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Review article

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Local and systemic mechanisms that control the hair follicle stem cell niche

Bing Zhang[1,2] ✉ & Ting Chen[3,4] ✉

Abstract

Hair follicles are essential appendages of the mammalian skin, as hair performs vital functions of protection, thermoregulation and sensation. Hair follicles harbour exceptional regenerative abilities as they contain multiple somatic stem cell populations such as hair follicle stem cells (HFSCs) and melanocyte stem cells. Surrounding the stem cells and their progeny, diverse groups of cells and extracellular matrix proteins are organized to form a microenvironment (called 'niche') that serves to promote and maintain the optimal functioning of these stem cell populations. Recent studies have shed light on the intricate nature of the HFSC niche and its crucial role in regulating hair follicle regeneration. In this Review, we describe how the niche serves as a signalling hub, communicating, deciphering and integrating both local signals within the skin and systemic inputs from the body and environment to modulate HFSC activity. We delve into the recent advancements in identifying the cellular and molecular nature of the niche, providing a holistic perspective on its essential functions in hair follicle morphogenesis, regeneration and ageing.

Sections

[1]School of Life Sciences, Westlake University, Hangzhou, Zhejiang, China. [2]Westlake Laboratory of Life Sciences and Biomedicine, Hangzhou, Zhejiang, China. [3]National Institute of Biological Sciences, Beijing, China. [4]Tsinghua Institute of Multidisciplinary Biomedical Research, Tsinghua University, Beijing, China. ✉e-mail: zhangbing@westlake.edu.cn; chenting@nibs.ac.cn

Introduction

Hairs and hair follicles are mammalian skin appendages that have diverse functions in body protection, thermal insulation and sensation. In mammals, the hair follicles undergo cyclical rounds of regeneration to produce hairs, driven by the periodic activation of hair follicle stem cells (HFSCs) throughout the organism's lifetime[1–4]. The regeneration of the hair follicle is tightly regulated on multiple levels. Inside the skin, HFSC-neighbouring cells within the niche control the behaviour of HFSCs through secreted factors or direct cell–cell interactions[5,6]. This ensures the precise and effective production of tissues as required. In addition, hormones, nutrients and neuronal signals influence the behaviour of HFSCs in response to physiological changes throughout the body[7–10]. Moreover, HFSCs demonstrate remarkable adaptability by responding to various external stimuli, such as temperature fluctuations[11,12]. This unique ability enables animals to adjust hair growth in response to changes in the environment.

For a long time, the mystery behind how different signals from multiple sources coordinate to control the behaviour of HFSCs remained unsolved. Recent studies have demonstrated the essential roles of niche cells in maintaining stem cell survival and adaptability, as well as in transmitting signals from internal physiological cues and external environmental inputs to regulate stem cells. In this Review, we explore the latest findings regarding the interplay between various niche cells and HFSCs in the skin. We highlight the key roles of the stem cell niche in transmitting, interpreting and integrating complex regulatory cues from multiple sources — local and systemic — as well as in deliberately calibrating stem cell activities during tissue regeneration and ageing conditions.

Niche–stem cell crosstalk

HFSCs are located at the bottom part of the permanent portion of a hair follicle known as the 'bulge'[13–17]. Multiple cell types and extracellular matrix (ECM) components are organized near the HFSCs, forming a rich microenvironment for support and regulation (Fig. 1a). Among them, the keratin 6-positive ($K6^+$) inner bulge cells, dermal papillae and the ECM deposited by the HFSCs and dermal mesenchymal cells are three classical stem cell niches[5,6,18]. Outside the bulge, various cell types intimately associate with the hair follicle and HFSCs, including dermal fibroblasts, adipose tissue, muscles, various innate and adaptive immune cells and sensory and sympathetic nerves, along with blood vessels and lymphatic capillaries[19–24]. Recent studies have uncovered important roles fulfilled by these diverse cell types in modulating the behaviour of HFSCs and their progeny. In this section, we explore these discoveries in depth and discuss the organization of this intricate network composed of cells and signalling molecules.

Epithelial–mesenchymal crosstalk

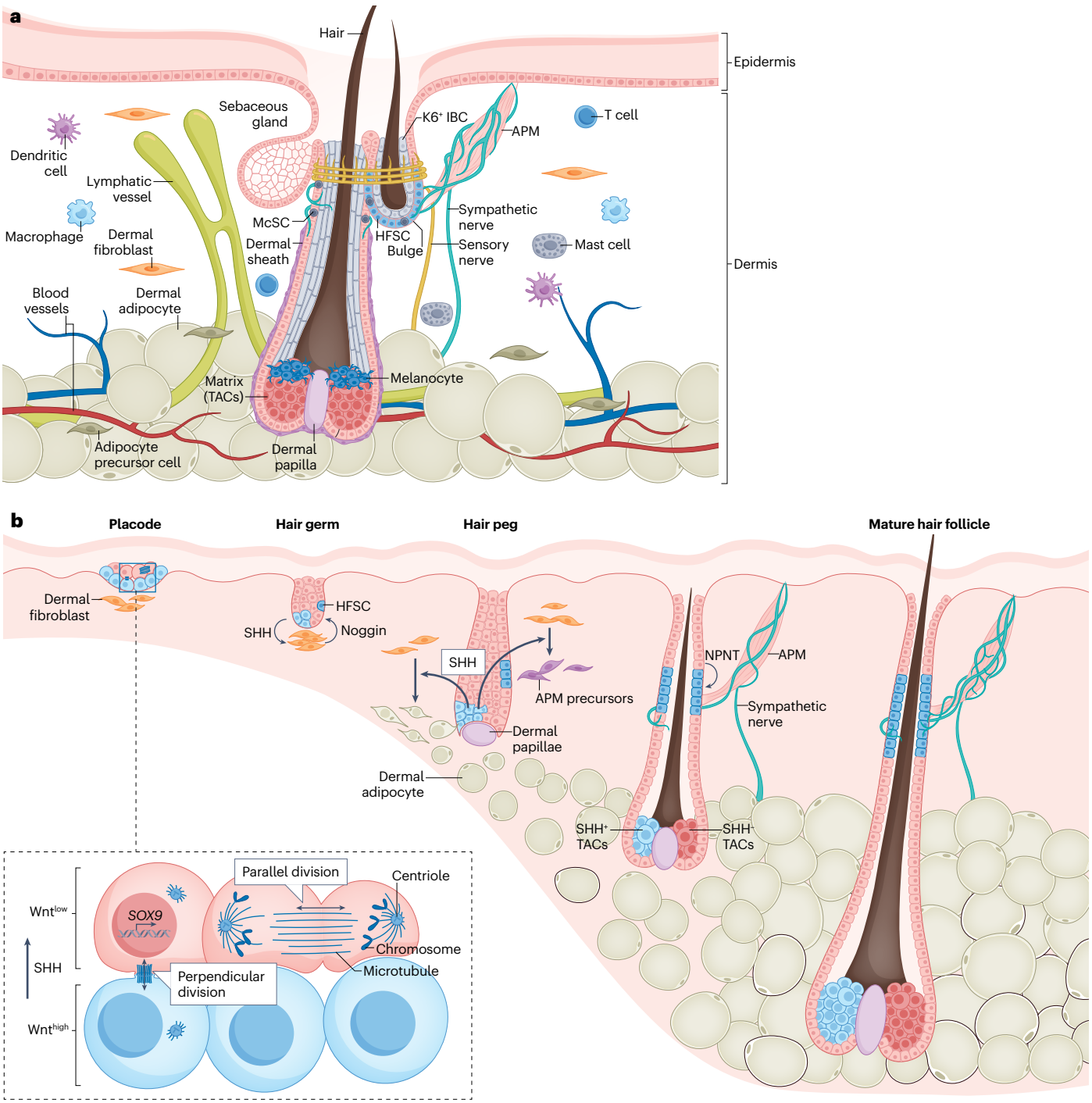
The crosstalk between epithelial and mesenchymal tissues is crucial for the specification of HFSCs during morphogenesis[25–29]. Starting from embryonic day 13 (E13) in mice, mesenchymal cells in the dermis aggregate to form the dermal condensate beneath the hair placode — a nascent ectodermal thickening that later develops into the hair follicle[30–32] (Fig. 1b). The reciprocal signalling between the placode and the dermal condensate generates gradients of signalling activities, especially of Wnt–β-catenin signalling, in different regions of the developing hair follicle[33]. Lineage-tracing experiments using multiple inducible Cre lines revealed that HFSC progenitors first appear in the upper part of the developing hair follicle where Wnt–β-catenin signalling is lower because they are further away from the signalling centre[31] (Supplementary Table 1). Lower levels of Wnt–β-catenin signalling facilitate the expression of the transcription factor SOX9, which is a prerequisite for the formation of HFSCs. Further investigation indicated that Sonic hedgehog (SHH) secreted from Wnt^{high} cells within the placode drives the symmetrical division of Wnt^{low} cells, expanding the pool of Wnt^{low} cells, which later become HFSCs[34]. Recently, live imaging using a long-term ex vivo culture system has shown that HFSCs are formed from a ring-like zone of the basal layer of the placode, emphasizing the importance of the relative position of progenitor cells in their fate determination[35].

