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Corresponding Author: Sekyu Choi

Authors: Sekyu Choi^{1,*}, Hansaem Jang¹, Yemin Jo¹, Jung Hyun Lee¹

Institution: ¹Department of Life Sciences, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea,

²Division of Dermatology, Department of Medicine, University of Washington, Seattle, WA 98109, United States,

³Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA 98109, United States,

⁴School of Medical Science and Engineering and ⁵School of Interdisciplinary Bioscience and Bioengineering, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea,

⁶Institute for Convergence Research and Education in Advanced Technology (I_CREATE), Yonsei University, Incheon 21983, Republic of Korea,

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Title: Aging of hair follicle stem cells and their niches

Author: Hansaem Jang^{1,†}, Yemin Jo^{1,†}, Jung Hyun Lee^{2,3}, Sekyu Choi^{1,4,5,6,*}

Affiliation:

¹Department of Life Sciences, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea.

²Division of Dermatology, Department of Medicine, University of Washington, Seattle, WA 98109, United States.

³Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA 98109, United States.

⁴School of Medical Science and Engineering, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea.

⁵School of Interdisciplinary Bioscience and Bioengineering, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea.

⁶Institute for Convergence Research and Education in Advanced Technology (I_CREATE), Yonsei University, Incheon 21983, Republic of Korea

[†]These authors contributed equally to this work.

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Corresponding Author's Information:

Tel: +82-54-279-2359; E-mail: sekyuchoi@postech.ac.kr

ABSTRACT

Hair follicles in the skin undergo cyclic rounds of regeneration, degeneration, and rest throughout life. Stem cells residing in hair follicles play a pivotal role in maintaining tissue homeostasis and hair growth cycles. Research on hair follicle aging and age-related hair loss has demonstrated that a decline in hair follicle stem cell (HFSC) activity with aging can decrease the regeneration capacity of hair follicles. This review summarizes our understanding of how age-associated HFSC intrinsic and extrinsic mechanisms can induce HFSC aging and hair loss. In addition, we discuss approaches developed to attenuate age-associated changes in HFSCs and their niches, thereby promoting hair regrowth.

INTRODUCTION

Stem cells have self-renewal capacity and ability to generate functionally differentiated cell types. Major roles of adult stem cells are to maintain tissue homeostasis and repair damaged tissues (1). Indeed, various adult tissues contain adult stem cells, such as hematopoietic stem cells (HSCs), mesenchymal stem cells, neural stem cells (NSCs), muscle satellite cells, intestinal stem cells (ISCs), dental pulp stem cells, and skin stem cells (2-8). Different types of stem cells have been found in the skin, including those associated with hair, i.e., hair follicle stem cells (HFSCs) known to regulate hair growth and melanocyte stem cells (MeSCs) associated with hair pigmentation (9, 10). Quiescent adult stem cells can be activated in response to physiological cues (11). For this transition to occur via intrinsic mechanisms of adult stem cells, these stem cells must communicate with their surrounding microenvironment, i.e., the stem cell niche (12), which offers external cues that can maintain and control the activity of stem cells.

The concept of the stem cell niche was first suggested in 1978 by Schofield (13), who hypothesized that the niche was an environment provided by neighboring non-HSCs, in which HSCs would retain their self-renewal ability and adult stem cell identity. This hypothesis is now supported by many studies. The concept of the stem cell niche has been extended (14-18). Including cells directly adjacent to stem cells, the niche consists of stem cells' own differentiated progenies and other cellular components, e.g., blood vessels, lymphatic capillaries, nerves, stromal cells, adipocytes, and tissue-resident immune cells such as regulatory T cells and macrophages (19, 20). In addition, secreted factors, the extracellular matrix (ECM), and various environmental signals such as those related to physical parameters (e.g., stiffness and shear stress), hypoxia, and cellular metabolism are closely associated with the stem cell niche (19-21). Although stem cell niches share some common characteristics,

niches around different adult stem cells (e.g., HSCs, ISC, NSC, and HFSCs) have been defined and their specific functions have been determined (22, 23).

