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Epidermal stem cells: skin surveillance and clinical perspective

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Abstract

The skin epidermis is continually influenced by a myriad of internal and external elements. At its basal layer reside epidermal stem cells, which fuels epidermal renovation and hair regeneration with powerful self-renewal ability, as well as keeping diverse signals that direct their activity under surveillance with quick response. The importance of epidermal stem cells in wound healing and immune-related skin conditions has been increasingly recognized, and their potential for clinical applications is attracting attention. In this review, we delve into recent advancements and the various physiological and psychological factors that govern distinct epidermal stem cell populations, including psychological stress, mechanical forces, chronic aging, and circadian rhythm, as well as providing an overview of current methodological approaches. Furthermore, we discuss the pathogenic role of epidermal stem cells in immune-related skin disorders and their potential clinical applications.

Keywords Epidermal stem cells, Aging, Wound healing, Immune-related skin disorders, Regeneration

Background

The skin serves as a vital barrier for mammals, providing protection against injuries, infections, radiation, and water loss. It also plays a key role in regulating temperature and enabling sensory perception [1, 2]. Structurally, the skin comprises two primary layers including the outer epidermis and the inner dermis as illustrated in Fig. 1. The epidermis, is a multilayered stratified epithelium characterized by a high turnover rate, primarily due to the continuous shedding of its superficial cornified cells [3]. This epidermal layer encompasses the interfollicular epidermis along with various functional appendages, including hair follicles (HFs), sebaceous glands, and sweat glands, each playing distinct roles [4]. Notably, the thickness of the interfollicular epidermis and the distribution of these appendages exhibit considerable variation across different regions of the body [5].

As the engine of the epidermis, epidermal stem cells (EpSCs) are located in the basal layer of the skin, imparting the skin with remarkable regenerative potential [6]. Not only can they fuel the epidermal turnover and hair regeneration during homeostasis, but they can also be activated to heal the wounds upon injuries [6]. However, dysfunctional EpSCs serve as malignant roots of skin disorders [7]. In this review, we primarily highlight recent advancements in various EpSC populations and their niche. We subsequently discuss multiple factors that exert influence on EpSCs and elucidate their significance, as well as summarizing classic signaling pathways and related metabolism. We also outline methods for studying EpSCs, ranging from in vitro experiments to in vivo approaches, which may inspire future researchers with practicable tools.

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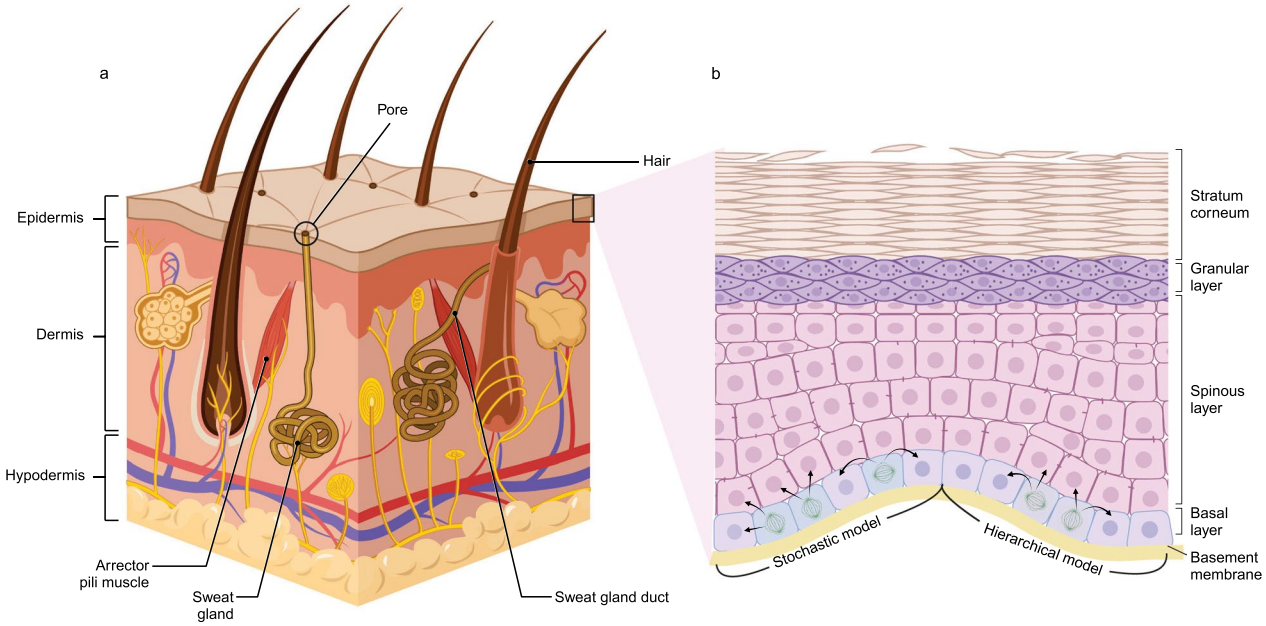

Fig. 1 Architecture of the skin and specific display of the interfollicular epidermis. **a** Skin Composition: the skin epidermis includes the interfollicular epidermis, extending to hair follicle infundibula, and other structures like sebaceous and sweat glands. The dermis, separated from the epidermis by a basement membrane, contains arrector pili muscles, nerves, blood vessels, cells, and extracellular matrix. Below this is the hypodermis, made up of dermal white adipose tissue. **b** Epidermal differentiation models: in the stochastic model, basal cells are uniform, and each division randomly results in: (i) one dividing progenitor and one differentiating cell moving upwards, (ii) two differentiating cells, or (iii) two progenitors. Conversely, the hierarchical model involves limited stem cells sporadically dividing into transit amplifying cells, which rapidly divide into numerous differentiated cells. As these cells move towards the surface, they differentiate, forming layers: basal, spinous, granular, and the continuously shedding stratum corneum

Epidermal stem cells in maintaining skin homeostasis

EpSCs universally exhibit the essential ability for self-renewal and differentiation, which can be categorized based on their specific locations into: interfollicular epidermal stem cells (IFESCs), HF stem cells (HFSCs), and sweat gland stem cells. A range of biomarkers are employed to identify these distinct EpSC clusters, each with unique functional properties (Fig. 2).

Stem cells in the interfollicular epidermis

The interfollicular epidermis serves as a crucial lipid barrier and is continuously renewed by IFESCs on the basal layers [8]. To maintain a stable stem cell pool and produce differentiated cells, IFESCs employ both symmetric and asymmetric divisions. Symmetric division, aligned with the basal membrane axis, yields two identical daughter cells and guarantees rapid expansion of the epidermis [9]. In contrast, asymmetric division, perpendicular to the basal membrane axis, generates daughter cells with different phenotypes, crucial for epithelial stratification [10]. Interestingly, recent studies suggest that perpendicular division of basal progenitors does not always result in distinct fates for daughter cells, with fate determination depending on separation from the basal layer [11].

Exploring how IFESCs facilitate epidermal turnover via symmetric and asymmetric divisions has given rise to various models. For over a decade, the stochastic and hierarchical models have been central to this debate [6]. The stochastic model suggests that the random self-renewal and differentiation of homogeneous IFESCs lead to basal and committed daughter cells [12], whereas the hierarchical model posits that rare IFESC divisions produce transit-amplifying cells (TACs), which subsequently generate differentiated cells in the upper layers [13]. Recent insights, however, indicate a more nuanced process, transitioning gradually from IFESCs to differentiated keratinocytes. Single-cell transcriptome studies have revealed four spatially distinct stem cell populations in the basal layer of both murine [14] and human epidermis [15], leading to a refined 'hierarchical-lineage' model of epidermal homeostasis [16]. This model acknowledges multiple stem and progenitor cell states [17]. Intravital imaging and a live cell reporter for the Keratin10 (Krt10) gene have tracked progressive transcriptional changes in differentiating IFESCs [11, 18], suggesting that the diversity in molecular profiles of proliferating basal cells can

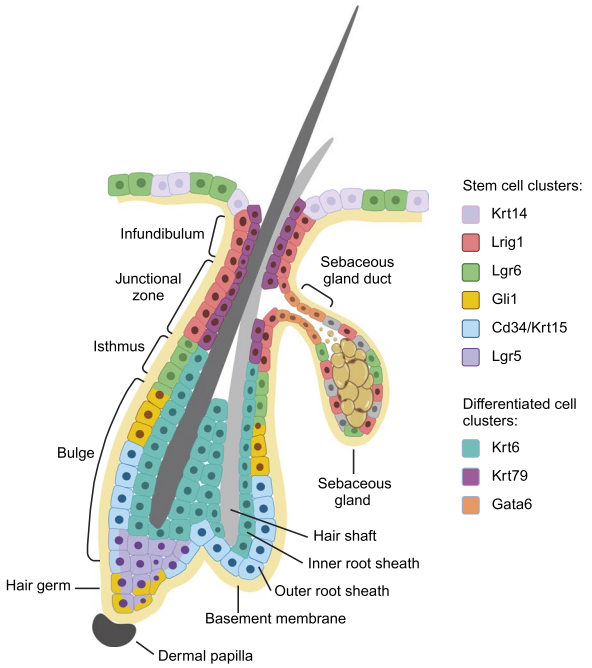

Fig. 2 Architecture of the hair follicle and cluster diversity of epidermal stem cells. This illustration uses a color-coded legend to identify and map distinct stem cell and differentiated cell clusters across various regions of the hair follicle and skin. These regions include the hair follicle infundibulum, junctional zone, isthmus, bulge, hair germ, sebaceous gland and duct, and the interfollicular epidermis

explain observed variations in stem cell commitment. Further research is essential to fully understand the cellular and molecular mechanisms at play.