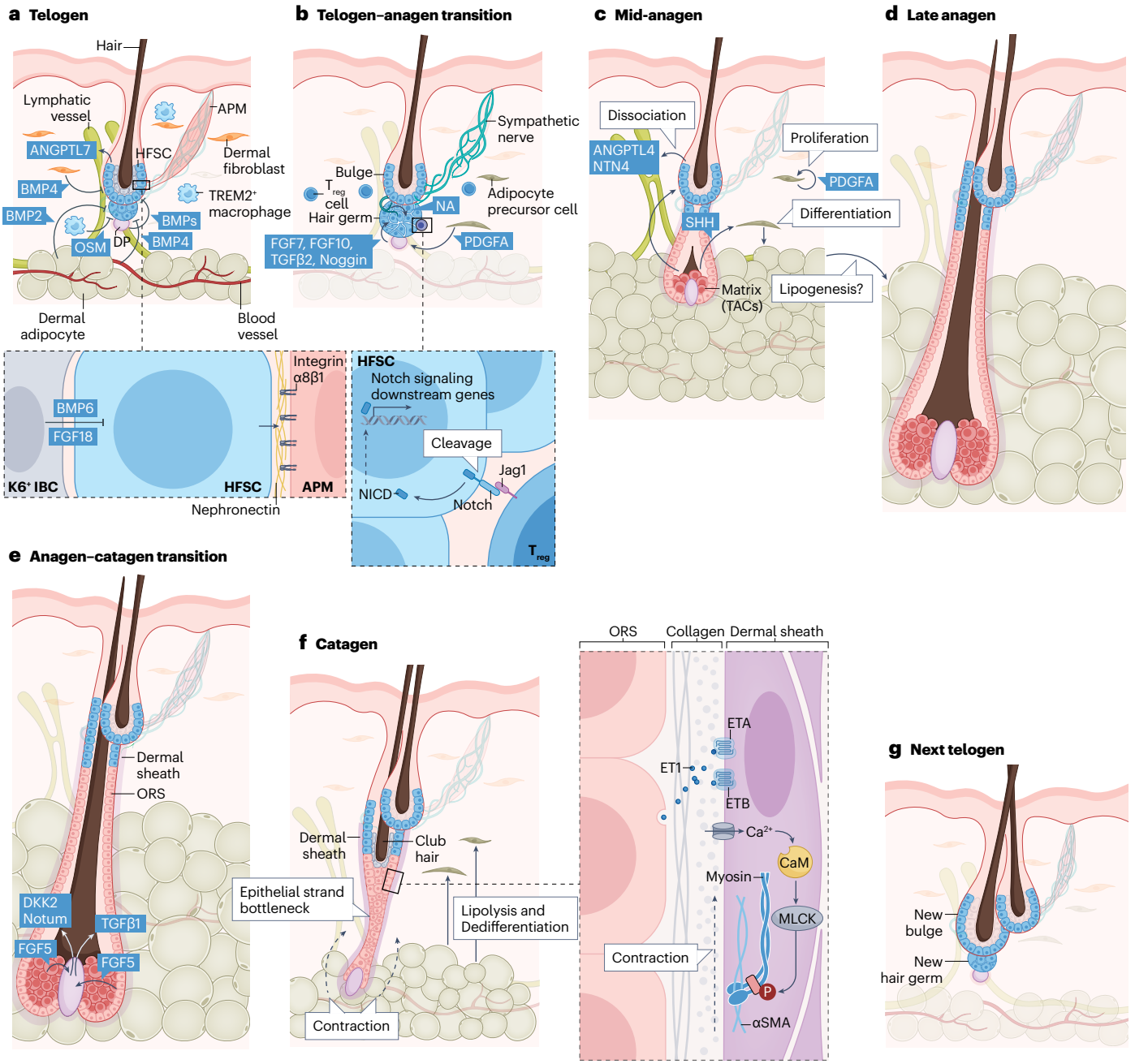
The dermal condensate develops into dermal papillae in the adult skin, which is located directly below the bulge base called 'hair germ' and is in direct contact with HFSCs (Fig. 2). Like many other somatic stem cell populations, HFSCs can be subdivided into a more quiescent and slow-cycling population in the bulge and a primed population that is more readily activated within the hair germ[3,13–17,36]. Dermal papillae were one of the first niche cell types identified as regulators of HFSCs[37,38]. In adult skin, hair follicles undergo a recurring sequence of growth (anagen), regression (catagen) and rest (telogen) phases known as the hair cycle[2,39]. During telogen, inhibitory signals such as bone morphogenetic proteins (BMPs) from dermal papilla cells act together with other inhibitory signals to maintain the quiescent state of HFSCs[5,40–42] (Fig. 2a). Upon transition to anagen, fibroblast growth factors (FGFs) and BMP inhibitors such as Noggin and transforming growth factor-β2 (TGFβ2) accumulate in the dermal papillae, and

Fig. 1 | Establishment of the niche surrounding hair follicle stem cells. a, Hair follicle stem cells (HFSCs) and their niche. Skin is a complex organ that consists of distinct layers — the epidermis, formed by interconnected epithelial cells, and the dermis, composed of connective tissue — and accommodates structures such as hair follicles, blood vessels and other components. Within the skin, HFSCs, together with melanocyte stem cells (McSCs), are embedded into the bulge and hair germ region of hair follicles. Surrounding HFSCs, diverse cell types converge and constitute a local niche to regulate stem cell behaviour and control hair growth. Inside the bulge, a layer of keratin 6-positive ($K6^+$) inner bulge cells (IBCs) resides next to HFSCs and maintains their quiescence. Mesenchymal dermal papilla cells are associated with hair follicles and act as a signalling centre to instruct the behaviour of HFSCs and progeny during the hair cycle. Outside the hair follicle, a vast array of cell types and structures send regulatory signals to HFSCs, including dermal fibroblasts, adipocytes and their precursors, the dermal sheath, various immune cells, sensory and sympathetic innervation, blood vessels and lymphatic capillaries. The bulge is also connected to arrector pili muscle (APM) (see below). These diverse cell types collaborate to establish a complex niche that supports the optimal functioning of HFSCs. Additionally, they serve as a central hub that regulates the regenerative activities of HFSCs in response to signals from the skin, the body and the external environment. **b**, Epithelial–mesenchymal crosstalk specifies HFSCs and their niche. During hair follicle morphogenesis, epithelial cells in the placode undergo asymmetrical divisions to generate Wnt^{low} suprabasal daughters and Wnt^{high} basal daughters. Wnt attenuation is required in the suprabasal cells to allow expression of the transcription factor SOX9, which is crucial for maintaining the fate of stem cells and formation of HFSCs at later stages. Wnt^{high} basal cells secret Sonic hedgehog (SHH), which signals dermal fibroblasts to induce their differentiation into dermal papillae, dermal adipocytes and the APM. Crosstalk between the developing hair follicle and dermal condensate promotes the downward growth of developing hair follicles. Later, HFSCs deposit nephronectin (NPNT) to facilitate the attachment of APM to the bulge and various neurotrophins to instruct sympathetic innervation. TAC, transit-amplifying cell.