Several studies have shown that age-related changes occur in adult tissues. For example, in aged mice, the small intestine exhibits a decreased regenerative capacity and altered structure (24, 25). The regenerative capacity of muscles is also decreased in aged mice and the fate of their satellite cells is altered (26, 27). Moreover, gray hairs appear in aged mice owing to depletion of MeSCs (28). Thus, adult stem cells are clearly affected by aging, which in turn can affect the maintenance of tissue homeostasis and reduce the restorative capacity of an aged organism.

Adult stem cells residing in hair follicles (HFs), namely HFSCs, are also affected by aging (29, 30). During the aging process, hair becomes thinner, hair production decreases, and graying and hair loss (senescent baldness) occur. Thus, hair aging is an obvious symptom of aging in long-lived mammals (29, 31). Aged adult stem cells of HFs, especially HFSCs or MeSCs, have been associated with this hair aging phenotype (29, 32).

In this review, we focus on HFSCs and their aging. Moreover, we discuss various HFSC intrinsic and extrinsic mechanisms involved in the hair aging process and how they actively communicate. Some researchers are attempting to rejuvenate aged HFSCs to treat aging hair symptoms, which could help advance regeneration therapy. Therefore, we will also summarize studies on hair regeneration therapies.

HFSC AND HF REGENERATION

The HF is a unique organ that undergoes regeneration and regression within a lifetime in periodic cycles. The hair cycle consists of telogen (rest), anagen (growth), and catagen

(regression) (Fig. 1) (33). According to a single cell transcriptome atlas of the skin during the hair growth cycle, several types of cells are found in the skin around HFs, including fibroblasts, keratinocytes, immune cells (macrophages, T cells, dendritic cells, and Langerhans cells), and neural crest-derived cells (melanocytes and Schwann cells) (Fig. 2) (34). In addition, dermal papillae (DPs), bulge cells, hair germ (HG), and sebaceous glands are present in HFs (34). Regeneration of HFs is regulated by HFSCs located in the bulge and HG, a distinct cell population that contacts DPs (9, 35-37). HFSC markers are known to include K15, Lgr5, Sox9, and Lhx2 (38-42). However, CD34 and Nfatc1 are only expressed in bulge HFSCs, whereas P-cadherin and Lef1 are expressed in HG. Thus, they are distinct expression markers that can distinguish functionally separated cells in the two regions (37, 43-45).

HFSCs are activated in early anagen for hair growth. In pulse-chase experiments, label-retaining cells were found in the bulge region and to a lesser extent in HG (35). BrdU-labeled cells indicating cell proliferation appeared earlier in HG than in bulge in the late telogen phase (37). Another proliferation marker, Ki67, is expressed in HG in the late telogen phase (37). Bulge HFSCs can promote new hair growth by proliferating during early anagen. They can preserve the quiescent state except during the early-to-mid anagen phase (46, 47). Indeed, HFSCs are considered to be comprised of two stem cell populations: quiescent stem cells (bulge) and primed stem cells (HG) (46). MeSCs located in the HF bulge region can produce hair pigmentation by providing melanocytes to the hair matrix during the hair growth cycle (48, 49). Similar to HFSCs, MeSCs are activated in early anagen to supply pigmentation to growing HFs (50).

Activation–quiescence transition of HFSCs is controlled by their local environment, i.e., the HFSC niche. Indeed, DP-promoting signals such as those associated with fibroblast growth factors and bone morphogenetic protein (BMP) inhibitors can activate HFSCs and initiate hair

regeneration (37, 51, 52). Immune cells such as macrophages and regulatory T cells contribute to HFSC quiescence and hair growth (53-56). Rather than simply being passive responders, HFSCs can also build their own niche and HFSCs can actively communicate with their niche to achieve tissue homeostasis and/or wound healing, similar to other adult stem cells (20). For instance, K6-positive inner bulge cells, which can maintain HFSC quiescence during telogen through elevated BMP6 and FGF18 signaling, are derived from the HFSC progenies of the previous anagen phase (57).

