Materials Today Bio 29 (2024) 101303

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Materials-based hair follicle engineering: Basic components and recent advances

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ARTICLE INFO

Keywords:
Hair follicle
Stem cells
Signaling pathways
Materials
Engineering methods

ABSTRACT

The hair follicle (HF) is a significant skin appendage whose primary function is to produce the hair shaft. HFs are a non-renewable resource; skin damage or follicle closure may lead to permanent hair loss. Advances in biomaterials and biomedical engineering enable the feasibility of manipulating the HF-associated cell function for follicle reconstruction via rational design. The regeneration of bioengineered HF addresses the issue of limited resources and contributes to advancements in research and applications in hair loss treatment, HF development, and drug screening. Based on these requirements, this review summarizes the basic and recent advances in hair follicle regulation, including four components: acquisition of stem cells, signaling pathways, materials, and engineering methods. Recent studies have focused on efficiently combining these components and reproducing functionality, which would boost fabrication in HF rebuilding ex vivo, thereby eliminating the obstacles of transplantation into animals to promote mature development.

1. Introduction

The hair follicle (HF) is the fundamental unit of hair growth, undergoing periodic changes that contribute to hair circulation. HFs serve various physiological functions, including temperature sensing, tactile sensation, and skin repair [1,2]. Meanwhile, hair loss may further raise the challenges of psychological issues including social identity, diminished self-esteem, and difficulties in social interactions [3,4]. Currently, there are three FDA-approved medicines, minoxidil, finasteride, and baricitinib, for hair loss treatments, as well as fundamental research, such as botanical extracts [5,6], platelet-rich plasma (PRP) [7,8], adipose stem cells (ASCs) [9,10], keratinocyte-conditioned media [11], nano-drug delivery [12]. Nevertheless, their therapeutic efficacy is still based on animal models, which may not accurately predict effects when used in hair regrowth. Hair transplantation, as an alternative effective treatment, is usually hindered by insufficient autologous HFs, which would be further limited by the immune rejection with allogeneic HFs. Therefore, ex vivo HF regeneration presents a promising approach for HF regeneration, further providing a platform for drug screening and anticipation to address the shortage personally and commercially.

The morphogenesis and circulation of HF within the full-thickness skin involve approximately 50 types of cells, necessitating intricate interactions between epithelial and mesenchymal cells [13–15]. Cells serve as the foundation for HF formation, and the extracellular matrix (ECM) regulates cell growth and differentiation by transmitting biological signals [16]. ECM is a complex network structure that plays a crucial role in regulating cell signaling, function, characteristics, and morphology [17]. Biomaterials have been utilized to mimic the ECM, supporting and facilitating cell interaction and signal communication between cells and their microenvironments. The technology for constructing tissues and organs is a crucial aspect of tissue engineering research. Commonly employed techniques for HF fabrication include cellular self-assembly [18,19], microfluidics [20,21], and 3D printing [22–24], which enhances the efficiency of HF formation, paving a feasible path for high throughput production of HF ex vivo.

This review highlights four essential components for HF engineering:

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https://doi.org/10.1016/j.mtbio.2024.101303
Received 24 July 2024; Received in revised form 11 October 2024; Accepted 17 October 2024
Available online 18 October 2024

stem cells, signaling pathways, materials, and engineering methods, as depicted in Fig. 1. Qualified seed cells should possess a high potential for efficient hair follicle induction and be obtainable facilely. Additionally, the various interactive biological signals transduction involved in hair follicle regeneration are essential for guiding the hair follicle regeneration. The biological signals exchanged between cells are the driving force behind the successful induction of hair follicles in vitro. Biomaterials can be prepared in various forms to provide physical support and create an appropriate cell microenvironment. Additionally, they can serve as carriers for biological signaling molecules that regulate cell behavior. Engineering techniques integrate cells, biological signals, and materials by adjusting the concentration and type of biological signals, which could significantly improve hair follicle regeneration. The primary challenge in hair follicle regeneration is restoring comprehensive structural and biological characterization ex vivo, mainly from the complexities associated with mimicking microenvironments in vivo. This review aims to explore the novel patterns in current research on HF preparation and strive to accurately simulate and reconstruct the function of natural HFs in the laboratory.