WNTs in the hair germ become elevated, providing activating signals that initiate the first steps of hair regeneration[3,43,44] (Fig. 2b). Ablation of dermal papillae using a laser-induced cell-ablation approach impaired the initiation of hair follicle regeneration[45]. In the regression phase, TGFβ signalling and Wnt antagonists DKK2 and Notum initiated from dermal papillae induce the progressive cell death of the basal epithelial cells, maintaining a balanced pool of HFSCs for the next rounds of regeneration[46–48] (Fig. 2e,f).

In addition to dermal papillae, other mesenchymal lineages also contribute to the regulation of the hair cycle. Dermal sheath cells are a group of specialized smooth muscle cells that encircle the hair follicle in anagen[49]. Upon catagen, dermal sheath contraction generates mechanical force that actively pulls the epithelial strand and dermal papillae upwards, allowing them to reconnect with HFSCs and form the telogen hair follicle[24,50] (Fig. 2f). When dermal sheath contraction is disabled, hair follicle regression will pulse[24]. Hair follicle-derived endothelin 1





(ET1) has been shown to control dermal sheath contraction[51]. ET1 is secreted by a group of progenitor cells located between the club hair and the epithelial strand bottleneck. It binds to the endothelin receptor on the dermal sheath cells, which triggers their contraction in collaboration with the calcium-activated myosin light-chain kinase pathway. Another regulatory signal comes from the adipocyte precursor cells (Figs. 2b,c). These specialized fibroblasts are responsible for adipogenesis in the dermis[52,53]. They secrete platelet-derived growth factor subunit A (PDGFA), which acts as an autocrine signal to drive their self-renewal[54]. Additionally, PDGFA secreted by adipocyte precursors functions as a paracrine signal that promotes HFSC activation by acting on the dermal papillae[21]. In contrast, once adipocyte precursors become differentiated into mature adipocytes, they start to secrete BMPs and inhibit HFSC activation[41,55] (Fig. 2a).

Dynamics between stem cells and their progeny

The process of hair follicle regeneration follows a hierarchical model[3,6,56]. As anagen begins, the HFSCs within the hair germ are the first to activate, giving rise to transit-amplifying cells (TACs; Figs. 2b–d). Melanocyte stem cells (McSCs) within the same niche also become activated, proliferate and differentiate into mature melanocytes. TACs are the essential intermediate cell types between HFSCs and their differentiated progeny[57]. They undergo rapid proliferation and differentiation while incorporating pigments secreted by mature melanocytes,

Fig. 2 | Temporal and spatial dynamics of local niche controls hair follicle regeneration. a, In telogen, hair follicle stem cells (HFSCs) are maintained in the quiescent state by multiple signals from keratin 6-positive ($K6^+$) inner bulge cells (IBCs), dermal adipocytes, dermal fibroblasts and blood vessels. These signals often belong to the group of bone morphogenetic proteins (BMPs, for example, BMP2 from adipocytes and BMP4 from fibroblasts and blood vessels) and inhibit HFSC proliferation. Triggering receptor expressed on myeloid cells-positive ($TREM2^+$) macrophages secrete cytokine oncostatin M (OSM) to suppress HFSC activation. Simultaneously, HFSCs produce the angiopoietin-like protein ANGPTL7 to maintain the attachment of lymphatic vessels and deposit nephronectin to maintain the attachment of arrector pili muscle (APM) via integrin α8β1. **b**, At the telogen–anagen transit, signals from the dermal papilla (DP) (including fibroblast growth factor 7 (FGF7) and FGF10, transforming growth factor-β2 (TGFβ2) and Noggin), sympathetic nerves (noradrenaline (NA)), regulatory T (T_{reg}) cells (Notch signalling) and adipocyte precursor cells (platelet-derived growth factor subunit A (PDGFA)) induce the activation of HFSCs in the hair germ. **c**, In mid-anagen, HFSC-derived transit-amplifying cells (TACs) in the matrix produce Sonic hedgehog (SHH), which induces the proliferation of bulge HFSCs and the differentiation of adipocyte precursor cells. Dividing HFSCs no longer express ANGPTL7, but instead secrete ANGPTL4 and netrin 4 (NTN4) to detach lymphatic vessels from down-growing hair follicles. **d**, In late anagen, the hair follicle continues to grow downwards driven by the fast proliferation of TACs. As TACs move away from the bulge, HFSCs return to quiescence. **e**, During the anagen–catagen transition, binding of FGF5 from the matrix and lower outer root sheath (ORS) to the FGF receptors on the DP may contribute to the initiation of catagen. DP cells secrete TGFβ1, dickkopf WNT signalling pathway inhibitor 2 (DKK2) and Notum to induce apoptosis in the matrix hair follicle cells. **f**, In catagen, dermal adipocytes begin to shrink through lipolysis and dedifferentiation. Epithelial cells in the retracting epithelial strand secrete endothelin 1 (ET1), which binds to the endothelin A (ETA) and endothelin B (ETB) receptors to induce calcium influx to and myosin-mediated retraction of the dermal sheath to relocate the dermal papilla to a position beneath the hair germ in the next telogen. **g**, The hair follicle enters the next telogen. A new bulge with the newly generated hair shaft is now located next to the old bulge. αSMA, α-smooth muscle actin; CaM, calmodulin; Jag1, Jagged-1; MLCK, myosin light-chain kinase; NICD, Notch intracellular domain.

leading to colouration of the hair shaft. In addition, TACs also supply the inner root sheath (IRS) and companion layer that form the channel for the growing hair. Subsequently, the HFSCs within the bulge region become activated[56]. They undergo self-renewal and contribute to the formation of the outer root sheath (ORS). During catagen, subsets of ORS cells return to quiescence and form a new bulge consisting of HFSCs and $K6^+$ inner bulge cells encircling the newly made hair shaft at telogen[6] (Figs. 2e–g).

Regulation of HFSC activity relies heavily on signals from their progeny. During telogen phase, the $K6^+$ inner bulge cells secrete BMP6 and FGF18 to maintain the quiescent state of resting HFSCs[3,6,15,58] (Fig. 2a). During anagen phase, TACs proliferate massively to amplify the limited amount of activated HFSCs and drive tissue production. Simultaneously, TACs secrete SHH, a crucial signalling molecule for the activation of the dormant HFSCs within the bulge[56] (Fig. 2c). Ablation of *SHH* from TACs interrupts the regeneration process, and the hair follicles arrest at the mid-anagen stage[56]. As the hair follicle grows deeper into the dermis, TACs move further away from the bulge and the effect of SHH diminishes, causing HFSCs to revert to their quiescent state (Fig. 2d). The continuous communication between HFSCs and their progeny provides a distinct advantage for controlling regeneration — by receiving input emanating from their progeny, a feedback mechanism is triggered to maintain a balance between stem cell maintenance and tissue production.

HFSCs and progeny shaping their niche

During morphogenesis, HFSCs and their progeny actively instruct the organization of various structures associated with hair follicles[11,59]. A notable example is the formation of the arrector pili muscle (APM, a band of smooth muscle that pulls the hair follicle during piloerection) and peripheral innervations, which attach to the hair follicles as they develop (Fig. 1b). TAC-mediated SHH secretion drives the differentiation of APM progenitor cells in the dermis[11]. HFSCs deposit nephronectin onto the basement membrane, which aids in the attachment of the newly formed APM[60] (Fig. 2a). Hair follicles also fulfil a crucial role in instructing the innervation by peripheral nerves by secreting multiple neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4 (ref. 61). In addition, ECM proteins such as epidermal growth factor-like protein 6 (EGFL6), as well as signalling molecules such as SHH[62,63] collectively guide axonal extension and ensure proper docking of the nerve fibres (reviewed in ref. 64).