HFSC activity associated with HF regeneration is coordinated with remodeling of vasculature and the lymphatic capillary network. Thus, each process can affect the other through molecular cross-talk (58-60). Similarly, thickness of dermal adipose tissue is associated with hair growth cycle. Immature or mature adipocytes can affect HFSC activity (61-63). In addition, HFSCs construct the niche structure consisting of sympathetic nerves known to regulate HFSC activation via norepinephrine and the arrector pili muscle known to maintain innervation of sympathetic nerves (64, 65).

As described above, the HFSC niche is highly heterogeneous and complex. Therefore, several classifications have been used to explain the HFSC niche effectively. Cells in the niche have been distinguished as three functional modules (i.e., signaling, sensory, and message-relaying modules), which are assembled into a multifunctional HFSC niche (66). Furthermore, because HFSCs reside in HFs and participate in HF cycling, extrinsic factors of HFSCs extend outside of HFs. Thus, the surrounding environment affecting HFSCs can be divided into the intrafollicular niche (e.g., the K6⁺ inner bulge layer and DP) and the extrafollicular macroenvironment (e.g., the adipose tissue, immune system, or hormone system) (67, 68).

EFFECTS OF AGING ON HF REGENERATION

Changes in HFs occur with aging. In aged mice, telogen is more than doubled, anagen is slightly shortened, hair regeneration is delayed, hair is shorter and more scattered, and hair loss eventually occurs (29, 30, 68, 69). According to changes in hair cycle and hair appearance, HFs of aged mice exhibit extended dormancy (30, 68, 69). The activity of HFSCs and their capacity to form colonies are decreased in aged HFSCs than those in young HFSCs. In addition, aged HFSCs grow slower than young HFSCs *in vitro* (30). However, the transcriptional identity of HFSCs is maintained in aged mice (69). Importantly, changes occur in the activity of HFSCs rather than in the death of HFSCs in aged mice (30). Compared with young mice, aged mice exhibit no reduction in the number of K15⁺ bulge stem cells (70). However, the number of HFSCs is decreased with aging (71). Considering other adult stem cells, the number of HSCs and their progenitor cells do not decrease sharply in aged mice. Conversely, aged mice exhibit an increase in the number of HSCs (72, 73). In contrast, the number of MeSCs in the skin decreases rapidly during aging. Depletion of MeSCs leads to graying hair (28). Although the number of stem cells does not always change during aging, stem cell populations are known to lose their function with aging (74). Loss of stem cell function can cause changes related to aging in tissues, which are derived from stem cells. Thus, the function rather than the number of HFSCs might be affected by aging. As stated in a previous study, two factors can affect the function of stem cells during aging: intrinsic factors and extrinsic factors (75).

INTRINSIC MECHANISMS RESPONSIBLE FOR HF AGING

BMP signaling is related to HFSC quiescence, whereas Wnt signaling is related to HFSC activation (76). Wnt signaling increases at the telogen-anagen transition, whereas BMP signaling increases during telogen when HFSCs are quiescent (77, 78). Wnt signaling and BMP

signaling are known to maintain the activation–quiescence transition in HFSCs via a competitive interaction (79). Aged HFSCs can affect hair regeneration as the signal associated with stem cell activity changes. Wnt signaling can be divided into a canonical pathway related to β -catenin and a non-canonical pathway related to intracellular calcium (80). In aged HFSCs, activity of the non-canonical Wnt pathway, but not that of the canonical pathway, is increased. The expression of Wnt5a is also increased. In addition, polarity of HFSCs is altered by increasing the activity of Cdc42 via Wnt5a (81). Apolarity of aged HFSCs has been associated with Cdc42 activity. It is a condition under which the regenerative ability of HFSCs is decreased (81). Aging and increased Cdc42 activity might be related. Mice deficient in Cdc42GAP (a negative regulator of Cdc42) exhibits genome instability that can lead to premature aging (82). Similar to HFSCs, melanocytes express nuclear β -catenin during the growth of HFs, although it is no longer expressed after the late anagen phase. β -catenin deficiency in melanocytes is known to induce hair graying (48). However, overexpression of Wnt ligands in aged skin can induce differentiation of MeSCs, eventually leading to the production of gray hairs owing to the exhaustion of MeSCs (83). Wnt signaling not only affects HFSCs, but also affects the differentiation of MeSCs responsible for hair pigmentation (83).