Stem cells in the hair follicle

The HF operates as a mini-organ, cyclically transitioning between involution and regeneration throughout life, crucial for hair production and body temperature regulation [19]. Structurally, the HF is a cylindrical assembly of epithelial keratinocytes and a fibroblast-rich dermal papilla (Fig. 2), segmented into the infundibulum, isthmus, and lower follicle connecting to the sebaceous gland [20]. The bulge region, located below the isthmus and extending into the lower follicle, is a critical site housing the hair germ and dermal papilla [21]. HFSCs, initially identified as slow-cycling 'label-retaining' cells in the bulge, are now known to inhabit all HF segments [4]. HFSCs from the bulge and isthmus exhibit high clonogenicity, capable of generating various lineages including the interfollicular epidermis, HFs, and sebaceous glands following transplantation or injury [22, 23]. A recent 'telescope model' of HF development has been proposed, illustrating the concentric arrangement of epithelial lineage precursors in the basal layer of the hair placode. These precursors extend towards the dermis to form a cylindrical structure with longitudinally aligned compartments [24].

The hair cycle's completion hinges on the orchestrated actions of HFSCs. It includes prolonged hair growth (anagen), brief degeneration (catagen), and a resting phase (telogen) [8]. In the telogen phase, HFSCs in both the bulge and hair germ are dormant. With the anagen phase's onset, hair germ stem cells rapidly proliferate, forming a matrix of TACs that divide swiftly to construct the hair shaft and inner root sheath. Bulge stem cells later become active, contributing to the outer root sheath. During catagen, matrix and inner root sheath cells undergo apoptosis [2]. Meanwhile, some lower outer root sheath cells differentiate into inner $Krt6^+$ bulge cells, middle cells initiate a new hair germ, and upper cells form a new bulge, setting the stage for the next hair cycle [19]. Notably, recent single-cell RNA sequencing studies on human scalp HFs have uncovered significant differences from mouse models, such as the presence of epithelial-mesenchymal transition features uniquely in human HFSCs [25].

Melanocyte stem cells (MeSCs), originating from the neural crest, notably share the bulge niche with HFSCs, contributing to hair pigmentation [26]. These MeSCs differentiate into melanocytes that migrate to the hair matrix during the onset of each anagen phase and undergo apoptosis with matrix TACs in the catagen phase [25, 26]. Recent studies have revealed that MeSC maintenance involves not only resident stem cells but also those reverting from a transit-amplifying state [27]. Furthermore, senescent melanocytes secreting Osteopontin have been found to stimulate adjacent HFSC activity and hair regeneration, shedding light on the dynamic interplay between EpSCs and melanocytes [28].

Stem cells in the sweat gland

Sweat glands, ubiquitous secretory epidermal appendages, are categorized mainly into eccrine and apocrine types in humans, with eccrine glands constituting about 90% of the total but notably absent in most lab animal models [3, 29]. Eccrine glands feature a coiled secretory section in the dermis, composed of myoepithelial and luminal cells, and a ductal portion extending to the epidermis, lined by two to three layers of epithelial cells [29]. Research on sweat gland stem/progenitor cells remains in its nascent stages. To date, two progenitor populations have been identified in developing sweat ducts: multipotent $Krt14^+$ progenitors forming myoepithelial cells and transient, proliferative $Krt14^{low}/Krt18^+$ suprabasal progenitors generating luminal cells, both displaying multipotency during morphogenesis [30]. In adults, four distinct stem cell populations in sweat glands

exhibit diverse behaviors in contexts like homeostasis, wound repair, and transplantation. Typically, sweat ducts undergo significant homeostatic turnover, akin to the epidermis, while the glandular portion remains relatively quiescent [30].

Diverse cell types interacting with epidermal stem cells in niche

The niche where stem cells reside, was traditionally understood to comprise heterologous cell populations like fibroblasts, immune cells, sensory neurons, arrector pili muscles, and blood vessels [19]. However, recent findings have identified apoptotic EpSCs as a novel niche component, significantly influencing stem cell proliferation and tissue regeneration, primarily through Wnt3 release [31].

Interactions between stem cells and their niches are bidirectional [32]. Not only does the niche influence stem cells and progenitors, but these cells also actively shape their residing niche [33]. Recent discoveries include the dermal sheath's role as smooth muscle, generating a constrictive force to position the dermal papilla near stem cells, vital for hair growth activation [34]. Further studies have revealed that this contraction is initiated by epithelial progenitors in the outer root sheath via endothelin signaling [35]. Additionally, the sympathetic neuron and arrector pili muscles, attached to HFs, form a dual-component niche regulating HF regeneration in adults. This system operates through norepinephrine released by sympathetic nerves, with the arrector pili muscles aiding nerve innervation stability [36]. Notably, HFSC progeny secrete Sonic Hedgehog, directing the formation of this AMP-sympathetic nerve dual-component niche [36]. These evolving researches are progressively elucidating the complexities of epithelial-mesenchymal feedback loops.

Factors influencing epidermal stem cell behavior

EpSCs are regulated by a spectrum of psychological and physiological factors, including stress, mechanical forces, aging, and circadian rhythms. Understanding these influences is crucial for identifying the underlying causes of various skin disorders and developing effective treatments (Fig. 3, Table 1).

Impact of psychological stress on epidermal stem cell functionality

Psychological stress can be broadly defined as an actual or anticipated disruption of homeostasis or an anticipated threat to well-being [37], which can be broadly divided into two types: acute and chronic. The former may activate the autonomic nervous system, mainly the sympathetic nerves, releasing noradrenaline in a burst manner [38], leading to hair greying through ectopic differentiation and depletion of MeSCs, both in mice [39] and ex vivo cultured human hair [40]. Chronic, sustained exposure to stressors, however, function primarily by activation of the hypothalamic-pituitary-adrenocortical axis and the consequently elevated circulating glucocorticoids [41]. Corticosterone in mice acts on the dermal papillae to suppress the expression of Gas6, resulting in prolonged quiescence of HFSCs and extended resting phase of HF [42]. Paradoxically, it has been reported that skin-resident regulatory T cells can respond to increased glucocorticoid signal to facilitate HFSC activation and HF regeneration through glucocorticoid receptor (GR)-transforming growth factor-β3 (TGF-β3) axis [43], which may suggest that various concentrations, sources, and exposure duration of glucocorticoid act on different cell types, so as to affect HFSCs in distinctive ways. Collectively, researches so far have identified HF as the core target of stress hormones in the epidermis, revealing the mechanism of stress-dependent hair loss and greying. Future studies may help to delineate the impact of psychological stress on other stem cell clusters in the epidermis, probably through stress-induced inflammation, which has been elucidated in the intestine [44], and interaction among EpSCs, nerve fibers, and immune cells in their niches.

The role of mechanical forces in regulating epidermal stem cell proliferation and differentiation

The epidermis, as the body's outermost barrier, is subject to a variety of mechanical forces, defined as forces resulting from contact and altering motion or rest states [45]. Common forms include compression and tensile stress, which can fluctuate with physiological and pathological processes like skin renewal and hair loss [46, 47]. Mechanical forces affecting cells originate either directly from the cytoskeleton and cell–cell adhesion in basal layers, or indirectly from the niche, impacting EpSCs [48, 49]. These forces are critical in regulating EpSC morphology and gene expression, influencing the balance between proliferation and differentiation. This regulation occurs through mechanosensory and mechanotransduction proteins within the epidermis [50, 51].

Mechanical feedback often acts as a suppressor of EpSC division [46]. Under mechanical compression, B-plexin, a transmembrane receptor, detects the force, subsequently inhibiting tissue overgrowth by repressing the transcriptional co-activator yes-associated protein 1 (YAP) [52]. THY1, integral to adherens junctions, also contributes to YAP repression [53]. Notably, in procedures like reconstructive surgery, stretching of the epidermis temporarily skews EpSCs towards renewal, mediated by activation of the Hippo and EGFR (epidermal growth factor