In adult skin, the regenerating hair follicles require the remodelling of their surrounding environment[65]. For instance, during the anagen phase, the regenerative part of the hair follicle grows more than 60 times longer in just 1 week (Figs. 2a–d). Such rapid tissue growth necessitates corresponding remodelling of the skin. The dermal adipose layer expands to accommodate this new growth, providing sufficient space for the regenerating hair follicle to develop. The coordinated growth of hair follicles and the expansion of the dermal adipose layer are coupled by SHH signalling from TACs[66]: SHH not only acts on HFSCs to drive anagen progression, but also activates the peroxisome proliferator-activated receptor-γ (PPARγ) pathway in the adipocyte precursors in the dermis and drives their differentiation into mature adipocytes[66].

The ability of HFSCs and their offspring to shape their environment confers an evolutionary advantage. This facilitates seamless integration between tissue growth and niche modifications, which is essential for the development of complex tissues with multiple lineages. Moving forwards, it is imperative to study the coordination between various niche cell types in the skin during regeneration and to explore how these mechanisms deteriorate during ageing and in disease settings (Box 1).

Interactions with skin vasculature

The skin is a highly vascularized organ to which arteries supply nutrients, hormones and growth factors, and blood capillaries allow the exchange of oxygen and metabolites while removing carbon dioxide and metabolic waste through veins[67–70]. Skin vasculature actively participates in the regulation of hair follicle regeneration. During the telogen phase, $CD31^+$ endothelial cells within the blood vessels beneath the hair germ secrete BMP4, which helps to maintain the quiescent state of HFSCs[23,71] (Fig. 2a). As the anagen phase begins, these blood vessels gradually disappear, thereby releasing the inhibition on HFSCs[23]. This coordinated process is controlled by Runt-related transcription factor 1 (RUNX1) from the hair follicles and activin A from the skin vasculature[23]. Disruption of these signals can result in defects in blood vessel remodelling and delayed progression from telogen to anagen of hair follicles.

Besides blood vessels, skin also houses a delicate network of lymphatic vessels. Lymphatic vessels aid in maintaining optimal interstitial

Box 1

Scarless wound healing and de novo hair follicle regeneration

It has been established that mesenchymal cells and their signals have a vital role in the regulation of the wound healing process in skin. Wound healing prompts skin fibrosis, loss of hair follicles and scar formation[163]. Scarred skin not only affects the cosmetic appearance, causing physical discomfort, but also hinders normal skin functions such as sensation and protection[164,165]. Research in mice has found that large wounds can induce the formation of new hair follicles in the centre of the wound[166,167]. Further investigation suggests that de novo hair follicle regeneration depends on Wnt signalling. Recently, studies on dermal fibroblasts have proved the existence of subpopulations with distinct functions[168–171]. Of them, the Homeobox protein engrailed 1 (EN1)-expressing fibroblast lineage is the major fibroblast subpopulation that mediates the fibrotic process in wound healing[169,172]. Furthermore, EN1-negative fibroblasts can be converted to EN1-positivity in response to wounding, exacerbating the fibrosis process and leading to scarring[169,172]. Intriguingly, it has been found that blocking the activation of EN1 can decrease fibrosis and promote wound healing without scarring, as well as de novo hair follicle formation[172]. This highlights the crucial role of epithelial–mesenchymal crosstalk in directing the wound healing process and opens up potential therapeutic strategies for managing scarring in patients by manipulating EN1-positive fibroblast populations.

fluid balance within the skin, and they also transport immune cells such as antigen-presenting cells to lymph nodes to strengthen the skin's defences against infections[69,72]. Within the skin, there are two sets of lymphatic vessels: the deep plexus situated in the lower dermis, which consists of larger vessels, and the superficial plexus, which includes lymphatic capillaries located in the upper dermis close to the hair follicles[69]. In mice, the hair follicles on the back are arranged in triads. Lymphatic capillaries connect these follicles throughout the hair cycle from the anterior side[73]. During anagen entry, HFSCs secrete lymphangiogenic factors such as angiopoietin-like protein 4 (ANGPTL4) to instruct the transient dilation of lymphatic vessels and their interaction with hair follicles[74,75] (Figs. 2a–c). This step is crucial for the activation of HFSCs, as genetic disruption of the lymphatic vessel structure hinders HFSC activation and hair follicle growth[74,75]. In addition, defects in skin lymphatic vessels lead to an unsynchronized growth pattern among hair follicles[74,75]. The specific mechanism by which lymphatic vessels influence the hair cycle is not fully understood. It would be intriguing to investigate whether lymphatic vessels regulate regeneration by actively transporting immune cells or facilitating the exchange of crucial nutrients, oxygen, metabolites, hormones and growth factors.

Regulatory signals from immune cells

The skin is a natural habitat for various immune cells owing to its constant exposure to pathogens from the environment[76]. Arising from indentations on the epidermis, hair follicles are the home of commensal bacteria and become the first line of defence against pathogenic invasion[77]. Around the hair follicle, various lymphocytic and myeloid cells work together with the epithelial cells to establish the barrier function of the skin[78]. These skin-resident immune cells go through dynamic changes during hair cycle progression, implying a functional role in regulating hair follicle regeneration[22,39,79]. For example, a subset of TREM2$^+$ macrophages reside near the bulge and secrete the cytokine oncostatin M (OSM) in telogen[80,81]. OSM negatively regulates the JAK–STAT5 pathway in HFSCs and maintains their quiescence[81] (Fig. 2a). Right before entry into anagen, these macrophages become apoptotic through an unknown mechanism and, as a result, release inhibition to encourage HFSC proliferation[80]. Resident lymphocytic cells in the skin can also affect HFSCs. Research has indicated that forkhead box protein P3 positive (FOXP3$^+$) regulatory T (T_{reg}) cells are present near hair follicles and interact with HFSCs through the Jagged-1 (Jag1)–Notch pathway to promote their activation[82,83] (Fig. 2b). If FOXP3$^+$ T_{reg} cells are removed or *JAG1* is deleted from T_{reg} cells, HFSC activation is hindered and normal hair follicle regeneration will be disrupted[82]. In the future, it would be fascinating to explore the regulatory roles of other immune cell types in the vicinity of the hair follicle. Additionally, their heterogeneity across various regions of the skin and their response under diverse physiological and pathological conditions should be examined (Box 2).

Systemic influences on hair follicle regeneration

Tissue regeneration is intricately intertwined with the physiological functioning of the body and environmental cues. The connection between systemic influences and alterations in hair growth has been well documented[8,84–90], yet the underlying mechanism remains elusive. Recent studies have begun to unveil the key roles of the HFSC niche in this process. Various niche cells transmit signals from a diverse array of factors that originate from the body and the environment to the skin, including nutrients, growth factors, hormones, neuronal signals, metabolites and oxygen, connecting hair follicle regeneration with systemic inputs such as mechanical force, nutrient intake, circadian rhythms, and fluctuations in light and temperature.