Dephosphorylated nuclear factor of activated T cells, cytoplasmic (NFATc) proteins are produced in response to intracellular calcium ions and translocated to the nucleus where they can regulate gene transcription (84). NFATc1 can maintain HFSC quiescence by inhibiting the expression of Cdk4, which is related to G1/S phase progression in telogen (44). In addition, Nfatc1 levels are decreased to a lesser extent in aged HFSCs than in young HFSCs (30). Furthermore, when Nfatc1 is expressed in aged HFs, the number of proliferative cells and colony formation ability are reduced (30). Thus, NFATc1 might play a role in inhibiting the progression of anagen in aged HFSCs.

Foxc1 is known as a transcription factor associated with HFSC quiescence through direct regulation of Nfatc1 and Bmp6 (85). Thus, Foxc1 expression is correlated with BMP signaling as an intrinsic mechanism in HFSCs. In a Foxc1-knockout model, genes related to HFSC quiescence are downregulated, whereas genes related to cell cycle are upregulated (85). Foxc1–conditional knockout mice also show faster progression to the next hair cycle than control mice (86), which might have been due to failure to maintain the duration of telogen. Without Foxc1, HFSCs cannot produce more than one bulge. Since old bulge plays a role in regulating HFSC quiescence, HFSC expenditure in Foxc1-conditional knockout mice eventually leads to thinning hair as mice age (86).

SIRT7 can activate HFSCs by deacetylating NFATc1. The expression of Sirt7 decreases with age in HFSCs. Indeed, additional expression of Sirt7 in aged mice can induce hair regrowth and pigmentation (87). In summary, factors associated with Wnt and BMP signaling are altered by aging, which in turn can affect the function of HFSCs.

EXTRINSIC MECHANISMS RESPONSIBLE FOR HF AGING

As activation of HFSCs is closely associated with their niche, extrinsic mechanisms also play important roles in HFSC aging. Several studies have demonstrated functional recovery of aged HFSCs relative to young HFSCs after their transplantation into the skin of a young mouse both *in vivo* and *in vitro* (88-91). Although the extrinsic mechanisms driving HFSC aging have not been clarified yet, several studies have shown the influence of extrinsic factors on HFSC aging.

Physical niche atrophy can promote HFSC aging. Xie et al. (71) have shown that the hair shaft could be a physical niche and that its miniaturization with aging could exert physical pressure on HFSCs, resulting in HFSC depletion. Within this process, mechanosensitive Piezo channels are activated by mechanical compression, which in turn can activate cellular TNF- α signaling

and increase HFSC apoptosis during the catagen-telogen transition (71). Moreover, changes in compositions of the ECM also exert mechanical stress that ages HFSCs. Alternative expression of ECM components in an aged HFSC niche, especially those associated with the basement membrane (BM), can elevate BM stiffness. A stiffened BM can silence HFSC bivalent promoters important for HFSC activation (Fig. 3) (91). Therefore, HFSCs can lose their hair cycle activation ability. Thus, HFSC aging can be promoted via an extrinsic mechanism.

HFSC aging can also occur via various secreted factors that regulate key signaling pathways in the HF cycle. In the early anagen phase of an aged mouse skin, expression levels of canonical Wnt signaling inhibitors such as Dkk1 and Sfrp4 are increased, whereas the expression of follistatin, a BMP signaling inhibitor that promotes hair wave propagation, is decreased in the interorgan macroenvironment, especially in intradermal adipose tissues (89). Wnt signaling is known to be important for the regulation of HFSCs and promotion of the HF cycle, whereas BMP signaling has opposite effects (23, 92). Nevertheless, studies have suggested that expression changes in extrafollicular modulators can act on HFSC aging.