2. Stem cells

Essentially, stem cells participate in the process of HF formation in vivo. Among various follicle cells, some stem cells can be used for hair follicle tissue engineering and are potential seed cells; however, obtaining and cultivating stem cells remains a challenge. Fig. 2 illustrates three methods for obtaining seed cells: 1) extraction from the tissue, 2) induction from stem cells, and 3) somatic cell reprogramming. The following outlines methods for extracting and identifying functional cells, which are anticipated to mitigate the shortage of HF seed cells.

2.1. Hair follicle stem cells

Hair follicle stem cells (HFSCs) with a minor percentage are located in the bulge region of the HF but regulate the cyclical growth and renewal of HF (Fig. 2a–i). The current research with HSFCs has predominantly focused on mouse or rat models. In humans, the bulge area housing HFSCs is highly inconspicuous, posing challenges for extraction and identification [25]. It is widely acknowledged that HFSCs are slow-cycling, with markers including K15 [26,27], CD133 [1], and Lgr5 [28–30], among others. Loss of $Lgr5^+$ cells in mice results in impaired hair regrowth, while activating the Wnt signaling pathway regulates $Lgr5^+$ cells and initiates hair germ recovery [31]. HF-associated pluripotent stem cells have demonstrated in vitro differentiation into neurons, glial cells, keratinocytes (KCs), smooth muscle cells, melanocytes, and beating cardiomyocytes [32,33]. Researchers are investigating the cultivation conditions of HFSCs to maintain their differentiation within a controllable range for potential application in HF tissue engineering.

Developing tissue-engineered HFs using HFSCs relies on replicating their behavior in vitro and establishing a culture system for accurate monitoring and manipulation. Wen et al. [34] successfully established an effective short-term culture system for primary human HFSCs with human fibronectin (FN) and the ROCK inhibitor Y-27632, which promoted human HFSCs proliferation by maintaining their stem cell characteristics with the ability of HF regeneration in vivo. Carlos et al. [35] optimized the traditional 2D medium by culturing HFSCs in KGM-3D substrate containing Y27632, FGF-2, and VEGF-A, leading to a significant increase in the population of $CD34^+\alpha6^+$ HFSCs in mouse HFs. They revealed that this bidirectional interconversion of HFSCs and their progeny achieved population equilibrium. Takeo et al. [36] identified a subpopulation of mouse HFSCs expressing triple-positive markers ($CD34^+/CD49f^+$/integrin $\beta5^+$) in HF protrusion for in vitro HF regeneration. Presently, there is no consensus on the markers for mammalian