Mechanical force on HFSCs

The skin is constantly subjected to physical pressures such as compression, shear and stretching. As a result, complex mechanisms have developed to detect and respond to these stimuli. For instance, the epidermis has the capability to expand when subjected to stretching forces, mediated by the induced proliferation of epidermal stem cells (EpiSCs)[91]. However, the effects of mechanical forces on HFSCs and hair follicle regeneration are poorly understood. A recent study revealed that a mechanical pushing force that results from hair shaft miniaturization can be sensed by HFSCs, leading to their apoptotic death[92] (Fig. 3a). During catagen, dermal sheath cells contract to generate an upward pushing force leading to hair shaft retraction[24]. At the end of a catagen phase, the upward movement ceases and the hair shaft docks at the bulge position[24]. During the ageing process, androgenetic alopecia or other hair genetic disorders, hair shafts undergo miniaturization[18,93,94]. This leads to transmission of the pushing force to the HFSCs at the end of catagen and shrinkage in the physical size of the telogen bulge. HFSCs sense the transmitted mechanical compression force through Piezo-type mechanosensitive ion channel component 1 (PIEZO1), leading to calcium influx, which functions synergistically with a catagen-specific tumour necrosis factor (TNF) signal to induce

abnormal cell death in the stem cells[92]. Prolonged hair shaft miniaturization during ageing or hypotrichosis diseases (that is, conditions that affect hair growth) exacerbates stem cell depletion[92]. This study revealed that the inert hair shaft is a functional niche component that governs stem cell pool size by regulating HFSC survival.

HFSC metabolism, nutrients and obesity

As in many stem cell systems, the metabolic status of HFSCs is dynamic during various regeneration phases[95]. Upon activation, HFSCs rely on glycolytic metabolism to divide further, resulting in higher levels of lactate production compared with other cell types in the skin[96]. Blocking glycolysis either genetically or through medication inhibits HFSC activation[96]. As the regeneration programme proceeds, the HFSC progeny undergo a pivotal metabolic shift towards oxidative phosphorylation (OXPHOS), enabling them to generate more energy for the production of new tissue[97]. These findings raise an interesting possibility that the metabolic status of HFSCs may be tightly regulated, and defects in their metabolic programmes may have an effect on their maintenance and behaviour. In fact, depletion of PPARγ, a transcription factor that regulates lipid metabolic pathways from HFSCs, resulted in permanent stem cell loss and scarring alopecia[98].

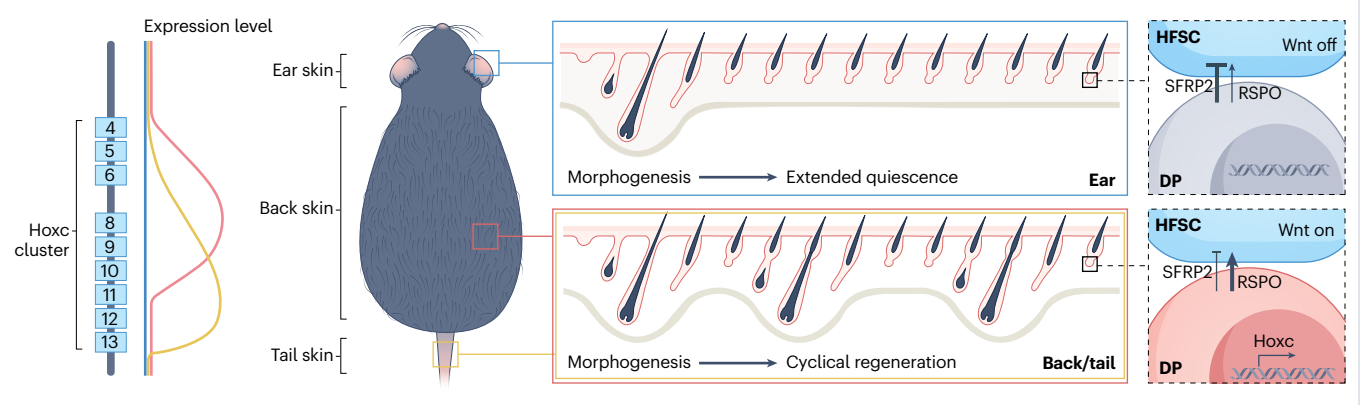
The detailed mechanisms that govern the metabolic programme changes in HFSCs during the regeneration process require further investigation. Interestingly, systemic nutrient supply has emerged as a crucial factor that influences the metabolism, regenerative activity and long-term maintenance of many somatic stem cell populations[95]. HFSCs may directly sense the cellular nutrient availability through the mammalian target of rapamycin complex 1 (mTORC1) signalling pathway[99] (Fig. 3b), as inhibiting mTORC1 during the telogen–anagen transition impedes HFSC activation and hair follicle regeneration. In addition, eating disorders such as anorexia nervosa can cause telogen effluvium, a condition characterized by the conversion of anagen hair follicles into telogen and subsequent hair loss[100–102]. Recently, a study on mice has uncovered that a high-fat diet (HFD) and obesity can lead to the loss of HFSCs[103]. The consumption of a HFD induced nuclear factor κB (NF-κB) signalling and accumulation of abundant lipids in HFSCs, which impaired the normal response to the SHH signalling pathway. Consequently, HFSCs underwent differentiation towards an