Several studies have shown that changes in inflammatory cytokine levels in the extrafollicular macroenvironment can affect HFSC aging. Doles et al. (93) have revealed that expression levels of various inflammatory cytokines are increased in an age-dependent manner in the epidermal layer of aged mouse skin. In addition, they found that an age-associated imbalance in epidermal JAK-STAT signaling could inhibit HFSC function (93). In aged mice, levels of inflammatory cytokines such as CXCL1 are also increased substantially in dermal white adipose tissues at telogen (94). Moreover, after treatment with veratric acid, which mitigates inflammation, HF regrowth is promoted in aged mice, suggesting that overactivated inflammation signaling could inhibit HFSC function with aging (94).

REJUVENATION OF AGE-ASSOCIATED HAIR LOSS

Aging of HFSCs can lead to hair senescence, which ultimately leads to age-related hair loss (i.e., senile alopecia), one of the most obtrusive symptoms of aging. Several treatments including synthetic drugs such as minoxidil and finasteride have been approved by the FDA. Transplantation therapy can be employed for recovery from general alopecia (95, 96). However, drug treatments have major side effects. In addition, young or rejuvenated stem cell transplantation could not fully regenerate the hair cycle because HFSCs actively interact with their external environment (96-98).

Several approaches have been reported to rejuvenate aged-related hair loss. Age-associated increase of cytokine signaling, especially epidermal JAK–STAT signaling, can impede the function of HFSCs. Thus, pyridine 6, a JAK2 inhibitor, has been applied as a topical treatment to aged mouse skin. After one week of treatment, the number of active hair follicles was increased (93). Although this stimulation ultimately accelerates stem cell exhaustion, pharmacologic inhibitors of JAK–STAT signaling can also induce hair growth. Therefore, with further development, the use of pyridine 6 could help rejuvenate aged HFSCs (93, 97, 99).

Treatment with CASIN, a Cdc42 pharmacological inhibitor, can rejuvenate aged HFSCs because Cdc42 is a downstream molecule of noncanonical Wnt signaling, which hinders HFSC activation during the aging process (81). After aged HFSCs were treated with CASIN, the aging phenotype of HFSCs was reduced and the hair regrowth ability of aged mice was increased by the reactivation of Wnt canonical signaling, which facilitated HFSC activation (81).

Platelet-rich plasma therapy and mitochondrial transplantation are possible strategies for hair loss treatment as they both can activate HFSCs (100, 101). Indeed, they are effective treatments for hair aging. In particular, pep-1-mediated mitochondrial transplantation can induce hair regrowth in aged mice, help maintain hair length for longer, and yield an increased number of

anagen follicles (102).

Photobiomodulation therapy (PBMT), which is an FDA-approved alopecia therapy, can decrease age-associated HF atrophy via intrinsic and extrinsic cues that regulate HFSCs (95). PBMT can stimulate cellular reactive oxygen species–activated intrinsic signaling transduction that promotes aged HFSC proliferation and increase the HF-inducing ability of skin keratinocyte precursors and Wnt ligand secretion in the HFSC niche, thereby enhancing aged HFSC activation (95).

CONCLUSION

As discussed in this review, intrinsic and extrinsic mechanisms are known to affect HFSC aging. However, studies on specific treatments for age-related hair loss are still lacking. Although the change in the number of HFSCs with aging remains controversial, e.g., in androgenic alopecia, HFSCs can be preserved in aged HFs with their own lineage identity (69). Therefore, we expect that rejuvenation of aged HFSCs based on mechanisms that cause HFSC aging will be effective in patients who suffer from age-related hair disorders. Future studies on age-associated mechanisms related to HFSCs will help us develop new therapeutics for maintaining proper HF function during aging.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FIGURE LEGENDS

Fig. 1. Scheme of the hair follicle structures during the hair cycle. The hair follicle goes through cycles of telogen (resting), anagen (growth), catagen (regression). HFSCs (light green) are found in the bulge and hair germ in telogen hair follicle. The sebaceous gland is located above the bulge and the dermal papilla (blue) is below the hair germ. In anagen hair follicle, the matrix is produced by the proliferation of the hair germ.