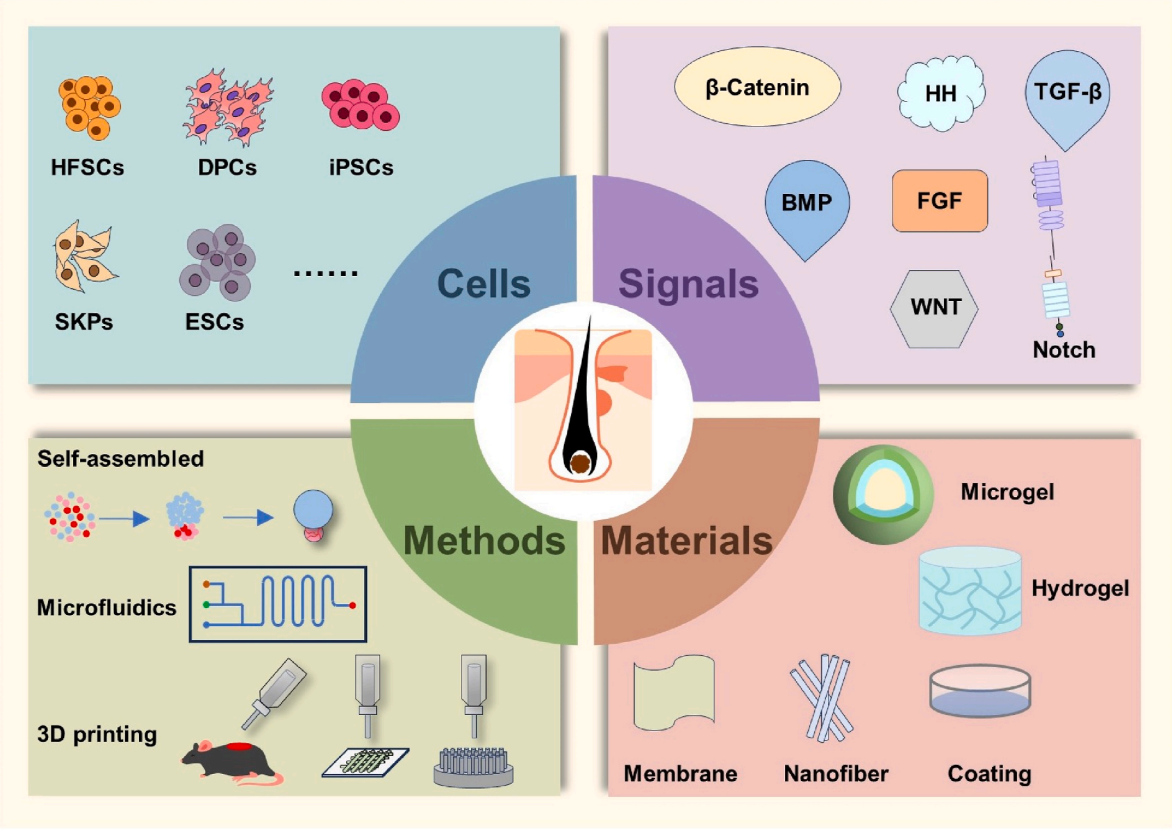

Fig. 1. Schematic illustration of the components involved in the fabrication of hair follicles.

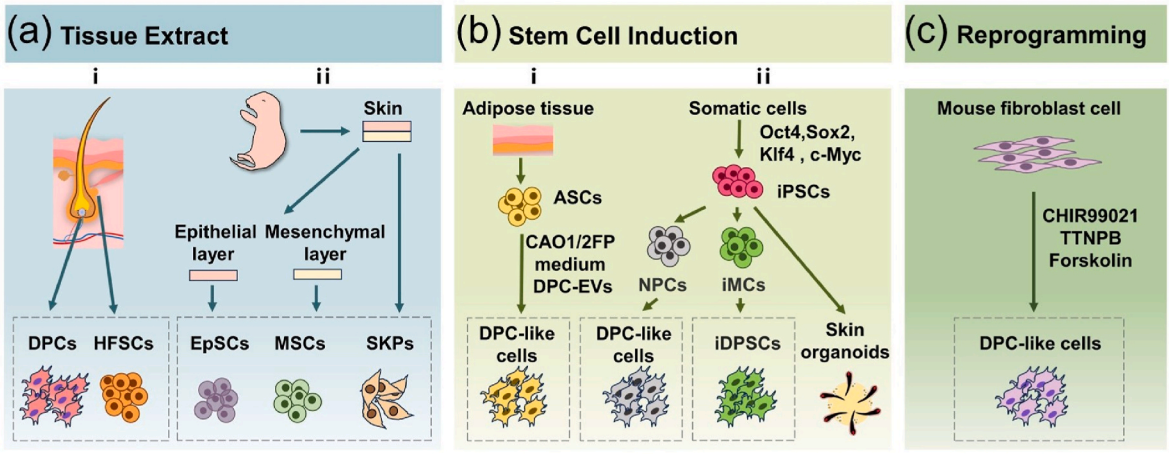

Fig. 2. Three methods for obtaining seed cells. (a) Extraction from tissue. (a–i) Dermal papilla cells (DPCs) are obtained from the base of the HF, while hair follicle stem cells (HFSCs) are extracted from the bulge of the HF. (a-ii) Extraction from neonatal skin. Neonatal skin tissue is directly digested to obtain skin-derived precursors (SKPs). When the epithelial and mesenchymal layers of the tissue are digested separately, epithelial stem cells (EpSCs) and mesenchymal stem cells (MSCs) can be harvested. (b) Stem cell induction. (b–i) Adipose stem cells (ASCs) are induced to differentiate into DPC-like cells by cultured with CAO1/2FP medium and DPC extracellular vesicles (DPC-EVs). (b-ii) Hair follicle cell-inducing potential of induced pluripotent stem cells (iPSCs). IPSCs can differentiate into neural progenitor cells (NPCs), which can further differentiate into DPC-like cells. Alternatively, iPSCs can differentiate into induced mesenchymal cells (iMCs) and then into DP-substituting cells (iDPSCs). Additionally, iPSCs can be directly induced into skin organoids with intact HFs. (c) Reprogramming of somatic L929 cells into DPC-like cells using CHIR99021, TTNPB, and Forskolin.