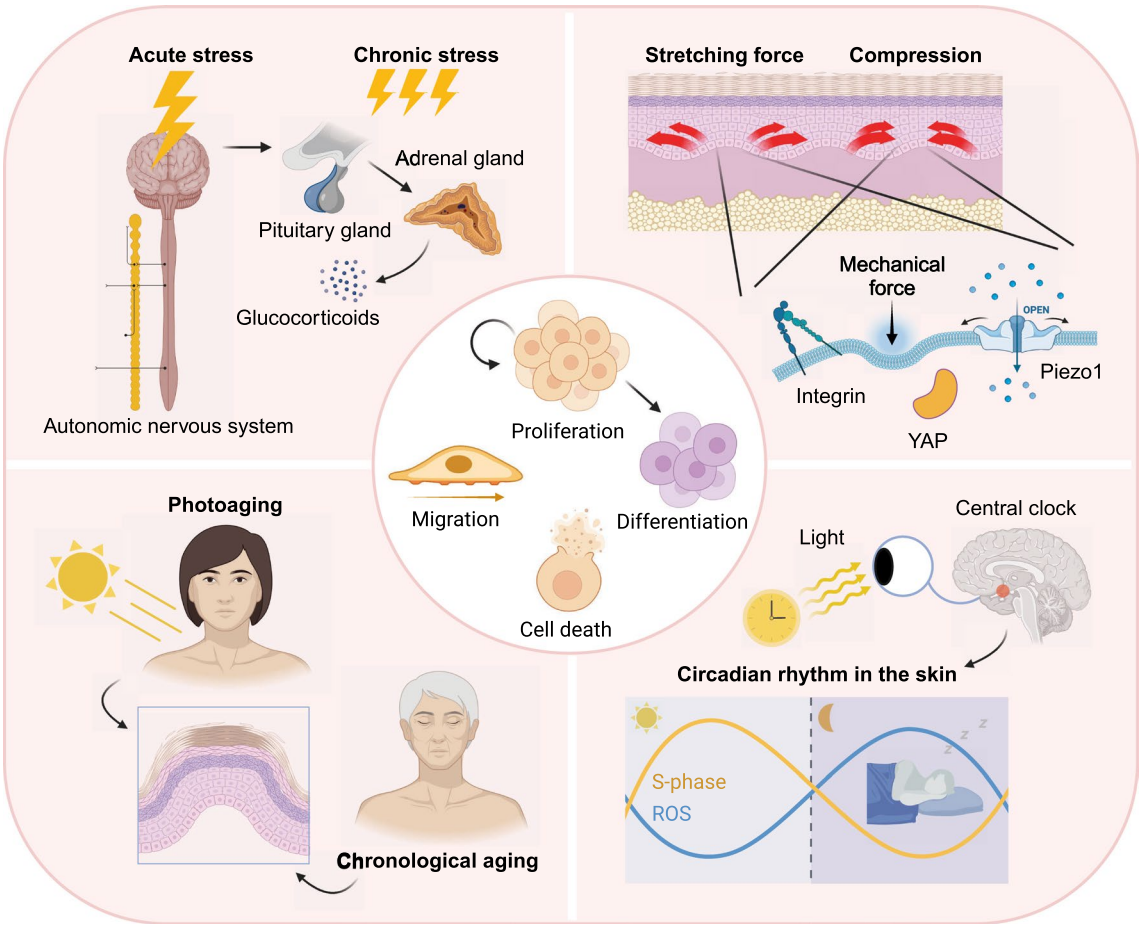

Fig. 3 Factors influencing epidermal stem cell behavior. Psychological stress, mechanical force, chronic aging, and circadian rhythm affect various activities of EpSCs. It includes the balance between cell proliferation and differentiation, the restricted movement and abnormal migration of EpSCs from the niche, as well as the necrosis and programmed cell death of them. Consequently, processes of epithelial renewal and hair regeneration may be altered by these factors, manifesting as abnormalities in the skin like cutaneous disorders, and symptoms of skin aging such as epidermal atrophy

receptor)-Ras-MAPK (Mitogen-activated protein kinase) pathways [54, 55]. Moreover, epidermal differentiation can be impeded by tension transferred to the nucleus through the linker of nucleoskeleton and cytoskeleton (LINC), which conveys mechanical forces from integrins to the cell membrane [56].

Mechanical forces originating from the differentiated epidermis and dermis indirectly influence the fate of EpSCs. It has been shown that increased contractility in the upper layers can induce intra-tissue tension, stimulating EpSC proliferation while inhibiting their differentiation and migration [57]. In conditions like aging and androgenic alopecia, hair shaft miniaturization reduces the physical niche size, leading to HFSC depletion via the Piezo1-calcium-TNF-α (tumor necrosis factor α) signaling pathway [47]. Interestingly, Piezo1 receptors of EpSCs also respond to stretching forces from adjacent dermal cell movements, enhancing regeneration in organoid culture [58]. This suggests that a single mechanosensitive receptor can produce different outcomes based on the stimulus. Overall, compression and tensile stress exert contrasting effects on EpSCs: compression typically causes depletion and suppressed division, while stretching promotes proliferation and hair regeneration. Given their safety and simplicity, the strategic application of mechanical forces holds promise for regenerative medicine research and applications.

Influence of chronic aging on epidermal stem cell dynamics

Aging, a progressive physiological process, can be divided into chronological aging influenced by intrinsic factors and extrinsic aging like photoaging [59]. EpSCs play a key role in aging, leading to visible skin changes such as thinning, hair loss, greying, and decreased dermal elasticity, which results in wrinkles

Table 1 Factors influencing epidermal stem cell behavior

Influence factor	Classification	Mechanism	Outcome	References
Psychological stress	Acute stress	Noradrenaline released by sympathetic nerves (autonomic nerve system)	Ectopic differentiation and depletion of MeSCs in mouse and human	[39]
	Chronic stress	Suppressed expression of Gas6 caused by hypothalamic-pituitary-adrenocortical axis activation	Prolonged quiescence of HFSCs and extended resting phase of HF in mouse	[42]
Mechanical force	Mechanical compression	Inhibition of YAP by B-plexin	Suppressed division of EpSCs in mouse and human keratinocytes in vitro	[52]
		Inhibition of YAP by THY1	Suppressed division of EpSCs in mouse	[53]
		Piezo1-calcium-TNF-α axis	Depletion of HFSCs in mouse	[47]
	Stretching force/tension	In part by Hippo pathway	Increased proliferation of EpSCs in mouse	[55]
		Activation of JUN, FOS, p63, etc., by EGFR-Ras-MAPK pathway		[54]
		The LINC complex	Repressed differentiation of EpSCs in mouse and mouse keratinocytes in vitro	[56]
		Increased actomyosin contractility caused by microtubule disruption; increased cell–cell adhesion stability	Hyperproliferation of EpSCs and prevented commitment to a HF lineage in mouse	[57]
		Upregulation of Piezo1	Hair regeneration upon transplantation of the skin organoid	[58]
Aging	Chronological aging	Elevated activity and changed spatial distribution of Cdc42 caused by increased expression of Wnt5a	Altered HFSCs polarity and impaired hair regeneration in mouse	[77] [65]
		Declined Sirt7 levels and subsequent NFATC1 degradation	HFSC quiescence and hair loss in mouse	[66]
		COL17A1 proteolysis	Skin aging (atrophy, fragility, dyspigmentation, and delayed wound healing)	[68]
			Exhaustion of HFSCs and HF aging in mouse	[69, 204]
		Downregulation of *Foxc1* and Nfatc1	HFSC reduction and HF degeneration in mouse	[70]
		Changed expression of ECM genes	Declined hair regeneration following wounding in mouse	[71]
		Vascular atrophy and dermal stiffening caused by increased expression of Ptx3	Augmented differentiation and hemidesmosome fragility of IFESCs in mouse	[72]
		Reduction in chromatin accessibility	Suppressed self-renewal and differentiation of HFSCs in mouse	[73]
		Dysfunction of HF mesenchymal progenitors	Diminished regenerative competence, HF degeneration, and progressive hair loss in mouse	[74]
		Imbalance in epidermal Jak-Stat signaling	Increased number of $Krt15^+$ population, decreased function, and an inability to tolerate stress of HFSCs in mouse	[60]
		Upregulation of Bmp2, Dkk1, Sfrp4, and downregulation of follistatin	Small hair cycle domains and telogen retention in mouse	[77]
		Decreased perlecan expression	Depletion of $Krt15^+\beta1^-integrin^+$ EpSC in human skin specimens	[61]
		Reduced dermal Igfbp3 gene expression and loss of DETCs	Maintained number but suppressed proliferation of $Krt15^+$ HFSCs, and loss of peripheral immune cell abundance in mouse	[62]
	Photoaging	Decrease of laminin-511 at the dermal–epidermal junction	Reduced level of $MCSP^+$ and $Krt15^+$ EpSCs in human skin specimens	[75]

Table 1 (continued)

Influence factor	Classification	Mechanism	Outcome	References
Circadian rhythm	Central circadian clock	Sympathetic nerves and hedgehog signaling	HFSC activation	[86]
	Peripheral circadian clock	BMAL1	Oscillation of S-phase and ROS in human and mouse; Oscillation of XPA in mouse	[81, 88],[205, 206]
		PER, CRY	Regulated differentiation of primary human keratinocytes	[84]

BMAL1, brain and muscle ARNT-like 1; Bmp, bone morphogenetic protein; COL17A1, collagen type XVII alpha 1; DETCs, dendritic epidermal T cells; EGFR, epidermal growth factor receptor; EpSCs, epidermal stem cells; ECM, extracellular matrix; HF, hair follicle; HFSC, hair follicle stem cell; IFESCs, interfollicular epidermal stem cells; Krt, keratin; LINC, linker of nucleoskeleton and cytoskeleton; MAPK, mitogen-activated protein kinase; MCSP, Melanoma-associated chondroitin sulphate proteoglycan; MeSC, melanocyte stem cells; NTATC1, nuclear factor of activated T cells 1; ROS, reactive oxygen species; TNF, tumor necrosis factor; XPA, xeroderma pigmentosum group A; YAP, yes-associated protein 1

[2]. The debate continues on whether a reduction in EpSC proliferative capacity contributes to skin aging [60–62]. Aging's effects on EpSCs can be divided into intrinsic changes affecting cell behavior directly and extrinsic changes impacting them indirectly, including altered physical niches, inflammatory cytokine release, and signaling inhibitor secretion [63].

