multiple lineages; for example, keratinocytes, smooth muscle cells, glial cells, neurons, and melanocytes and promote angiogenesis [60–63]. Many reports perform in-vitro and ex-vivo analysis using rodent and human samples showed that the HF stem cell can differentiate into audiogenic, osteogenic lineages as well as

illustrate similar properties as bone-marrow-derived mesenchymal stem cells [64, 65]. Because of this property, the HF stem cells are regarded as one of the powerful stem cell candidates for cell therapy in the case of cutaneous wound healing and tissue regeneration [66]. In clinical studies, using graft transplantation from the scalp in patients with leg ulcers showed better therapeutic potential compared to the non-hairy grafts [67–70]. Performing double-label analysis and lineage tracing in the wound-repair model in animal reports showed that HF stem cells rapidly mobilize to the epidermis after injury and participate in epidermal repair by proliferating TA cells [36, 49, 71]. Using HF patch transplantation assay it has been demonstrated that HF stem cells contribute to generating new follicles in wounded mouse skin areas [72]. A complete reduction of HF stem cells in transgenic mice displayed a delay in wound healing after a full-thickness wound in the dorsal area [73]. Similarly, a delay in re-epithelization after the wound is observed in *Edaraddcr/cr* mice, that have a mutation in HF development [74]. Additionally, it has been shown that administration of HF stem cell in the wound area accelerates the healing process [75, 76].

2.2.3 HF stem cell markers

Several signaling pathways are important for the regulation and initiation of the anagen phase in the quiescent, slow-cycling label-retaining bulge stem cells [77]. Wnt/ β catenin pathway plays an essential role in HF stem cells activation, maintenance, and differentiation [78]. The importance of Wnt/ β catenin signaling in HF development is further proven by the report that showed complete HF follicle loss in a transgenic mouse with ectopic expression of Wnt inhibitor (Dickkopf 1) [79]. The fibroblast growth factor (FGF) signaling plays a crucial role in HF stem cell differentiation, hair cycle clock regulation, and angiogenesis [80, 81]. Sonic hedgehog (Shh) signaling expressed in the HF matrix is crucial for HF regeneration and neogenesis [82, 83]. Bone morphogenetic proteins (BMP) are also essential for HF regeneration, activation, quiescence, and TA cell differentiation and are expressed in the matrix [77, 84].

There are primarily four techniques to study skin stem cells; for example, label retention, clonogenic assays, skin reconstitution, and genetic lineage tracing [85]. Several markers have been identified to locate bulge and non-bulge stem cells in murine and human skin. Among the epithelial stem or progenitor markers, the most widely used marker for murine bulge stem cells are Keratin 15 (K15) and Clusters of differentiation 34 (CD34) [86–88]. In the case of human bulge stem cells, the most used markers are K15, Keratin 19 (K19), and Clusters of differentiation 200 (CD200) [89, 90]. The leucine-rich G protein-coupled receptor 5 (*Lgr5*), a Wnt target gene label the mouse lower bulge stem cells during the telogen phase and lower ORS HF during the anagen phase [91]. Several transcriptional factors are used to mark HF stem cells; such as Lim-homeodomain transcription factor *Lhx2*, *SRY* (Sex-determining region Y)-box 9 (*Sox-9*), transcription factor 3 (*TCF-3*), cytoplasmic 1 (*NFATC1*) (**Figure 3**) [92–94].

2.3 The sebaceous gland (SG) stem cell

Among other appendages in the skin, the sebaceous glands produce sebocytes and sebum to keep the lipid homeostasis and plays important role in barrier functions [95]. Unlike HF's cyclic growth, the SG has a continuous growth similar to the epidermis, and SG is typically found in association with the HF or as a modified version found independently in eyelids [96]. The resident stem cells in SG proliferate in the basal layer of the SG, differentiate into sebocytes and gather sebum, then move upwards and rupture the content inside into the pilosebaceous canal [97].

The specific markers that are used to identify the SG stem cells are K5, K14, K79, Leucine Rich Repeats, and Immunoglobulin Like Domains 1 (LRIG1), leucine-rich repeat-containing G protein-coupled receptor 1 (LGR6), B lymphocyte-induced maturation protein 1 (Blimp1) [98–101].

3. Epidermal stem cells and aging

Skin stem cells, residing in a protective niche, maintain the skin homeostasis by self-renewal and terminal differentiation. Unlike other somatic stem cells, the skin stem cells are quite resistant to aging as the number and self-renewal capacity of the stem cell do not reduce with age [102]. In general, stem cells stay at a quiescent state for a long time in their niche, and upon activation by numerous intrinsic and extrinsic factors these stem cells can exit this quiescent stage and differentiate into multiple lineages. Stem cell exhaustion is a state where the stem cells fail to renew themselves and thereby decrease in number which is mainly caused by aging. Several reports compared IF stem cells between young and old mice showed no difference in the number of stem cells, telomere length, gene expression related to aging, an abundance of K15 positive HF stem cells, and multipotency [103, 104]. On the contrary, by performing colony-forming essays in human keratinocytes, one report demonstrated that the cells from the aged donor have retarded colony-forming ability [105]. As we age there is an increase in senescent cells accumulation and DNA damage resulting in a decline in stem cells' function to produce new progenitor and effector cells [106, 107]. In this notion, Ultraviolet radiation (UVR) plays a crucial role in DNA damage in stem cells that ultimately lead to photoaging [108].