HFSCs, leading researchers to choose different markers for screening and study.

HFSCs initiate the HF cycle by receiving external signals from the dermal papilla, regulating the surroundings of HF. Dormant HFSCs reside in quiescent ecological niches in the bulge near the HF and are quickly activated to divide during the new hair cycle [37]. Upon successful activation, HFSCs exit their ecological niche to generate outer root sheaths. Some progeny of the outer root sheath cells return to the microniche and revert to the stem cell state [38]. Senescence and depletion of HFSCs cause contraction of the hair shaft ecological niche, resulting in hair loss [39,40]. HFSCs are regulated by signaling from the skin microhabitat through short-range cell contact or paracrine action. DPCs, immune cells, adipocytes, and macrophages participate in regulating the bioactivity of HFSCs [41,42]. Furthermore, HFSCs can contribute to remodeling the skin microenvironment [43,44], which have great potential to differentiate into various types of HF cells, while their application is hindered by challenges in large-scale cultivation.

2.2. Dermal papilla cells

Dermal papilla cells (DPCs) constitute a cluster of MSCs that are crucial for starting a new hair cycle activation (Fig. 2a–i). Once the number of papilla cells drops to a native level, initiating a new hair cycle becomes impossible [45–47]. Extracting and culturing DPCs has been ongoing since 1981, which currently could be obtained from hair follicles using different methods [48,49]. DPC clusters can be isolated from HFs through either microscopic manipulation or enzymatic digestion. Under suitable culture conditions, these cells undergo limited expansion [50]. Current markers for DPCs cultured in vitro include ALP [51,52], α-SMA [53], Versican [54,55], Corin [56], and CD133 [57], among others. Extensive research has been conducted on the extraction and in vitro maintenance of DPCs in rodents. Human DPCs pose more differentiation and cultivation challenges in vitro compared to those from rodent HF extracts.

Primary DPCs have the advantage of being easy to obtain, but maintaining their biological characteristics in vitro is challenging due to the loss of epithelial signals. With increasing in vitro culture generations, hair induction ability weakened. The quest for suitable cultural conditions for DPCs remains ongoing. 3D cell spheres were observed to mimic the in vivo environment compared to traditional 2D cell culture, consequently restoring some of the hair-inducing capacity [58,59]. In addition, supplying epithelial signals during DPC culture enhances their ability to induce hair growth. The conditioned medium collected from interfollicular KCs proves more effective than traditional 3D culture, as evidenced by DPCs expressing more biologically active markers and displaying increased aggregation capacity [60]. DPCs have emerged as the most promising seed cells in tissue-engineered HF regeneration owing to their abundant availability.

In addition to cell harvesting from HFs, there are two other methods: stem cell induction and somatic cell reprogramming. These approaches involve transforming cells with unlimited passaging capacity into seeding cells capable of initiating HF regeneration. ASCs can be prompted to differentiate into DPC-like cells when cultured with CAO1/2FP medium and DPCs extracellular vesicles [10] (Fig. 2b–i). Three small molecules-CHIR99021, TTNPB, and Forskolin have been discovered to induce the transformation of human dermal fibroblasts (HDFs) into DPC-like cells due to the high similarity between dermal fibroblasts and hair papilla cells [61,62] (Fig. 2c). When mixed with mouse dermal cells, these DPC-like cells induced hair regeneration on the back of nude mice. The effective induction of HFs by DPC-like cells derived from stem cells and somatic cells greatly expands the source of seed cells.