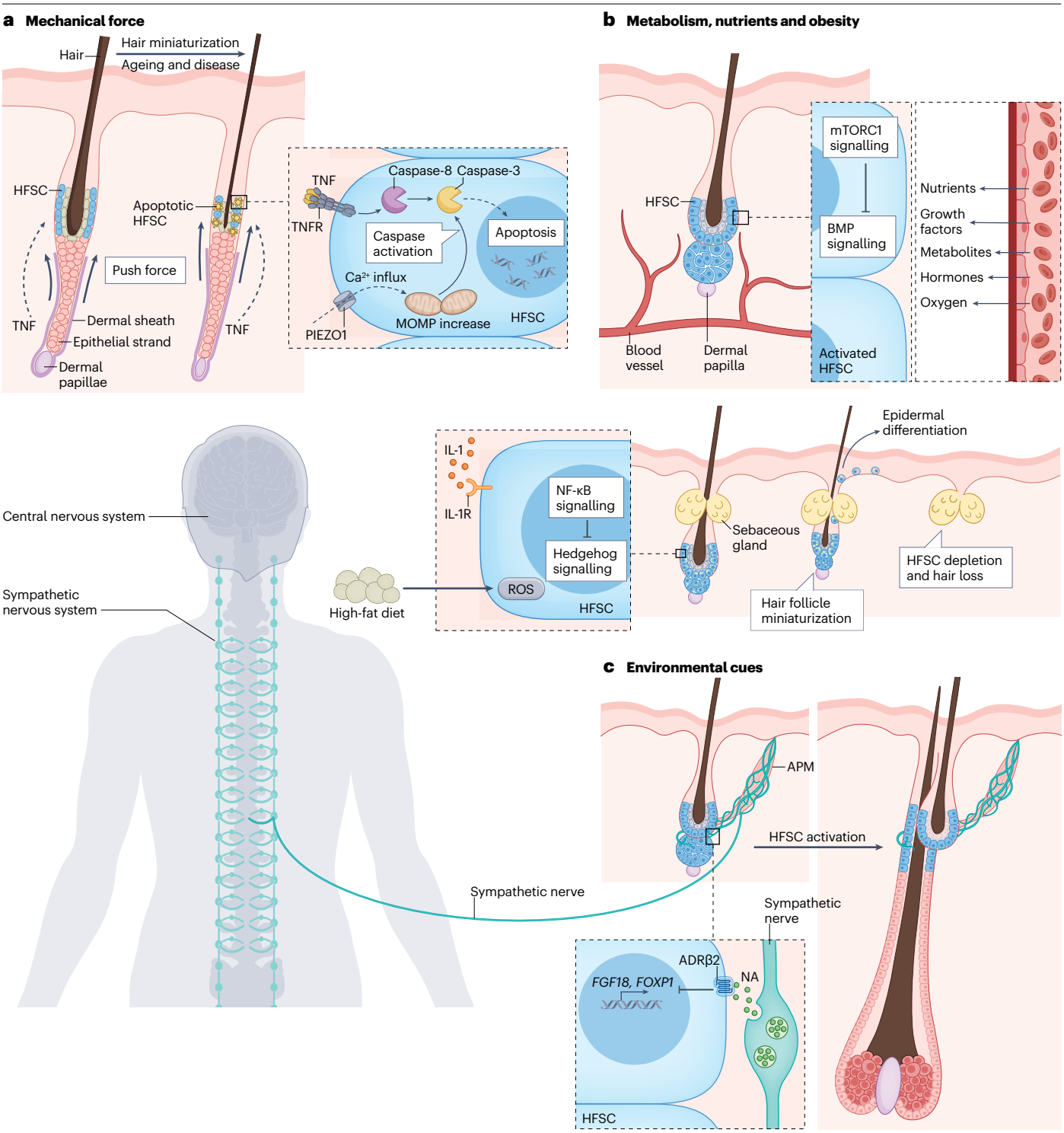
Box 2

Niche heterogeneity along the body axis

The growth of hair in mammals varies substantially in patterns across different sites of the body. For instance, in mouse, hair follicles in the ear skin exhibit a prolonged telogen phase, whereas hair follicles in the dorsal and tail skin show cyclical regeneration[173]. The underlying cause of this heterogeneity has long remained unclear. A recent study indicated that epigenetic differences in the dermal papilla (DP) cells across distinct body regions could account for the variation (see Box figure)[174]. Specifically, the Hoxc cluster genes (encoding Homeobox proteins C) on chromosome 15 carry different epigenetic markers owing to differential activity by the Polycomb complex in DP cells from different body regions. The Hoxc genes promote expression of SFRP2 and R-spondin (RSPO) and act upstream of Wnt–β-catenin signalling, which is necessary to activate hair follicle stem cells (HFSCs)[174]. In the ear skin, DP cells lack all expression of Hoxc genes, whereas in dorsal and tail skin, DP cells express *Hoxc4–Hoxc10* and *Hoxc10–Hoxc13*, respectively[174]. It is noteworthy that an inversion mutation in this area of the chromosome disrupts the inhibitory domains, leading to an increase in Hoxc gene expression in the ear skin, resulting in the elongated hair follicles found in the ears of Koa mutant mice[174].

Besides these differences in DP cells, Hox genes also exhibit differential expression in dermal fibroblasts from different regions of the skin[174,175]. A recent study suggests that the heterogeneity of the dermal niche also underlies distinct autoimmune patterns in the skin[176]. An example of this is vitiligo, an autoimmune disease that typically occurs in bilateral symmetrical areas of the body, but the mechanisms responsible are unclear[177]. Research indicates that interferon-γ (IFNγ) signalling in dermal fibroblasts sustains an autoimmune response against melanocyte lineages in the skin[176]. Intriguingly, there are dermal fibroblasts that are resistant to IFNγ signalling. They are distributed in a bilateral symmetrical pattern across the body, driving the formation of a distinct pattern of vitiligo in patients.





epidermal fate, depleting the pool of HFSCs and resulting in long-term hair loss[103]. Moving forwards, it will be important to characterize the detailed mechanism through which the influences of systemic nutrient supply are transmitted into the skin and how they influence the maintenance and behaviour of HFSCs through the regulation of stem cell metabolism.

Synchronizing regeneration with circadian rhythms

Circadian rhythms affect numerous biological processes including tissue regeneration[104,105]. Emerging evidence suggests that these rhythms affect the behaviour of HFSCs and their progeny[106–108]. Within HFSCs, circadian molecular clock genes such as *CLOCK*, *BMAL1*, *PER1* and *PER2* exhibit notable circadian rhythmicity and changes in expression during

Fig. 3 | Systemic regulation of hair follicle stem cells. Beyond the regulation from the local niche, hair follicle stem cells (HFSCs) are responsive to systemic changes in the whole body and the external environment. **a**, In conditions such as ageing and disease, the hair undergoes miniaturization. The decreased physical support from the hair shaft causes mechanical compression of HFSCs, which activates Piezo-type mechanosensitive ion channel component 1 (PIEZO1). The influx of calcium through PIEZO1 channels collaborates with catagen-specific tumour necrosis factor (TNF) to trigger HFSC apoptosis. **b**, Top: vasculature within the skin transports nutrients, growth factors, hormones, metabolites and oxygen and collect waste to support hair follicle regeneration and tissue homeostasis. Within HFSCs, mTOR complex 1 (mTORC1) signalling is activated during the transition from telogen to anagen. It facilitates stem cell activation through suppression of inhibitory bone morphogenetic protein (BMP) signalling. Bottom: long-term high-fat diet and obesity induce elevated levels of IL-1 in the skin. IL-1 binds to interleukin receptor (IL-1R) and induces nuclear factor κB (NF-κB) signalling in HFSCs. Oxidative stress in HFSCs impairs Hedgehog signalling and promotes epidermal differentiation and depletion of HFSCs in the long term. **c**, In response to cold and blue light stimulation, the activated sympathetic nervous system transmits signals from the central nervous system and promotes hair growth in the periphery. Sympathetic nerves form synapse-like connections with HFSCs and activate them by producing noradrenaline (NA), which binds to β_2-adrenergic receptor (ADRβ2) on the HFSC surface. This signalling pathway inhibits expression of inhibitory factors such as Forkhead box protein P1 (FOXP1) and fibroblast growth factor 18 (FGF18), releasing the inhibition of HFSC activation. MOMP, mitochondrial outer membrane permeabilization; ROS, reactive oxygen species; TNFR, tumour necrosis factor receptor.

the different regenerative phases[106–108]. Ablation or mutation of CLOCK and BMAL1 from HFSCs impedes cell cycle progression and halts hair regeneration. Over time, the absence of circadian clock genes in the skin epithelium leads to early ageing and impaired function[109–111].

Circadian clock genes also participate in regulation of the mitotic activities of the stem cell progeny, TACs. Throughout the day, these genes exhibit substantial oscillations, which synchronize the progression of mitosis and generate a daily rhythm of mitotic activity in TACs[112]. As TACs are the driving force of tissue production in hair follicle regeneration, their mitotic rhythm results in varying hair growth speeds during the day — faster in the morning and slower in the evening. This observation has been noted in both humans and mice[113]. Consequently, when radiation therapy is administered in the morning, it causes more severe hair loss compared with administration in the evening[112]. The mechanism of how the systemic circadian rhythm is transmitted to the stem cell niche remains to be studied.

Responding to environmental cues

Skin acts as the interface between the environment and our body systems. As the body's largest sensory organ, it is densely supplied with nerves from both the sensory and sympathetic nervous systems[114,115]. Diverse types of nerve ending innervate hair follicles, enabling essential functions such as mechanosensation and pili erection[116–118]. Research has provided evidence that signals from peripheral nerves have a significant impact on HFSCs during the regeneration process[64] (Fig. 3c). For instance, a group of sensory nerves that innervate the hair follicles release SHH, promoting the maintenance of a cluster of HFSCs that can transform into EpiSCs in the event of acute wounding[119]. In addition, the sympathetic nerves located in the vicinity of hair follicles form synapse-like connections with HFSCs. Activation of these nerves leads to the release of noradrenaline, which binds to the β_2-adrenergic receptor (ADRβ2) present on HFSCs and triggers their activation[11].

Nerve–stem cell interactions have a vital role in connecting environmental sensory experiences with hair regeneration. Hair follicles, APMs and their innervation by sympathetic nerves make up a tri-lineage unit that can detect environmental changes such as cold exposure[11]. When stimulated, they contract APMs to form goosebumps, allowing more air to be trapped between hairs to keep the body warm. Simultaneously, this activation stimulates HFSCs and hair regeneration, thus fulfilling the long-term needs of the animal to grow more hairs[11]. Similarly, blue light promotes hair regeneration through the retinal ganglion cells–suprachiasmatic nucleus (SCN)–sympathetic nerves pathway[120]. Moving forwards, it will be intriguing to study the other regulatory functions of the diverse skin innervations in hair follicle regeneration and to investigate additional niche factors that convey systemic influences for stem cell regulation in skin.