Intrinsic alterations in epidermal stem cells due to aging

Aging has been shown to modify factors within Wnt and bone morphogenetic protein (BMP) signaling pathways, pivotal for HFSC activation and quiescence, thereby influencing HFSC functionality [64, 65]. For instance, aged HFSCs exhibit a lack of nuclear factor of activated T cells 1 (Nfatc1) deacetylation due to reduced Sirt7, impeding the transition from the telogen to anagen phase and causing delayed hair growth [66]. Aging is also marked by diminished expression of cell adhesion and extracellular matrix (ECM) genes in EpSCs, notably changes in collagen type XVII alpha 1 (COL17A1), a hemidesmosome component [67]. Both chronological aging and photoaging prompt a spread of COL17A1^{high} cells in the interfollicular epidermis, eventually depleting EpSCs [68]. Furthermore, aging-induced hemidesmosome instability due to COL17A1 proteolysis leads to asymmetric HFSC division, migration, differentiation, and depletion [69]. Foxc1 and Nfatc1-mediated alterations in cell adhesion and ECM are implicated in EpSC migration in aged mice [70]. Overall, aging-induced changes in gene expression affect EpSC interactions with their niches, altering division and motility, contributing to epidermal atrophy, fragility, and hair thinning. This suggests COL17A1 as a potential target for reversing age-associated disorders in clinical or cosmetic applications.

The compromising effect of an aged niche on epidermal stem cells

Environmental alterations linked to aging, particularly those within the niche, exert a significant impact on the dynamics of EpSCs. Recent studies have shown that the rejuvenation of aged EpSCs is possible when paired with young dermis in transplantation assays. Conversely, young EpSCs lose regenerative capacity when combined with aged dermis, highlighting the critical role of the niche in EpSC regulation and skin aging [71]. Mechanistically, an age-associated secretory molecule in dermal fibroblasts, pentraxin 3, leads to dermal sclerotization, stimulating Piezo1 in IFESCs and causing dysregulation [72]. Furthermore, microenvironment stiffening during aging impairs HFSC function by altering the accessibility of bivalent promoters, dependent on the niche [73]. Aging also impairs dermal papilla function, diminishing HF regeneration and contributing to age-related hair loss [74]. In photoaging, a reduced level of laminin-511 at the dermal–epidermal junction is linked to a decrease in MCSP^{+} (Melanoma-associated chondroitin sulphate proteoglycan) Krt15^{+} EpSCs in humans [75].

Elevated inflammatory cytokines and secreted factors during aging are reported to affect EpSCs by regulating signaling pathways. Recent single-cell sequencing data has verified the elevation of inflammatory response gene in IFESCs during aging, including S100A9 and S100A8 [76], and global repression of cytokine signaling through Jak-STAT inhibition has a proproliferative effect directly on aged EpSCs [60], Additionally, an upregulated expression level of canonical Wnt signaling inhibitor Dkk1 and Sfrp4, as well as a downregulated expression level of BMP signaling inhibitor follistatin have been reported to retain telogen phase of hair cycle in aged mouse [77]. It follows that, through direct alterations in structure or components in niches, aging may direct the dynamic of EpSCs

in an indirect way, which offers more options for clinically beneficial targets in anti-aging therapies.

The coordination of epidermal stem cell activities by circadian rhythms

The circadian system, including the central pacemaker in the suprachiasmatic nucleus and peripheral clocks like the epidermis, regulates physiological homeostasis in organisms [78, 79]. The core circadian transcription factor complex brain and muscle ARNT-like 1 (BMAL1)/circadian locomotor output cycles kaput (CLOCK), along with clock-controlled genes such as period (Per) and cryptochrome (Cry), modulate the expression of EpSC regulatory genes, influencing cell behavior [80]. BMAL1 deletion leads to an accumulation of reactive oxygen species (ROS) and continuous, unvaried cell proliferation [81]. Notably, circadian rhythms affect the rate, not the phase, of EpSC proliferation [82]. Contrarily, other studies show that BMAL1 depletion impairs proliferation and migration following injury, increases ROS levels, and delays wound healing, possibly due to ROS dual functions and variances in mouse age across studies [83]. Disruptions in circadian rhythms, such as overexpressing PER1/PER2 or deleting CRY1/CRY2, also induce premature differentiation [84], while DNA damage and repair are regulated by clock genes[85]. Intriguingly, the timing of maximum ultraviolet radiation B (UVB) exposure and the peak S-phase activity of human EpSCs in the late afternoon may contribute to higher skin cancer risks [85].

Circadian rhythms orchestrate the activities of EpSCs through innervation from the suprachiasmatic nucleus and peripheral tissue signals. Recent findings reveal that light exposure prompts the suprachiasmatic nucleus to activate HFSCs via sympathetic nerves and downstream hedgehog signaling [86]. Additionally, peripheral circadian clocks can respond to light and sustain normal diurnal rhythms independently of the central pacemaker, possibly via photopigments in epidermal keratinocytes [87]. Notably, clock genes exhibit uniform expression in HF progenitor cells in both humans and mice but show a patchy pattern in bulge HFSCs, suggesting that HFSCs may be at different circadian phases, leading to varied responses to circadian cues [88].

Regulatory mechanisms of epidermal stem cell activities

EpSCs are central to skin homeostasis, where their proliferation, differentiation, and decision between activation and quiescence are intricately regulated. Critical to this process is the delicate equilibrium between cell number increase and fate determination, influenced by classical signaling pathways and various key molecules (Fig. 4, Table 2).

Impact of classical signaling pathways on the fate of epidermal stem cells

The activities of EpSCs are naturally controlled by a series of signaling pathways under physiological conditions, and the alteration of which usually leads to pathological states [89, 90]. Among them, the Wnt/β-catenin pathway, Sonic hedgehog (Shh) pathway, Notch pathway, and BMP pathway are four major regulating mechanisms that determine the fate of EpSCs collectively [8].

The Wnt/β-catenin pathway

Wnt proteins, belonging to a large family of extracellular signals, are crucial for developmental processes. They engage Frizzled receptors on cell surfaces, triggering reactions that stabilize β-catenin in the cytoplasm, thus initiating transcription [91]. The Wnt/β-catenin pathway is key in driving the transition of HFs from the resting phase (telogen) to the growth phase (anagen), facilitating both proliferation and differentiation [92]. Recent studies have also identified the receptor tyrosine kinase-like orphan receptor 2 (ROR2) as an additional functional receptor in Wnt signaling, expanding the understanding of β-catenin-dependent pathways [90].

The Sonic hedgehog pathway

Shh, an extracellular protein like Wnt, is vital for animal development [93]. It functions by binding to its receptor Patched (Ptch), thereby liberating Smoothened (Smo) from Ptch inhibition. This activation relieves the suppressor of fused homologue (Sufu) inhibition on the transcription factor Gli, leading to the activation of target genes [94]. Shh signaling plays a crucial role in stimulating the proliferation of both quiescent EpSCs and TACs [8]. Dysregulation of Shh signaling in EpSCs is implicated in severe skin disorders, including basal cell carcinoma and hair loss [95, 96].

The Notch pathway

Notch is a transmembrane receptor that modulates various cell fate decisions across species [97]. Functional Notch receptor binds to a ligand on a neighboring cell, then it is successively cleaved by a disintegrin and metalloprotease and γ-secretase into the active intracellular domain, which translocate to the nucleus and induces transcription with coactivators [97]. The Notch pathway is highly related to the differentiation of EpSCs, while its impacts on cell proliferation are seemingly distinct in different parts of the epidermis [8, 98]. Moreover, its function in regulating metabolism in HFSCs has been reported [99].