3.1 Photoaging and epidermal stem cell

The major characteristics of aged HF stem cells are imbalance in the phases of the hair cycle, stem cell exhaustion, and loss of hair (alopecia) and the appearance of the hair becoming dry, gray, or thin [109, 110]. A proper balance between the proliferation and quiescence state of the hair cycle is a prerequisite for HF stem cell lifespan and self-renewal. In this regard, the competitive balance between Wnt and BMP pathways is essential for HF homeostasis and cycle activation. During the regression phase, there is a decreased expression of Wnt and increased expression of BMP pathways which cause inhibition in keratinocyte proliferation and differentiation [111]. Specifically, the Wnt10 activated the anagen phase and BMP6 is the inhibitor of the hair cycle [77]. One report showed that persistent expression of Wnt1 causes mice HF to retain in the growth phase, initiate cellular senescence, and finally cause stem cell exhaustion and premature hair loss [112]. Increased Wnt signaling pathway, specially Wnt10 and β -catenin expression is observed in C57BL6/J mice exposed to UVR which causes HF miniaturization and gray hair [113]. UVR exposure can cause p53, a checkpoint protein, overactivation through DNA damage which is also associated with decreased stem cell renewal capacity, stem cell exhaustion, and premature aging [114]. The stem cell niche or microenvironment homeostasis is maintained by the interaction among mesenchymal cells, integrins expressed by the stem cells, and the extracellular matrix. It has been reported that UVR increased the expression of c-Myc, a transcriptional factor, which reduces the β 1 integrin expression and thus impair β 1 integrin-initiated adherence to the niche and migration [115–117]. Reactive oxidative species (ROS) induced by the UVR also cause a decrease in stem cell renewal capacity, senescence, and exhaustion [118, 119]. Another indication of stem cell aging is telomere shortening which resulted in hair loss and impaired stem cell proliferation and ultimately premature aging [120]. One report demonstrated

chronic UV exposure to transgenic mice causes DNA damage and telomere shortening by modulating telomerase activity [121, 122]. A major hallmark of photoaged skin is altered wound repair capacity. Mitogen-activated protein kinase (MAPK) plays an essential role in cutaneous wound healing and an in-vivo study one report showed that chronic UV irradiation cause MAPK downregulation [123, 124].

3.2 Chronological aging and epidermal stem cell

A progressive decline in skin regeneration, repair, and homeostasis, thin hair, loss of hair, wrinkle, thin dermis, and epidermis, etc. are associated with accelerated aging. The major characteristic of the aged hair follicles is the hair density reduction and the resting period of the hair cycle increase. One report compared HF stem cell functions between 2 month and 24-month-old mice and found that the old mice HF showed a longer telogen phase, defective proliferation, and shorter hair growth phase [109]. Loss of HF stem cells is also associated with age-related hair shaft miniaturization [125]. Another typically aged phenotype related to hair is hair thinning, graying, or hair loss. There are several genetic mutation mice models that depicts accelerated aging phenotypes, for example, gray, brittle, and fragile hair and alopecia as a result of genetic instability [126]. It has been reported that DNA damage causes downregulation of Collagen 17 (Col17) expression in HF stem cells and these defected stem cells start to differentiate terminally and pushed themselves upward and eliminate [127]. As it is well known that Col17 is a crucial component in HF homeostasis and Col17 deficit can cause premature aging phenotype in hair, for example, alopecia or atrophy in HF [128]. In comparison to HF stem cells the role of aging on IF stem cells are not yet clarified. Some reports showed increased proliferation in epidermal stem cells and others confirmed the proliferation decreased as organisms aged. There are several proteins (Heat shock cognate 71, Stress protein 70, Myc associated protein, Cyclin D1, Glucose related protein) that expressed similarly in epidermal stem cells of adult and aged human skin and epidermal stem cells collected from the neonatal and aged mice have the same plasticity when injected into the blastocysts [129].

In normal physiological conditions, melanocytes, differentiated from the Melanocyte stem cell in the hair matrix, produce melanin during the anagen phase and transfer it to the neighboring keratinocytes. Following hair cycles, the TA melanocytes produced from the melanocyte stem cells are responsible for producing melanin and pigmenting new hair follicles. Several external or internal factors can cause aging-associated modifications in Melanocyte stem cells which cause gray hair, one of the most evident signs of aging. The genotoxic stress caused by radiation results in differentiation of the Mc stem cells in the niche and thereby diminish their self-renewal ability and which leads to hair pigmentation impairment in the following hair cycle [130]. Aging, itself is associated with Melanocyte stem cell reduction. An age-associated decline in Melanocyte stem cells measured by immunofluorescence with Kit antibody was observed in aged mice [109]. Another paper confirmed that the number of melanoblasts in the niche decreased with aging as well as the incidence of pigmented melanoblasts which means the ectopic differentiation increased with aging [131]. It can be speculated that due to the lack of enough progenitor cells the melanin production may be hampered and cause hair graying.

4. Conclusions

Skin stem cells participate in wound healing and maintain skin integrity and homeostasis by self-renewal and producing progenitor cells. Unlike other stem cells,

Figure 4.
Major effects of chronological and photo aging on different skin stem cells.

epidermal stem cells maintain an appropriate number throughout life and showed quite a resistance against aging. However, as we age the increased amount of DNA damage response and senescence can affect the epidermal stem cell’s functions; for example, self-renewal capacity, increase exhaustion, mobility to the wound area or reduction in the number and that lead to skin aging phenotypes, for example, premature hair loss, gray or thin hair, reduced wound healing capacity (**Figure 4**).

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Conflict of interest

The author declares no conflict of interest.

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