Niche–stem cell crosstalk in stress and ageing

Tissue regeneration is the fundamental biological process that maintains the healthy function of our bodily systems. However, this complex mechanism can be hindered by negative changes in body physiology, resulting in diseases[121,122]. Stress and ageing are recognized as prominent contributors to conditions associated with hair regeneration[123–125], although the underlying mechanisms remain poorly understood. Recent research has started to unveil these mechanisms, highlighting a crucial role of niche–HFSC crosstalk in mediating these adverse effects.

Stress

Stress can greatly impact our body's overall health, including the skin[123,126–128]. It is a substantial risk factor for various skin conditions such as premature hair greying, hair loss, psoriasis and vitiligo[129–131]. Although the exact way in which stress affects the regeneration of skin tissue is not fully understood, recent research on mice has highlighted the crucial role of both neural and hormonal signals in communicating the effects of stress to influence HFSC behaviour (Fig. 4a). Upon stress, elevated levels of stress hormones known as glucocorticoids (equivalent to cortisol in humans) produced by the adrenal gland can cause defective activation of HFSCs, leading to hair loss[132]. Mechanistically, glucocorticoids bind to the glucocorticoid receptor in the dermal papillae, the crucial niche for HFSCs. This downregulates growth arrest-specific 6 (GAS6), a secreted factor that is essential for stem cell activation[132]. It is noteworthy that the impact of stress hormones can be considerable even in the unstressed state, as the surgical removal of adrenal glands can lead to continuous HFSC activation and hair follicle regeneration[132].

Acute stress also triggers an overactive sympathetic nerve response across the body. Recent research has found that the elevated sympathetic activity in the skin can lead to the development of grey hairs during times of stress[12]. Surrounding the hair follicle, sympathetic nerves innervate bulge and hair germ, in which HFSCs and McSCs reside[133]. Burst-like release of the neurotransmitter noradrenaline into the niche upon acute stress can negatively impact McSCs, leading to their ectopic activation, differentiation and eventual exhaustion[12]. In humans, similar mechanisms may also exist. Application of noradrenaline in an ex vivo human hair follicle model can induce the ectopic differentiation of McSCs[134]. In addition, patients with partial sympathectomy were observed to have fewer grey hairs on the sympathectomized side

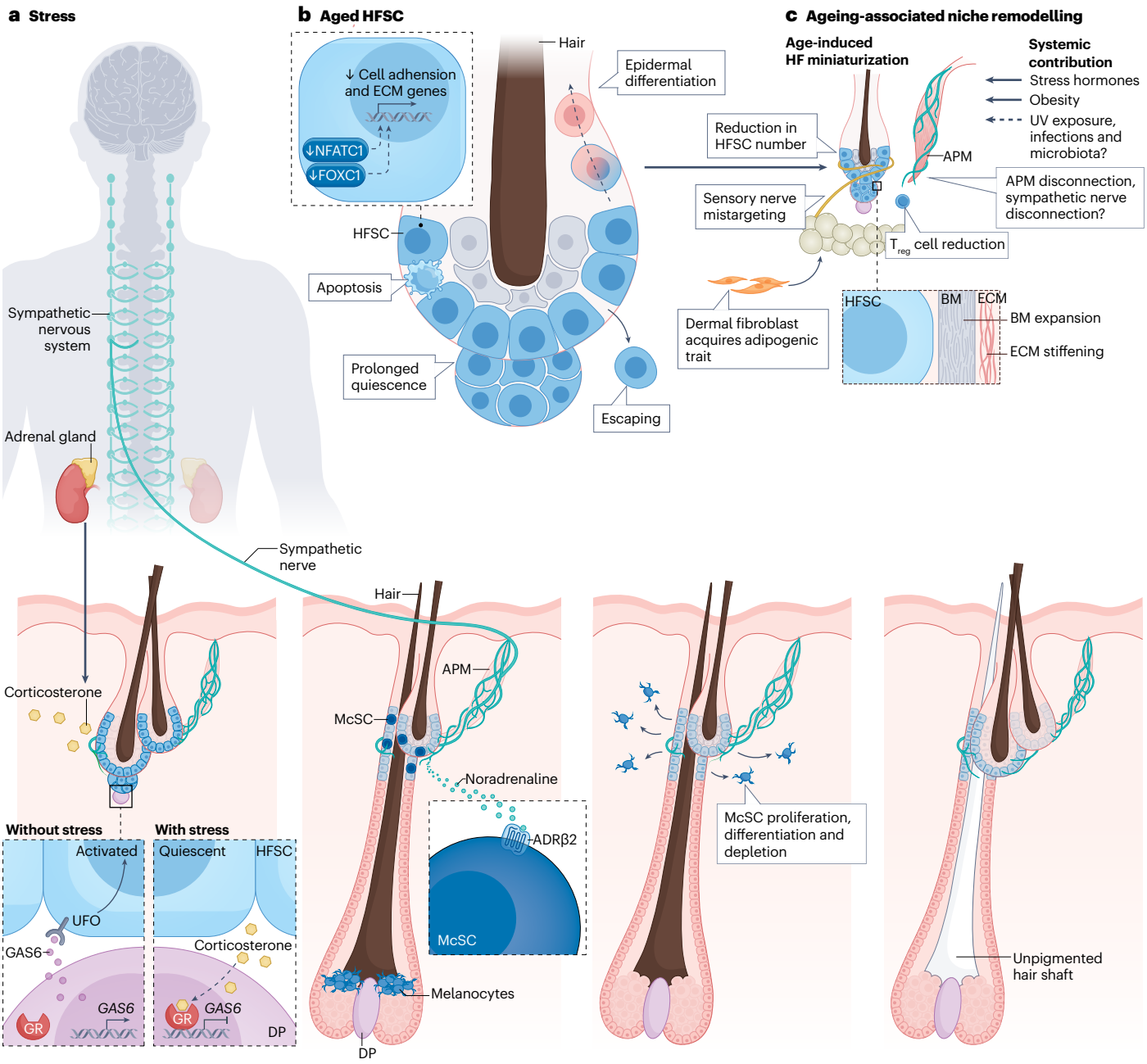


Fig. 4 | Niche–stem cell crosstalk in stress and ageing. a, Under normal condition, growth arrest-specific 6 (GAS6) from the dermal papilla (DP) facilitates the activation of hair follicle stem cells (HFSCs) by binding to the transmembrane receptor tyrosine kinase receptor AXL (also known as UFO). During chronic stress, the adrenal gland-derived stress hormone corticosterone acts on the glucocorticoid receptor (GR) in DP, which in turn blocks the expression of GAS6. This leads to the inhibition of HFSC activation. Under acute stress, the overactivation of sympathetic nerves activates the quiescent melanocyte stem cells (McSCs) through noradrenaline binding to β_2-adrenergic receptor (ADRβ2), driving their proliferation and ectopic differentiation. This leads to the rapid depletion of the McSC pool and hair greying. **b**, Hair follicle ageing is marked by decreased expression of cell adhesion and extracellular matrix (ECM) genes in HFSCs, which are regulated by nuclear factor of activated T cells cytoplasmic 1 (NFATC1) and forkhead box protein C1 (FOXC1). Aged HFSCs maintain prolonged quiescence and are lost through multiple avenues, including apoptosis, epidermal differentiation and migration into the dermis. **c**, Besides these fate switches in HFSCs, the HFSC niche undergoes profound remodelling that could contribute to stem cell dysregulation. These age-related changes include regulatory T (T_{reg}) cell reduction, arrector pili muscle (APM) disconnection, sensory nerve mistargeting, basement membrane (BM) expansion and ECM stiffening. Dermal fibroblasts exhibit a more pro-adipogenic trait with decreased ability to secrete ECM proteins. Additionally, systemic factors such as stress, obesity, ultraviolet light (UV) exposure, infections and microbiota might contribute to the remodelling of HFSCs and their niche, which accelerates hair follicle ageing.

with age[135,136], suggesting that the input from the sympathetic innervations may be related to age-induced hair greying. Moving forwards, it would be interesting to explore how stress may be related to other skin conditions such as alopecia areata, psoriasis and cancer.