Fig. 2. HFSC and components of the HFSC niche.

HFSCs (light green) are quiescent during the telogen phase and are found in the outer layer of the bulge and hair germ. K6+ inner bulge cells maintain the quiescence of HFSC in telogen. HFSC activity related to HF regeneration is coordinated with a number of HFSC niches. Around HFs, the skin contains several HFSC niches, including dermal papilla, dermal fibroblasts, immune cells (T cells, dendritic cells, and macrophages), dermal adipocytes, the arrector pili muscle, blood vessels and lymphatic vessels, which regulate HFSC activity.

Fig. 3. Scheme for the hair follicle aging. The HFSC is kept in a prolonged quiescent state in the HF bulge during aging. The alternate ECM component expression in the aged HFSC niche result in an increase in basement membrane stiffness. Intrinsic and extrinsic mechanisms that influence HFSC aging cause the HF miniaturization as well as hair thinning and loss.

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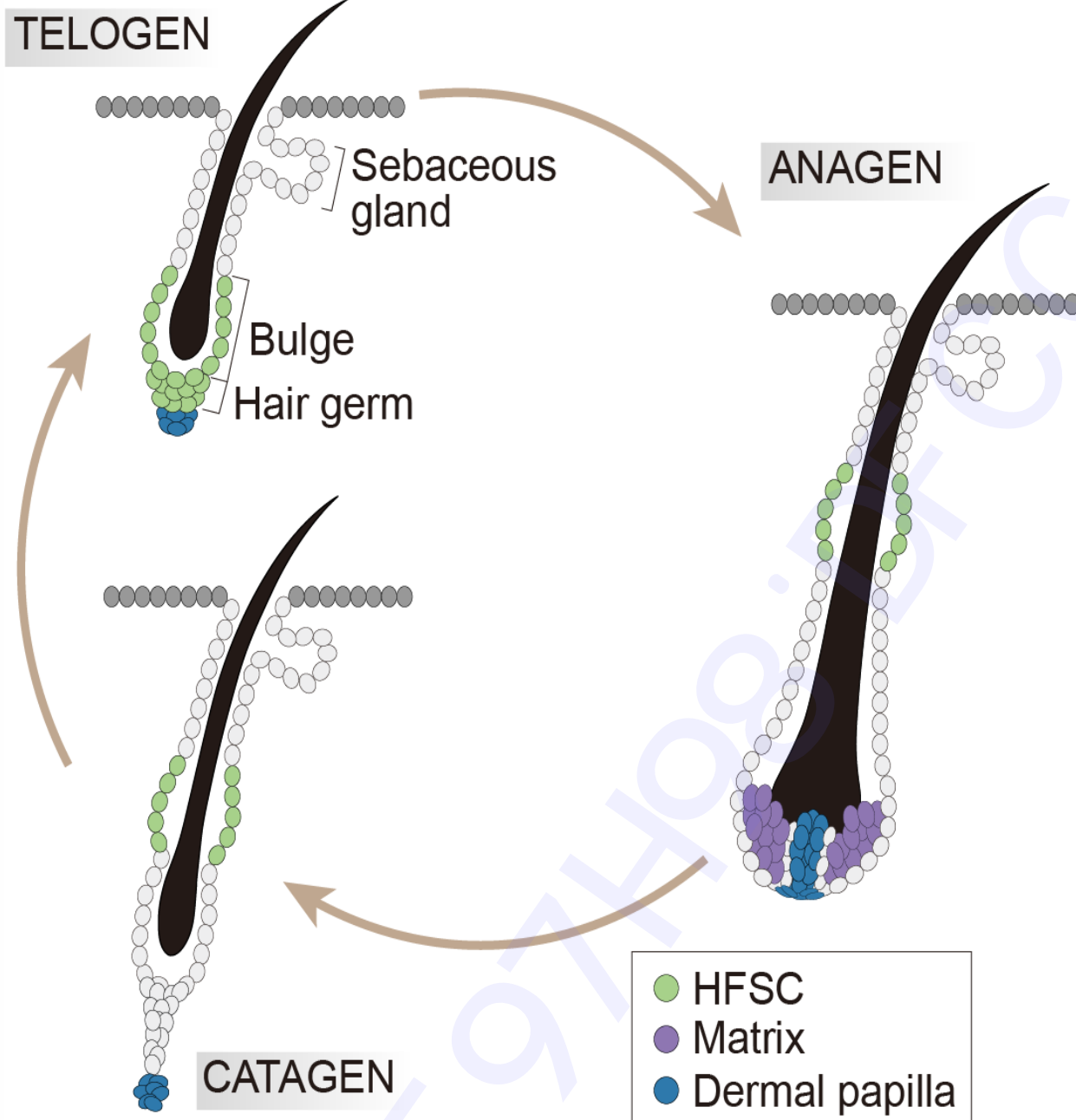