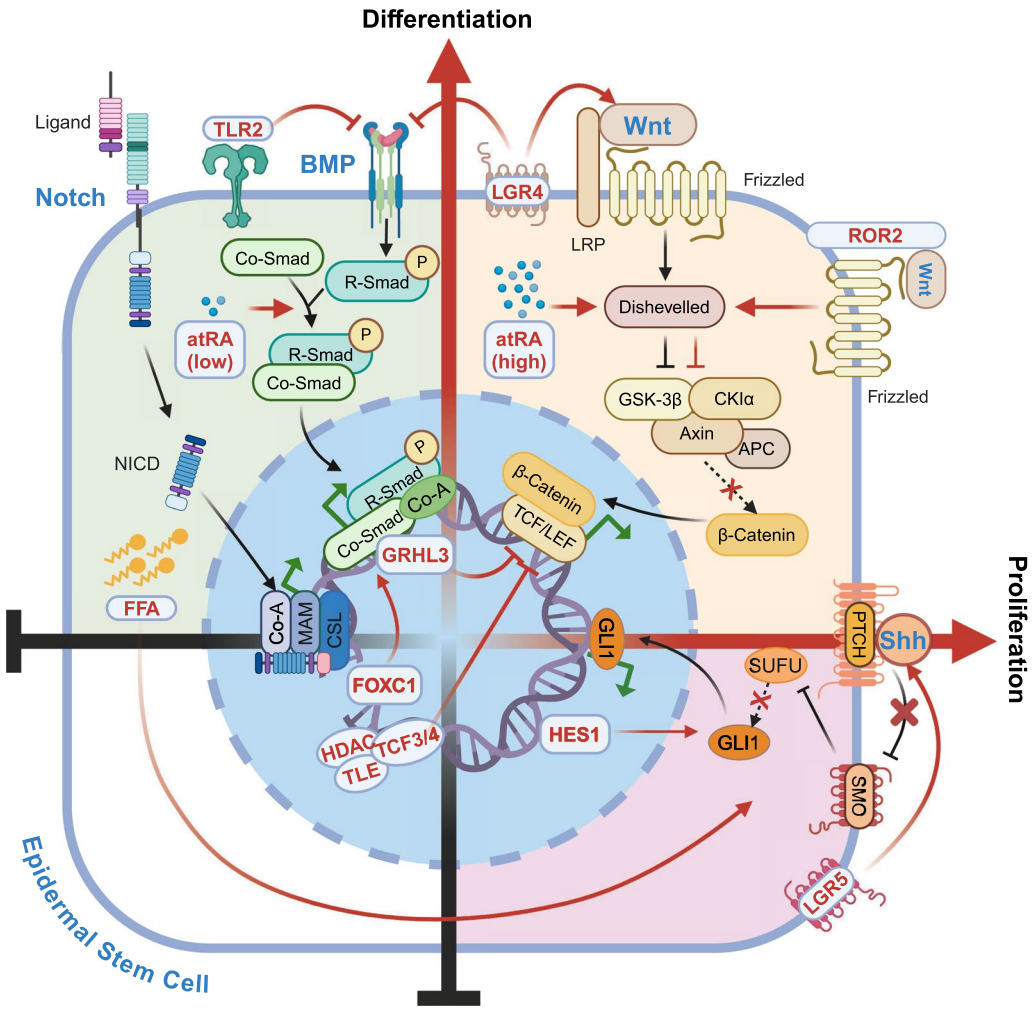

Fig. 4 Regulatory mechanisms of epidermal stem cell activities. The delicate equilibrium of EpSC between cell number increase and fate determination is majorly influenced by four classical signaling pathways and various key molecules. The horizontal and vertical axes represent "proliferation" and "differentiation" respectively. To elaborate, the red arrows of which represent "promote" and the suppression symbols in black represent "inhibit". Signaling pathways and molecules positioned in different quadrants indicate their roles in promoting or inhibiting EpSC differentiation and proliferation. Specifically, the Wnt/β-Catenin signaling pathway is responsible for promoting both cell proliferation and differentiation. The primary role of the Sonic hedgehog (Shh) signaling pathway is to enhance cell growth, with only a modest effect on differentiation. As for the Notch and BMP pathways, they foster the differentiation of EpSCs while concurrently suppressing their proliferation. Molecules that steer the activities of EpSCs by interacting with the four signaling pathways are also illustrated in the figure

The bone morphogenetic protein pathway

BMPs, part of the TGF-β superfamily, are secreted proteins often modulated by inhibitors like Noggin [100]. Upon binding to specific receptors, BMPs trigger the phosphorylation and activation of R-Smad in the cytoplasm, which then associates with co-Smad partner Smad 4, initiating transcription [100]. BMP signaling primarily maintains EpSCs in a quiescent state, inhibiting self-renewal and differentiation [101, 102]. However, it is also pivotal in guiding activated stem cells towards specific lineages [103]. Notably, growth differentiation factor 5 (GDF-5), also known as BMP-14, has been shown to enhance mouse EpSC proliferation through the Foxg1-cyclinD1 axis [104].

Emerging insights into cell metabolism in regulating epidermal stem cell states

Recent findings highlight cell metabolism as a key regulator of EpSCs, influencing their state and functions including energy production, signaling, and gene expression [105]. HFSCs in hypoxic niches primarily rely on anaerobic glycolysis, minimizing ROS damage [106]. During differentiation, they switch to oxidative phosphorylation, using glutamine as an additional carbon

Table 2 Regulators compromising epidermal stem cell activities

Regulator	Classification	Proliferation	Differentiation	Apoptosis	Mechanism	References
SOX9	Transcription factor	+	+	NE	Chromatin remodeling and redistribution of epigenetic co-factors	[207]
DNMT1	Epigenetic regulator	+	+	NE	Increase the methylation of miR-214-3p promoter to derepress MAPK1/p-ERK1/2 axis	[208]
PRC1/2	Epigenetic regulator	+	+	NE	Repress nonlineage transcription factors in the absence of its counterpart	[209]
Glutamine	Amino acid	+	+	NA	Partly by providing carbon source and ATP; activating IL-1β-MyD88 signaling	[108, 109, 210]
HES1	Transcription factor	+	NE	NE	Potentiating Shh signaling in anagen initiation	[211]
LGR5	Membrane receptor	+	NE	NE	Inducing Shh signaling	[212]
IL-24	Cytokine	+	NE	NE	Acting in autocrine and paracrine signaling to regulate proliferation and metabolism	[115]
GDF-5	Cytokine	+	NA	NA	Activate Foxg1-cyclin D1 axis as a member of the BMP family	[104]
IRX5	Transcription factor	+	–	–	Repressing FGF18 expression	[213]
ROR2	Membrane receptor	+	–	–	Regulate Wnt-activated signaling as a receptor; maintain proper ATM/ATR-dependent DNA damage response	[90]
TLR2	Membrane receptor	+	–	NE	Countering inhibitory BMP signaling	
LGR4	Membrane receptor	+	–	NE	Influencing the activities of mTOR, Wnt, and BMP signaling	[214]
HNRNPL	RNA-binding protein	+	–	–	Recruit and stabilize RNA polymerase II in transcription of integrin/ECM genes	[215]
HNRNPK	RNA-binding protein	+	–	–	Transcript proliferation genes and degrading differentiation promoting mRNAs	[216]
atRA	vitamin A metabolite	–/+	–	NA	Maintaining a HFSC identity, maintaining quiescence with BMPs (low levels) or mediating HF regeneration with Wnts (high levels)	[113]
NFIB, NFIX	Transcription factor	NE	–	NE	Govern super-enhancer maintenance of the key HFSC-specific transcription factor genes	[127]
H1B	Histone	NE	–	NE	Binding to promotorial regions of differentiation-related genes in a FOXM1-dependent manner to inhibit transcription	[217]
VAMP2	Membrane protein	NE	+	NE	Binding to FIP200 to regulate nucleophagy during epidermal differentiation	[218]
Serine	Amino acid	NE	+	NE	Stimulate α-ketoglutarate-dependent dioxygenases to derepress H3K27me3	[112]
miR-148a	miRNA	–	+	NA	Regulate the expression of Rock1 and Elf5	[219]
Free fatty acids	Lipid	–	+	NE	Induce accumulation of ROS and lipids; active NFκB signaling and IL-1R signaling to inhibit Shh signaling	[95]
Ceramides/glucosylceramides	Lipid	–	+	NA	Unclear, possibly by modulating the cell membrane or junctional proteins	[110]
GRHL3	Transcription factor	–	+	NA	Transcriptionally activate terminal differentiation genes; suppress Wnt signaling	[220]
DUSP10/6	Phosphatase	–	+	NA	Down-regulate the basal and pulse ERK activities respectively	[221]
miR-24	miRNA	–	+/NE	NA	Target Plk3 to reduce expression of CCNE1	[222]
SUV39H2	Epigenetic regulator	–	–	NE	Increase H3K9me3 to repress the Wnt/p63/adhesion axis	[223]
FOXC1	Transcription factor	–	–	NA	activating NFATC1 and BMP signaling	[224]
TCF3/4	Transcription factor	–	–	NE	Recruiting TLE repressors and HDAC1 to TCF3/4-bound genes to keep expression of Wnt/β-catenin targets low	[225]

Table 2 (continued)

+, promote; −, inhibit

ATM, ataxia telangiectasia mutated; ATP, adenosine triphosphate; ATR, ATM- and Rad3-related; atRA, all-trans retinoic acid; CCNE1, cyclin E1; DNMT1, DNA methyltransferase 1; DUSP, dual specificity phosphatase; ECM, extracellular matrix; Elf5, E74 like ETS transcription factor 5; ERK, extracellular regulated protein kinases; FGF18, fibroblast growth factor 18; FOXC1, forkhead box C1; FOXM1, forkhead box M1; FIP200, focal adhesion kinase family interacting protein of 200 kDa; GDF-5, growth/differentiation factor 5; GRHL3, grainyhead like transcription factor 3; H1B, histone H1.B; H3K27me3, histone H3 lysine 27 methylation; H3K9me3, histone H3 lysine 9 methylation; HDAC1, histone deacetylase 1; HES1, hairy and enhancer of split 1; HFSC, hair follicle stem cell; HNRNPK, heterogeneous nuclear ribonucleoprotein K; HNRNPL, heterogeneous nuclear ribonucleoprotein L; IL, interleukin; IRX5, Iroquois homeobox 5; LGR, leucine-rich repeat-containing G protein-coupled receptor; MAPK1, mitogen-activated protein kinase 1; mTOR, mammalian target of rapamycin; miRNA, microRNA; MyD88, myeloid differentiation primary response protein 88; NA, not assessed; NE, no effect; NFATC1, nuclear factor of activated T cells, cytoplasmic 1; NFκB, nuclear factor kappa-B; NFIB, nuclear factor IB; NFIX, nuclear factor IX; plk3, polo-like kinase 3; PRC1, polycomb repressive complex 1; ROR2, receptor tyrosine kinase-like orphan receptor 2; Rock1, Rho-associated kinase 1; ROS, reactive oxygen species; Shh, Sonic hedgehog; SOX9, SRY-Box transcription factor 9; SUV39H2, suppressor of variegation 3–9 homolog 2; TLE, transducin-like enhancer of split; TCF3/4, T cell transcription factor 3/4; TLR, toll-like receptor; VAMP2, vesicle-associated membrane protein 2