Aged HFSCs

The regeneration of hair follicles is significantly impacted by ageing. In ageing skin, hair follicles remain in an extended telogen stage and gradually lose HFSCs, resulting in hair follicle miniaturization, thinning of hair and the development of bald spots[137,138]. Simultaneously, McSC numbers also gradually decline, resulting in hair greying[139]. The root cause of these changes is not well understood. Various hypotheses have been postulated, such as the impact of reactive oxygen species, shortening of telomeres and cellular senescence[140,141]. Bulk and single-cell RNA sequencing analysis in aged HFSCs demonstrated global transcriptome changes, particularly in genes that are associated with cell adhesion and ECM[142–144]. Loss of cell adhesion molecules causes aged HFSCs to migrate from the bulge to the epidermis and dermis, leading to loss of HFSCs and hair follicle miniaturization[18,144] (Fig. 4b). It is worth noting that many of the cell adhesion and ECM genes that are affected in aged HFSCs are regulated by the transcription factors nuclear factor of activated T cells cytoplasmic 1 (NFATC1) and forkhead box protein C1 (FOXC1), highlighting the crucial role of these factors in controlling HFSC ageing[55,145,146]. Genetic ablation of *NFATC1* and *FOXC1* leads to premature ageing of hair follicles[144]. In addition, accumulation of DNA damage in ageing HFSCs could lead to elevated expression of neutrophil elastase, which degrades key cell adhesion molecules such as type XVII collagen (ref. 18).

Apart from reduced attachment to ECM components, aged HFSCs also display impaired ability to self-renew and differentiate. They tend to be more quiescent and harder to activate, leading to delayed anagen entry after plucking[55]. Parabiosis with young mice can only slightly alleviate the regeneration defects of HFSCs, implying that these defects may be stem cell intrinsic[55]. Indeed, aged HFSCs isolated from both human and mouse skin exhibit decreased colony-forming ability in culture[142,147]. Analysis of assays for transposase-accessible chromatin with sequencing (ATAC–seq) on aged HFSCs revealed a noteworthy decrease in chromatin accessibility within the genes related to self-renewal, differentiation and cell–cell adhesion[148]. In addition, this reduction was accompanied by a decline in trimethylated histone H3 lysine 4 (H3K4me3) marks at their promoters[148]. These findings favour a mechanism by which aged HFSCs encounter difficulties in activating these genes, which ultimately hinders their ability to efficiently self-renew and differentiate. Collectively, these discoveries imply that cell-intrinsic alterations within HFSCs make a substantial contribution to their ageing process.

Ageing-associated niche remodelling

In addition to changes in HFSCs, substantial changes also occur within the HFSC niche (Fig. 4c). As the skin ages, there is a decrease in both dermal thickness and ECM density[149,150]. This is accompanied by a reduction in the number of fibroblasts and increased thickness and stiffness of the basement membrane[148,151]. Further analysis revealed that aged fibroblast populations lose their distinct subgroups with unique gene expression patterns observed in young fibroblasts[19,152]. Instead, they acquire a more pro-adipogenic trait and a reduced ability to produce and secrete ECM components. Simultaneously, the dermal papilla experiences a decline in cell numbers and eventual miniaturization, which leads to reduced regulatory signals to guide HFSC behaviour[18,153]. Dermal papillae are maintained by a group of mesenchymal progenitor cells called hair follicle dermal stem cells (hfDSCs)[49]. With skin ageing, hfDSCs exhibit progressive depletion, gradually losing their self-renewal and differentiation abilities, and start to show senescence-like characteristics[154].

Apart from changes in the mesenchymal lineages in dermis, age-related alterations can also be observed in other cell types in the skin[143]. The number of immune cells, especially T_{reg} cells, is noticeably reduced[143]. T_{reg} cells have an essential role in promoting hair cycling and activating HFSCs[82,155,156] (see above). Hence, the decline in T_{reg} cells may contribute to the impediment of regeneration observed in aged hair follicles. In addition, aged skin exhibits heightened expression of genes linked to cytokines, innate immunity and inflammation[142]. Together, this creates an inflammatory environment, which may result in elevated JAK–STAT signalling observed in aged HFSCs. Besides immune cells, APMs also separate from the hair follicles in aged skin, possibly owing to diminished expression of nephronectin, a crucial ECM component that HFSCs excrete to attach APMs to the bulge[143]. Lastly, as the skin ages, the basement membrane becomes increasingly stiff, creating mechanical stress on HFSCs and ultimately hindering the expression of genes related to stem cell functions[148].

Collectively, these studies demonstrate that the inadequate niche in aged skin greatly affects the integrity and function of HFSCs, leading to the regenerative defects observed in aged hair follicles. It is worth noting that the transplantation of aged HFSCs into younger skin can restore their transcriptional features and regenerative abilities[143]. In the future, it will be essential to further explore the cellular and molecular intricacies of niche–stem cell interactions during ageing and how they are influenced by systemic factors such as stress, ultraviolet light exposure, infections and microbiota. This understanding will help to develop strategies to reverse or mitigate the effects of skin ageing in humans.

Concluding remarks

The hair follicle regeneration system presents a fantastic opportunity to examine interactions between stem cells and their niches. The regenerative processes in this system are meticulously controlled both spatially and temporally, and any changes in hair growth can be observed without requiring animal death. As we have summarized here, studies of hair follicle regeneration have offered valuable insight into how stem cell behaviour is controlled in tissue morphogenesis, regeneration and ageing. Many interesting open questions in this field remain to be answered.

The fate specification of HFSCs

The ultimate objective of the complex network of regulatory mechanisms in the hair follicle regeneration cycle is to ensure the proper production and anchoring of hairs within the skin, thereby allowing them to fulfil their biological functions, such as camouflage, thermoregulation, communication and sensing. HFSCs have a crucial role in this process by generating TACs that drive the regeneration cycles[14,56]. They also communicate with other cells, particularly McSCs that occupy the same niche[133,139,157–160]. Intriguingly, HFSCs do not seem to be defined by their inherent abilities, but instead by their physical location — the bulge. After the ablation of HFSCs, the vacant niche can be replenished by cells from other compartments of the hair follicle[31,161]. The precise mechanisms by which the bulge governs the specification of HFSCs are not yet fully understood. However, it is notable that this specific location is where the newly formed club hairs become anchored at the

end of the catagen phase, held together by the K6$^+$ inner bulge cells and HFSCs[6]. We propose that the primary role of HFSCs is to physically anchor the telogen hair shaft within the skin. The positioning and physical interaction between HFSCs and the hair shaft may be crucial factors that can determine the fate of HFSCs. The exact mechanism by which the hair shaft ceases retraction and becomes anchored at the bulge position remains incompletely understood and will be of interest in future studies.

Timing mechanisms of regeneration duration

In comparison with our knowledge of what can trigger hair follicle regeneration, very little is known about what controls the 'stop' signal of hair growth. Dermal papillae and dermal sheath cells are required to induce catagen[24,45], and ablation of the FGF5 receptors FGFR1 and FGFR2 in dermal papillae extends anagen[48]. However, two outstanding questions remain unanswered. First, which cell type sends the first signal to trigger the cascade of cell death and hair shaft retraction during catagen? Epithelial cells in the hair follicle are likely not the origin of the first trigger, as blockade of apoptosis in epithelial cells by overexpression of the apoptosis regulator BCL-2 does not delay or block catagen occurrence[162]. Second, what is the molecular clock that controls the duration of anagen? When and whether a hair follicle ends anagen and enters catagen is a hair follicle-intrinsic ability, as indicated by earlier graft experiments in which hair follicles grafted into different anatomical positions maintained their original hair growth ability and morphology[37,38]. A prerequisite to answer this question is to first understand whether HFSCs or other cell types within the niche determine this intrinsic clock. As the clock mechanism is evolutionarily and developmentally conserved, answers to these two questions will help us to understand many fascinating phenomena related to evolution and ageing.

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