Fig. 1.

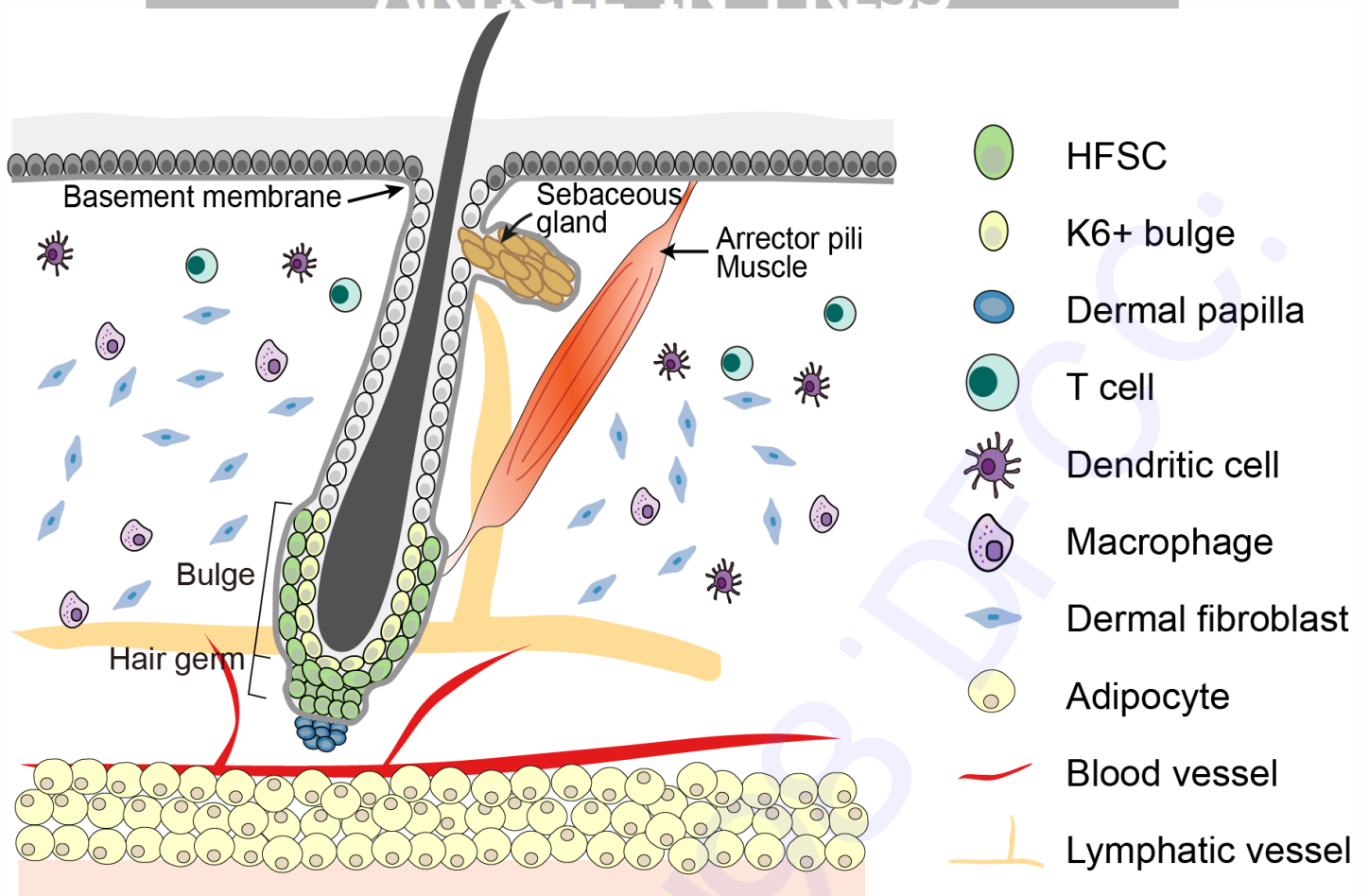