source to optimize ATP production [107]. Inhibiting glutaminase via mTORC2-Akt signaling has been shown to revert progenitor cells to a stem cell state post-anagen phase [108]. Additionally, glutamine enhances skin and HF regeneration under bacterially induced hypoxia via interleukin (IL)-1β-MyD88 signaling, demonstrating its complex role in metabolism [109]. Furthermore, various lipids impact EpSC proliferation and differentiation. For instance, free fatty acids in high-fat diets promote ROS accumulation and short-term epidermal differentiation, but long-term can deplete HFSCs by inhibiting the Shh pathway through NFκB (nuclear factor kappa-B) and IL-1R (type I IL-1 receptor) signaling [95]. Ceramides and glucosylceramides also induce keratinocyte differentiation, though the specific mechanisms remain unexplored [110]. The dysregulation of differentiation is closely linked to oncogenesis, with abnormal EpSC behavior being a potential root of malignancy [111]. Recent studies suggest that limiting extracellular serine encourages EpSCs to stimulate de novo serine synthesis, activating differentiation programs and potentially advancing malignancy, offering new insights into targeting oncogenic stem cells [112]. Apart from metabolites derived from the three primary nutrients, recent research indicates that all-trans retinoic acid (atRA), a metabolite of vitamin A, plays a crucial role in resolving lineage plasticity following injury. Specifically, atRA promotes the identity of HFSCs while simultaneously suppressing the fate of EpSCs at the chromatin level [113].

Other key molecules that govern the identity and regenerative capacity of epidermal stem cells

In addition to metabolites, the fate determination, clonal proliferation, and even apoptosis of EpSCs are influenced by a diverse array of cell-intrinsic and extrinsic molecules. These include transcription factors, epigenetic regulators, membrane receptors, and cytokines [114]. Many of these molecules act by modulating the four established signaling pathways, while others exert direct and independent effects. Recent studies have demonstrated that upon injury, EpSCs express and respond to IL-24 through both autocrine and paracrine mechanisms to proliferate. This process also stimulates the proliferation of dermal endothelial cells and fibroblasts [115]. Remarkably, this molecular cascade bears similarities to immune responses triggered by microbes, B cells, or T cells, highlighting its distinct yet functionally analogous nature. These newly identified regulators have unveiled novel functionalities and potent capabilities. However, further research is necessary to uncover the specific triggers that initiate changes in these molecules during the anagen or catagen phases, and to elucidate the intricate crosstalk among these key modulators.

Epidermal stem cells in immune-related skin diseases

EpSCs play a crucial role in re-epithelialization during wound healing, a key aspect of skin homeostasis. Dysfunctional EpSCs are also implicated in various skin disorders including psoriasis and vitiligo. Moreover, the concept of 'inflammatory memory' in EpSCs has emerged as a significant factor in both normal and pathological skin processes [116] (Fig. 5).

Wound healing

The wound healing process in the skin involves a coordinated effort of various tissue components, with EpSCs playing a central role. This process encompasses four stages: hemostasis, inflammation, proliferation, and remodeling [4]. Hemostasis involves forming a coagulation and fibrin clot that supports cellular migration and immune cell recruitment [117]. During the second stage, immune cells clear pathogens and release cytokines to activate skin stem/progenitor cells like EpSCs, enhancing cell proliferation, differentiation, and shaping the regenerative microenvironment [118]. For instance, IL-1α is known to accelerate the regeneration of $Lgr5^+$ HFSCs and initiate HF formation, though the origin of regenerated HFSCs is unclear [119]. EpSCs, in turn, secrete Ccl2 to influence macrophage behavior, facilitating tissue repair via keratinocyte-macrophage interactions [120]. Subsequently, the proliferation stage requires collaboration between keratinocytes and fibroblasts for re-epithelialization and dermal repair [121]. Finally, in the

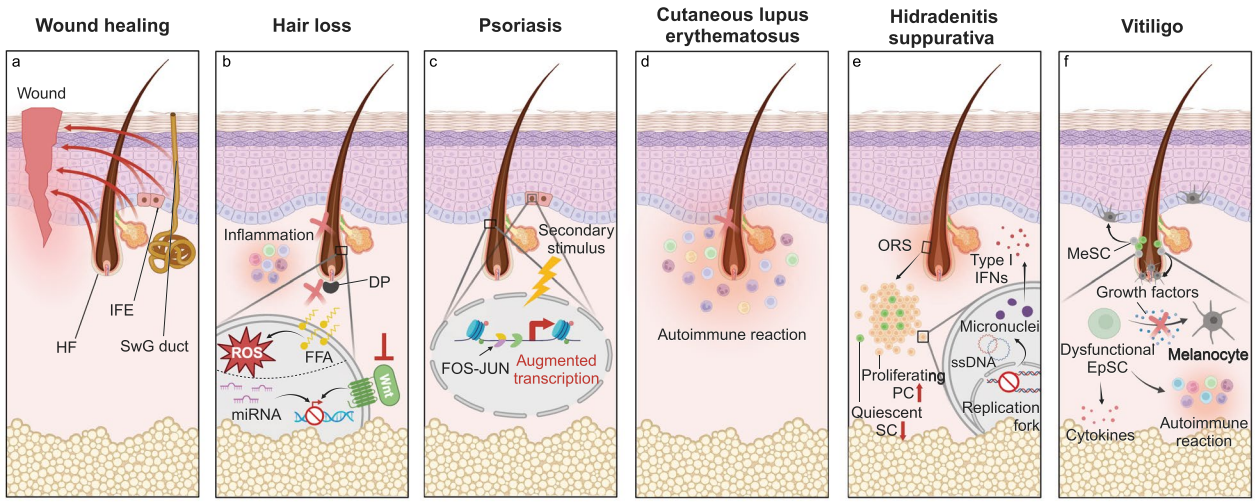

Fig. 5 Epidermal stem cells in wound healing and immune-related skin diseases. **a** Wound Healing: epidermal stem cells (EpSCs) from various hair follicle (HF) regions, including the infundibulum, isthmus, bulge, and sebaceous glands, aid in repairing the interfollicular epidermis (IFE). Under stress, HFSCs transition towards IFESCs, expressing markers of both populations during migration and retaining epigenetic changes for a rapid response to future injuries. Additionally, stem cells and progenitors in the IFE and cells from the sweat gland duct contribute to wound healing. **b** Hair Loss: the dysfunction or loss of HFSCs, often due to inflammation in the bulge or dermal papilla, oxidative stress, and disrupted gene regulation, is a key factor in hair loss. **c** Melanocyte Homeostasis: EpSCs, co-existing with melanocyte stem cells in the bulge, are crucial for melanocyte health. Dysfunctional EpSCs can lead to melanocyte damage and the formation of white patches. **d** Psoriasis and EpSCs: the 'inflammatory memory' of EpSCs, characterized by enhanced transcriptional responses to inflammation, contributes to the pathology of psoriasis. **e** Cutaneous lupus erythematosus: inflammation-related damage to HFSCs, particularly in the bulge area, may cause permanent hair loss in this condition. **f** Hidradenitis Suppurativa: cells from the outer root sheath in affected patients show an increased number of proliferating progenitors and fewer quiescent stem cells. This imbalance contributes to inflammation through the promotion of type I interferon synthesis

remodeling stage, excess cells are removed, and the ECM in the wound bed is restructured [117].

During wound healing, EpSCs are crucial in the proliferation phase, contributing to re-epithelialization via migration, population dynamics, and plasticity [67, 122]. Intriguingly, EpSC migration and proliferation occur in distinct zones: rapid migration without proliferation at the wound's leading edge, and concentrated proliferation with minimal migration in a distant zone [4]. Migration is regulated by mechanisms such as the Piezo1 ion channel, which when activated at the cell's rear, induces cell retraction and slows migration, thus impacting wound healing [123]. Further research is required to fully understand these dynamics. Additionally, EpSCs adapt by increasing symmetric cell division and decreasing differentiation to replenish lost cells [124].

EpSCs exhibit remarkable plasticity, enabling them to rapidly alter their fate for effective tissue regeneration. Originally, HFSCs were believed to contribute to wound repair 2–3 days post-injury [125]. However, recent evidence indicates that HFSCs commence fate determination within 24 h post-injury, even before leaving the bulge area [126]. Under stress, migrating HFSCs enter a state of 'lineage infidelity' near wounds, expressing markers of both IFESCs and HFSCs, driven by factors like ETS2 [127, 128]. They also retain an epigenetic memory of the wound, which enhances their responsiveness to subsequent injuries [129]. Furthermore, single-cell RNA sequencing has revealed that IFESCs undergo a progression from a quiescent state in the proliferation zone to a more differentiated state in the migration zone, demonstrating a unique aspect of stem cell plasticity [14]. In more severe wounds, EpSCs near blood vessels can differentiate into vascular endothelial cells, aiding angiogenesis [130]. While this plasticity is promising for regenerative medicine, its potential role in tumorigenesis warrants careful consideration [125].

Hair loss

Hair cycle dysregulation often leads to hair loss, primarily caused by impaired functions or irreversible damage to HFSCs, such as apoptosis, depletion, and abnormal differentiation. These issues can disrupt the normal hair growth cycle, leading to conditions like permanent scarring alopecia [131]. Contributing factors include hormonal imbalances, autoimmune and nutritional disorders, genetic predisposition, radiation, chemotherapy, and aging [131, 132]. Scarring alopecia, for example, is marked by excessive autoimmune responses in the HF bulge and infiltration of Th1 cytotoxic T cells [133]. Early inflammation in the dermal papilla or other HF components affecting HFSC activities can lead to reversible

hair loss forms like alopecia areata and androgenetic alopecia [134]. Although the exact cellular and molecular mechanisms of hair loss remain elusive, ongoing research is exploring various triggers and pathways potentially impacting EpSC proliferation and differentiation, as discussed above (Table 2).