2.3. Induced pluripotent stem cells

Shinya Yamanaka utilized viral vectors to transfer a combination of four transcription factors (Oct4, Sox2, Klf4, and c-Myc) into differentiated fibroblasts, thereby reprogramming them to resemble embryonic stem cells. These reprogrammed cells were defined as induced pluripotent stem cells (iPSCs) [63]. iPSCs have been successfully induced and derived from somatic cells of various species, including mice, rats, rhesus monkeys, pigs, and humans [64,65]. iPSCs exhibit a gene expression profile and pluripotency similar to embryonic stem cells. Human iPSCs have been shown to differentiate into various cell types, including endothelial cells (hiPSC-ECs), fibroblasts (hiPSC-FBs), and keratinocytes (hiPSC-KCs) [66,67]. Theoretically, iPSCs have the potential to differentiate and generate all HF lineages, offering a method to produce large quantities of seed cells for HF tissue engineering [68,69].

Generally, iPSCs can induce the production of functional seed cells for skin repair and HF regeneration (Fig. 2b–ii). Zhou et al. [70] employed a human acellular amniotic membrane with iPSC-derived

$CD200^{+}/ITGA6^{+}$ epithelial stem cells (EpSCs) to address full-thickness skin damage. Their findings indicated successful restoration of both the skin and its appendages. Typically, iPSCs are induced to differentiate into intermediate cells before further differentiation into DPC-like cells [71]. For instance, human iPSCs were differentiated into mesenchymal stem cells (MSCs), which were then exposed to retinoic acid and DPC-activated medium to attain DP properties. Upon co-transplantation with human KCs in vivo, fibrous structures resembling the hair shaft with a hair cuticle were produced [72]. Skipping differentiation into seed cells, iPSCs can also be directly induced in vitro to become hair-bearing skin organoids. Transplanting these skin organoids into nude mice has led to the reconstruction of flat skin with normal hair [73–76]. However, iPSCs' prolonged induction time and the potential tumorigenic risk associated with residual, incompletely differentiated iPSCs are the primary factors limiting their application [77]. If these limitations can be overcome through technological advancements in the induction process, it could serve as an excellent source of seed cells for personalized hair follicle preparation.

2.4. Other potential cells

Several types of seed cells with multiple differentiation potentials can be extracted from the skin tissue of embryos or newborns, including skin-derived precursor cells (SKPs), EpSCs, and MSCs (Fig. 2a–ii). The following will introduce the applications of these cell types in HF regeneration.

SKPs are a population of neural crest-derived stem cells originating from the skin exhibiting diverse differentiation potentials. The HF papilla serves as an enriched niche for SKPs. Derived from dermal cells, SKPs possess dermal stem cell functional properties, usually utilized as a cell source for constructing engineered dermal components of the skin [78,79]. Chen et al. [80] developed a 3D co-culture system for SKPs and found that amphiregulin augmented the proliferation and HF induction activity of SKPs via PI3K and MAPK pathways. SKPs and EpSCs were mixed in Matrigel and grafted into excisional wounds in nude mice after being cultured, leading to the development of HFs, sebaceous glands, and other skin appendages [81]. At present, the extraction, cultivation, and induction of differentiation of SKP are not fully understood, which is still an obstacle to HF tissue engineering.

EpSCs and MSCs can be extracted from the epidermal and mesenchymal layers of embryos or newborns (Fig. 2a–ii). While EpSCs possess the capability to differentiate into various cell types within the epidermis, they cannot regenerate HFs independently if mesenchymal is absent. DPCs, in particular, belong to the MSCs category. EpSCs and MSCs were combined in Matrigel to generate HF-like structures exhibiting typical morphological characteristics in vitro, achieving a hair stem induction rate approaching 100 % [82]. In addition to MSCs derived from skin tissue, those from other tissues can also positively affect HF induction. Treatment with exosomes from bone marrow-derived MSCs enhances the proliferation and migration of DPCs and facilitates the transition of HFs from telogen to anagen in mice [83,84]. Dermal papilla-like tissues can be cultivated in vitro using human bone marrow or umbilical cord MSCs, and their capacity to induce hair growth has been validated in nude mice [85]. HF regeneration is not just the cell recombination process; it also involves the differentiation of stem cells. The driving force behind intercellular recombination and differentiation is various biological signals.