Fig. 2.

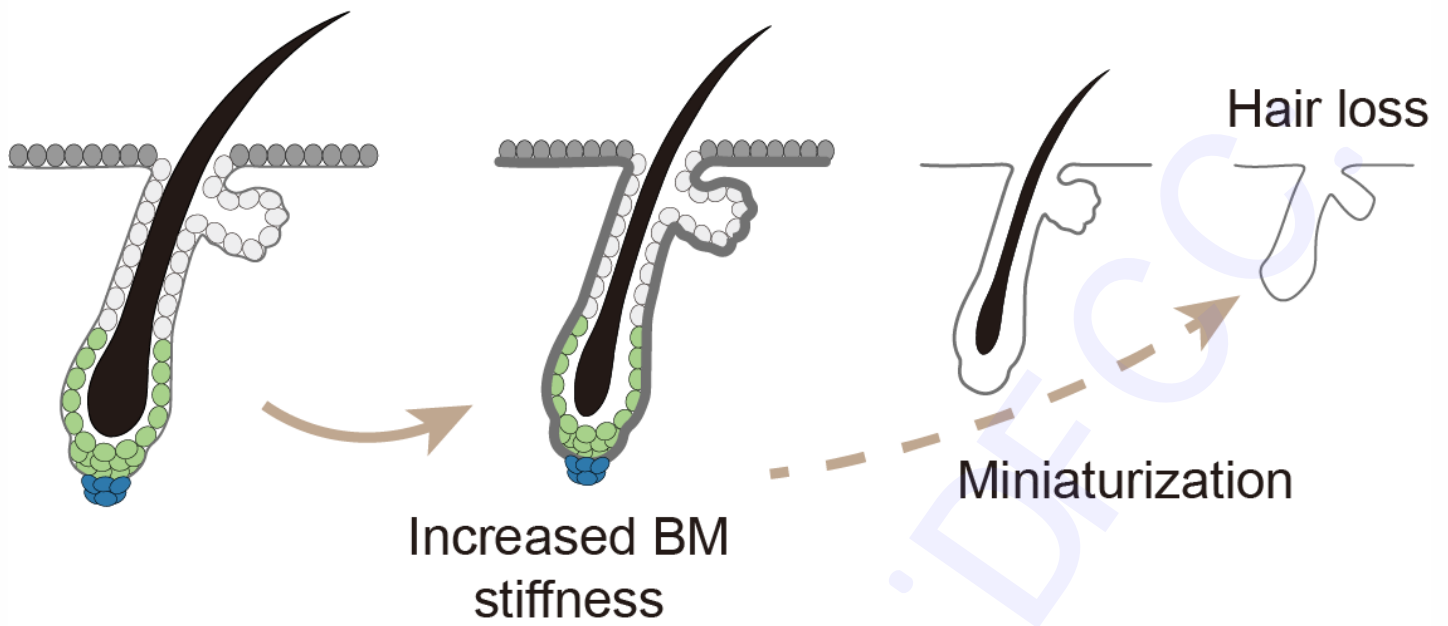


Fig. 3.