Psoriasis

Psoriasis, a chronic inflammatory skin condition, affects over 60 million people globally and is closely linked to the behavior of EpSCs [135]. Disruptions in the balance between EpSC proliferation and differentiation, often regulated by key factors like p63, are associated with psoriatic conditions. Depletion of the primary p63 isoform ΔNp63 leads to a less proliferative keratinocyte population, triggering an inflammatory, psoriasis-like state, while its overexpression may suppress this condition [136]. Similarly, the knockout of ΔNp63 effectors c-JUN and JUNB results in psoriasis-like symptoms, with mutant HFSCs compensating by stimulating the proliferation of neighboring cells [137]. The role of EpSC subsets in psoriasis severity and types is also notable. For instance, deleting the Wnt receptor Evi/Wls in Krt14-expressing IFESCs and progenitors induces a psoriasiform dermatitis-like phenotype in mice [138]. Additionally, imiquimod treatment in HFs can trigger premature hair cycle entry through Wnt-independent mechanisms [139].

Moreover, the 'inflammatory memory' of EpSCs is a significant factor in psoriasis pathogenesis. This memory, characterized by sustained chromosomal accessibility for rapid response to secondary challenges, is influenced by factors like absent in melanoma 2 (AIM2) and transcription factors FOS and JUN, which collaborate with stimulus-specific STAT3 [140, 141]. This heightened sensitivity of EpSCs to tissue damage might partly explain the excessive immune reactions observed in psoriasis and other recurrent inflammatory skin diseases [142]. Targeting the inflammation-rewired EpSCs could be a potential therapeutic strategy for these conditions.

Other inflammatory skin diseases

EpSCs dysfunction is increasingly linked to various inflammatory skin conditions, including cutaneous lupus erythematosus, hidradenitis suppurativa, and vitiligo. In cutaneous lupus erythematosus, inflammation in the HF bulge area can lead to permanent hair loss, akin to some forms of alopecia [143]. Research indicates that in these cases, HFSCs are either repurposed for repair or damaged by secondary inflammatory responses [144]. Conversely, in hidradenitis suppurativa, an inflammatory disease affecting the pilosebaceous-apocrine unit, HFSCs have been found to produce type I interferon (IFN) [145, 146]. This condition is also marked by increased HFSC proliferation and differentiation. The underlying mechanism involves replication stress in HFSCs due to stalled replication forks, activating the ATR/CHK1 pathway, which in turn stimulates IFN synthesis via the IFI16/STING pathway [146].

Vitiligo, an autoimmune skin disorder characterized by depigmentation, involves complex interactions between keratinocytes and melanocytes. Keratinocytes play a crucial role in maintaining melanocyte homeostasis and melanogenesis, and in modulating immune responses [147]. They support melanocyte function by providing essential growth factors and regulate melanocyte activity through metalloproteinases and basement membrane remodeling [148]. However, in vitiligo, dysfunctional keratinocytes can exacerbate autoimmune reactions by presenting melanocyte antigens and releasing pro-inflammatory cytokines and chemokines in affected areas [149]. The presence of abnormal keratinocytes and melanocytes in vitiligo lesions further underscores the pathogenic role of epidermal cells [147]. Research also suggests the potential of leveraging EpSCs in vitiligo treatment through the melanocyte-keratinocyte system.

Clinical applications of epidermal stem cells

Since the initial cultivation of human skin stem cells in vitro and their successful engraftment in murine models [150–152], EpSCs have become a focal point in research and clinical applications for wound management and other skin disorders, thanks to their accessibility and regenerative properties [153]. Additionally, the secreted factors and extracellular vesicles from EpSCs show great potential in novel therapeutic approaches for wound healing and hair regeneration [154].

Epidermal stem cells in wound repair and alopecia treatment

In recent decades, cultured epidermal autografts enriched with EpSCs and HF transplantation have advanced wound repair and alopecia treatments [153, 155]. However, challenges persist: cultured epidermal autografts currently lack epidermal appendages like sweat glands, and EpSC proliferation is time-consuming for patients in urgent need of treatment [153, 156]; in alopecia treatment, the availability of transplantable HFs is limited, and transplanted HFs risk dysfunction due to unchanged microenvironment [132]. Innovations are addressing these challenges. Tissue-engineering approaches, such as skin and HF organoids, offer potential solutions, especially in inducing de novo regeneration of HFs and sebaceous glands using dermal papilla cells and skin-derived precursors [157, 158]. Following the discovery that skin organoids can be developed from

human pluripotent stem cells [159], recent researches using human induced pluripotent stem cells (iPSCs) have successfully developed skin organoids with sweat glands and Merkel cells [160]. The optimized protocol exhibited greater clinical application value while tackling the ethical concerns surrounding fetal tissue-derived stem cells. As for the delay in treatment, Rho-associated kinase inhibitors have shown promise in expediting EpSC proliferation for cultured epidermal autografts [161]. Recent advancements include biomimetic ECMs that regulate HFSC fate, eliminating the need for feeder cells [162]. Overall, further research is necessary to develop vascularized skin organoids that incorporate immune cells. This advancement holds potential to address challenges such as large non-healing skin wounds in hypoxic conditions, deficiencies in micronutrients like those seen in diabetic ulcers, and the dysregulated immune microenvironment in alopecia patients. To achieve clinical applicability, it is essential to establish standardized cell sources, consistent differentiation protocols, and robust validation assays for the functional capabilities of EpSCs.

3D bioprinting, encompassing techniques like inkjet, laser-assisted, extrusion, and scaffold-free spheroid-based bioprinting, is revolutionizing bioengineering by creating precise skin organoids with functional appendages [163–165]. These bioinks, combining EpSCs, mesenchymal cells, and biomaterials, enhance the viability and differentiation of EpSCs. Innovations in biomaterial scaffolds, including nanoscale biomimetic ECM, molecular hydrogen, and platelet-rich plasma, are improving microenvironment for EpSC regeneration and angiogenesis [162, 166, 167]. Safety and effectiveness of EpSC therapies are being validated through preclinical studies and deep learning-based cell tracking technologies [168, 169].

Paracrine factors from EpSCs, contributing significantly to their regenerative potential, may be utilized independently as cell-free therapy that promote angiogenesis and epithelialization in skin defect treatments [155, 170]. EpSC-derived extracellular vesicles, enhancing both EpSC and dermal cell proliferation, are emerging as promising therapies for wound repair and tissue regeneration [154, 171, 172].

Transgenic epidermal stem cell therapy for epidermolysis bullosa treatment

Epidermolysis bullosa (EB) is a severe skin disorder arising from genetic defects in the dermo-epidermal junction [173]. Classified mainly into simplex, junctional, dystrophic, and mixed types based on blister formation, EB requires different treatments tailored to specific molecular and genetic abnormalities [173, 174]. Transgenic EpSC transplantation has shown remarkable results in EB treatment. In 2006, a junctional EB patient received transgenic EpSCs, demonstrating stable and durable skin improvement over 16 years [175, 176]. A notable 2017 case involved replacing 80% of a patient's skin with transgenic epidermis, resulting in a fully functional skin barrier maintained over six years [177, 178]. Laminin subunit beta 3 (LAMB3)-deficiency in junctional EB, leading to reduced YAP activity in EpSCs and subsequent cell depletion, presents a new gene therapy target [179]. In recessive dystrophic EB, autologous cultured transgenic EpSCs have restored collagen VII expression in patients, with over 70% of treated wounds healed and maintaining collagen VII expression after two years [180, 181]. However, gene modification techniques, such as integrating vectors carrying functional genes, have proven effective primarily for recessively inherited EB. For EB simplex, which is dominantly inherited, there is a critical need for integrated ex vivo cell and genetic therapies to precisely correct the mutated allele. This approach holds promise for advancing treatment options in these cases.

Emerging gene-editing technologies like CRISPR/Cas9 offer potential for correcting both dominant and recessive mutations [182, 183]. Recent studies have demonstrated targeted cleavage of the mutant allele in EB simplex, restoring a normal cellular phenotype without affecting the normal functions of EpSCs, which represents a significant advancement in precision medicine for treating EB simplex [184]. Although genetically edited EpSCs are mainly in the preclinical stage, their full development holds significant promise for EB treatment. To this end, future studies are expected to optimize gene-editing tools, such as prime editing, base editing, and Cpf1/Cas12-based editing, to attain greatest on-target efficiency and minimal off-target effects. Notably, genotoxicity and genomic instabilities are two serious issues that requires careful prevention and thorough verification.

Cultured epidermal stem cells with melanocytes for vitiligo treatment

EpSCs are integral to vitiligo treatments, encompassing tissue and cellular grafting methods [185]. The melanocyte-keratinocyte co-cultured system, initially used in autologous cultured epidermal grafting for stable vitiligo, achieved significant permanent repigmentation [186]. Subsequently, non-cultured epidermal cell grafts emerged as a rapid and efficient approach for treating extensive vitiligo [187]. The autologous melanocyte-keratinocyte suspension, despite requiring larger donor biopsies, is favored for its convenience and cost-effectiveness [188].