3. Signaling regulation in hair morphogenesis and circulation

Biomolecular signals regulate gene expression and cell behavior through a variety of molecules or compounds. The cycling of the HF from neogenesis to the hair cycle is mediated by different signals that regulate the physiological function of the HF. Signaling pathways determine the number and location of HFs in the epidermis and their spacing [86,87]. The development of HFs in the embryo initiates with the onset of Wnt signaling, followed by the gradual involvement of other signals. This progression includes follicular placode formation, the hair germ stage, hair peg development, bulbous peg formation, and finally, the maturation of the HF. The biosignals involved in HF neogenesis and the hair cycle are shown in Fig. 3.

3.1. Wnt signaling pathway

The Wnt signaling pathway is highly conserved and pivotal in biological growth and development, tissue homeostasis, and carcinogenesis [88]. The Wnt pathway is transmitted in cells through the classical Wnt/β-catenin pathway, the Wnt/Ca^{2+} pathway, and the planar cell polarity pathway. In the classical pathway, two scenarios exist: in the absence of Wnt, cytoplasmic β-catenin can be degraded by a destruction complex consisting of Axin, adenomatous polyposis coli tumor suppressor protein (APC), glycogen synthase 3 (GSK3), and casein kinase 1 (CK1); in the presence of Wnt, Wnt binds to its receptors Frizzled and LRP5/6, forming a receptor complex that targets and disrupts the APC/Axin/GSK3 complex. β-catenin stabilizes and accumulates in the cytoplasm, then translocates to the nucleus to form active complexes with lymphoid enhancer factor/T cell factor (LEF/TCF), thereby regulating target gene expression [89,90] (Fig. 4a). From the development of the HF during the embryonic period to the cyclic cycle of the HF, accurate involvement of the classical Wnt signaling pathway is an indispensable link.

Wnt signaling initiates the development of placodes and hair shafts during the embryonic period [91–93]. If Wnt is deleted during embryogenesis, placode formation is blocked. Deletion of Wnt after HF formation leads to complete hair loss after the first hair cycle. HF induction and formation are generally regulated by epithelial-mesenchymal interactions (EMI). Epithelial β-catenin and Wnt ligands activate dermal Wnt/β-catenin signaling, thereby regulating fibroblast proliferation and initiating follicular plate formation [94–96]. The Wnt/β-catenin pathway interacts with the Eda/Edar/NF-kB signaling pathway, where Edar expression inhibits BMP, guiding proper stromal development [97]. HFs are primarily formed during the embryonic period. Still, activation of the Wnt pathway in the skin near wounds can also lead to the development of new HFs [98–103]. Correct activation of the Wnt pathway is crucial for stimulating the formation of the correct follicular structures in skin tissue.

Activation of the Wnt pathway serves as an initiator in the hair growth cycle, and its dysregulation is strongly linked to follicle-associated diseases. The Wnt pathway typically maintains HFSCs in a quiescent state, and the specific activation of β-catenin results in new hair growth [104,105]. The activity of β-catenin in DPCs also regulates hair morphogenesis and regeneration [106–108]. Hair loss arises when the signaling of the HF is disturbed. Sufficient activation of the Wnt pathway in the HFSCs or DPCs can promote hair regeneration, which can be achieved through various means such as plant-derived chemicals [109,110], macrophage exocysts [111], or photobiomodulation therapy [112].

3.2. HH signaling pathway

The Hedgehog (HH) proteins are part of a small family of secreted signals, which include Indian Hedgehog (IHH), Desert Hedgehog (DHH), and Sonic Hedgehog (SHH). The classical HH signaling pathway has two scenarios [113] (Fig. 4b). In the absence of HH, the receptor patched (Ptch) inhibits the expression of the receptor smoothened (Smo). Gli binds to fused (SuFu) suppressor to form Gli repressor (GliR), suppressing the target genes' expression. In the presence of HH, Ptch binds to HH, relieving the inhibition of Smo, which leads to the dissociation of SuFu from Gli. This results in the formation of a Gli activator (GliA), which promotes the expression of target genes. Among the three types, the SHH pathway directly affects HF neogenesis and the hair cycle.