Recent advancements show that epidermal cell suspensions combined with follicular cells, rich in MeSCs, fibroblast growth factor, and stem cell factor, lead to superior

and faster repigmentation [189]. This effectiveness is likely due to the diverse types of HFSCs and MeSCs in the bulge area. The dynamic interplay between various EpSC populations and melanocytes presents significant clinical potential, suggesting that specific EpSC clusters might enhance melanocyte proliferation and improve outcomes to meet growing clinical demands.

Methods for studying epidermal stem cells

The distinctive biological properties of EpSCs, such as unique biomarkers, self-renewal, differentiation capabilities, slow-cycling nature, and adhesion traits, have paved the way for diverse research methodologies. Advances in research techniques have further deepened our understanding of EpSC biology, origins, and clinical applications (Fig. 6).

Isolation, enrichment, and expansion of epidermal stem cells in vitro

Primary human epidermal keratinocytes, often sourced from neonatal foreskin, and basal layers of mouse skin are common reservoirs for EpSCs [190, 191]. EpSCs can also be derived from iPSCs, expressing CD200 and ITGA6, capable of forming all HF lineages and reconstituting the interfollicular epidermis [192]. Explant culture and enzymatic digestion are standard isolation methods, with recent studies favoring hyaluronidase and collagenase I over trypsin for higher cell viability and stemness [193].

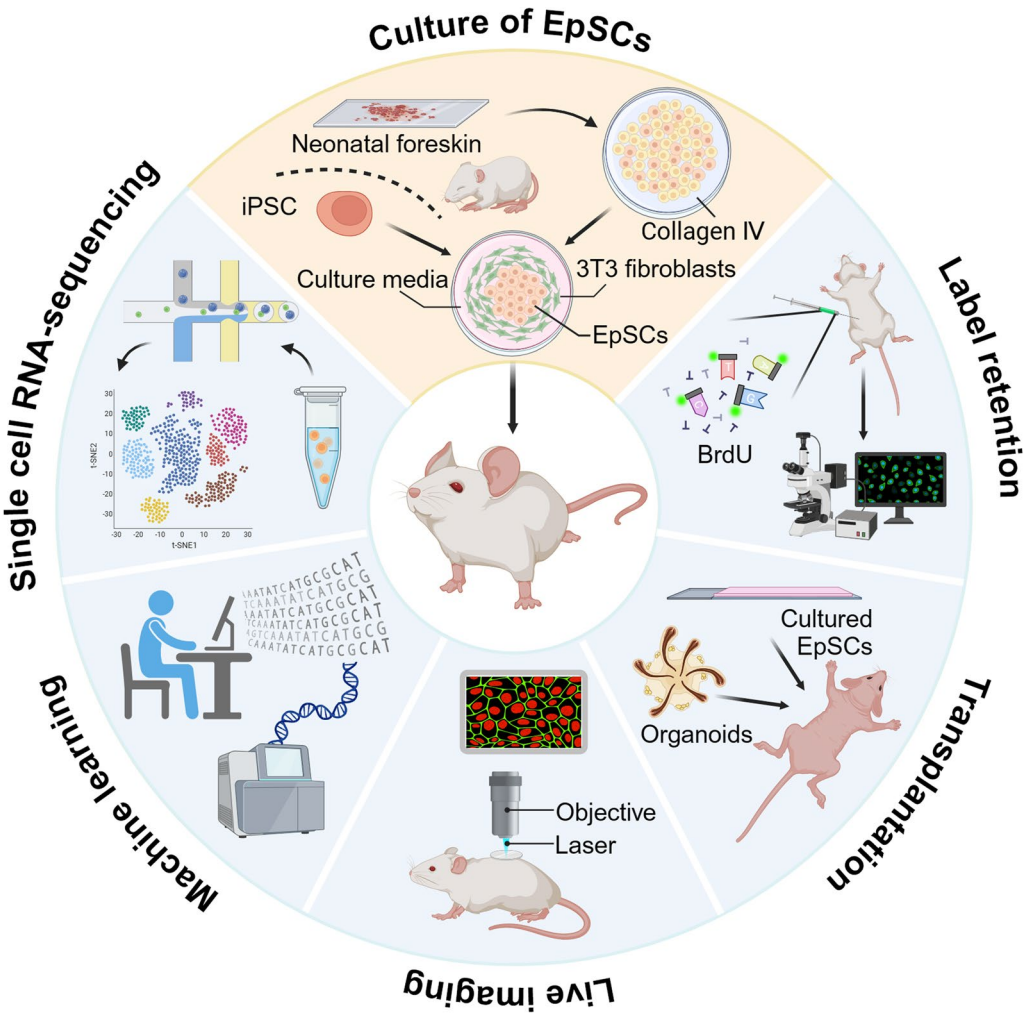

Fig. 6 Methods for studying epidermal stem cells. EpSCs can be obtained from neonatal foreskin samples and mouse skin, enriched after 20-min incubation on collagen IV, and expanded in culture media with 3T3 fibroblasts as feeder cells. iPSCs are also optional sources of EpSCs. Specific research methods corresponding to the slow cycling nature and regenerative ability of EpSCs include label retention and skin regeneration assays. Live imaging, machine learning, and single cell RNA-sequencing are novel techniques currently in use. All the figure created using BioRender (https://biorender.com/)

Fluorescence-activated cell sorting is used for cell selection, identifying EpSCs through markers like high integrin β1 and Krt19/5/14 expression [194, 195]. A simple and special method for EpSC enrichment involves incubation on collagen IV, leveraging fast adhesion through integrin β1 [194].

Culture media advancements have enabled efficient and quality in vitro EpSC expansion [165]. The Rheinwald and Green method, using co-culture systems with feeder cells like 3T3-J2 and mitomycin-C, is prevalent [152]. Serum-free media with lower immunogenicity have also been developed for more refined culture conditions [196]. Except for culture media, multiple devices have popped up to optimize culture systems [197]. Finally, three-dimensional culture systems to mimic the real expansion condition of EpSCs have been developed at lightning speed, which has been discussed in the previous section.

Label retention and transplantation of epidermal stem cells in vivo

Utilizing their slow-cycling nature, EpSCs are able to be studied through label retention techniques. Radioactively-labeled nucleotides like 5-bromo-2'-deoxyuridine (BrdU) help identify EpSCs in vivo due to their infrequent division [198, 199]. The use of GFP-tagged histone H2B (H2B-GFP) in a tet-controllable manner enhances specificity in chromatin transition studies [200, 201]. Skin regeneration assays test EpSC regenerative abilities and are complemented by transplanting cultured EpSCs or organoids onto mice for more comprehensive functional assessment [58, 159].

Novel techniques in epidermal stem cell research

Advanced tools like live imaging, machine learning, and single-cell RNA-sequencing have transformed EpSC research. Genetic lineage tracing with the Cre-loxP system and intravital microscopy can capture dynamics of EpSCs via live imaging [202, 203]. Moreover, machine learning facilitates in-depth analysis of EpSC behavior and interactions with high efficiency [168]. Single-cell RNA-sequencing offers insights into lineage hierarchies, signaling networks, cell state predictions, and stem cell quantification in cell populations [15, 25]. These methods, coupled with the evolution of artificial intelligence and bioinformatics, are propelling significant breakthroughs in EpSC research.

Conclusions

This review provides an updated perspective on EpSCs in skin homeostasis, potential factors influencing their behavior, their involvement in clinical perspectives, as well as regulatory mechanisms and methods used for studying them. However, limitations remain in translating findings to clinical applications due to differences between species, and in the widespread adoption of EpSC-based treatments because of high costs and associated risks. With the aid of rapidly evolving techniques, it is likely that we will gain a more comprehensive understanding EpSCs in the near future.

Abbreviations

AIM2	Absent in melanoma 2
atRA	All-trans retinoic acid
BMAL1	Brain and muscle ARNT-like 1
BMP	Bone morphogenetic protein
BrdU	5-Bromo-2'-deoxyuridine
CLOCK	Circadian locomotor output cycles kaput
COL17A1	Collagen type XVII alpha 1
Cry	Cryptochrome
EB	Epidermolysis bullosa
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EpSC	Epidermal stem cell
GDF-5	Growth differentiation factor 5
GR	Glucocorticoid receptor
H2B-GFP	GFP-tagged histone H2B
HF	Hair follicle
HFSC	Hair follicle stem cell
IFESC	Interfollicular epidermal stem cell
IFN	Interferon
IL	Interleukin
IL-1R	IL-1 receptor
iPSCs	Induced Pluripotent stem cells
Krt	Keratin
LAMB3	Laminin subunit beta 3
LINC	Linker of nucleoskeleton and cytoskeleton
MAPK	Mitogen-activated protein kinase
MCSP	Melanoma-associated chondroitin sulfate proteoglycan
MeSC	Melanocyte stem cell
Nfatc1	Nuclear factor of activated T cells 1
NFκB	Nuclear factor kappa-B
Per	Period
Ptch	Patched
ROR2	Receptor tyrosine kinase-like orphan receptor 2
ROS	Reactive oxygen species
Shh	Sonic hedgehog
Smo	Smoothened
Sufu	Suppressor of fused homologue
TAC	Transit-amplifying cell
TGF-β3	Transforming growth factor-β3
TNF-α	Tumor necrosis factor α
UVB	Ultraviolet radiation B
YAP	Yes-associated protein

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