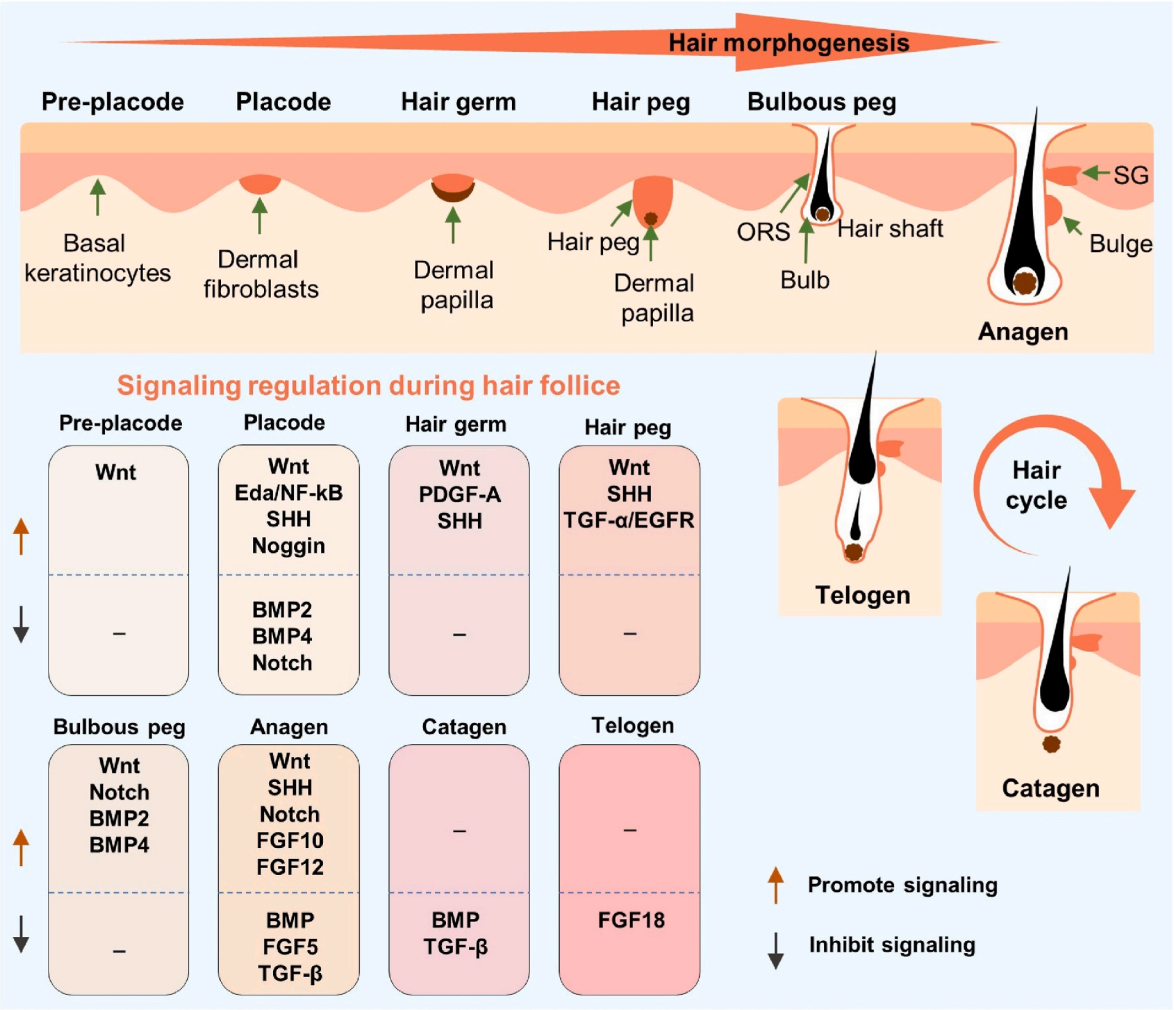

Fig. 3. Signals involved in HF morphogenesis and circulation. HF morphogenesis occurs through six stages with distinct signals. Placode formation is initiated by Wnt signals in the dermis, while Wnt/β-catenin, ectodysplasin (Eda)/NF-kB, sonic hedgehog (SHH), and noggin promote HF placode formation. Conversely, bone morphogenetic protein 2 (BMP2), bone morphogenetic protein 4 (BMP4), and Notch inhibit placode formation. Wnt/β-catenin facilitates dermal papilla formation, platelet-derived growth factor-A (PDGF-A), and SHH signaling. Subsequently, hair peg formation is promoted by Wnt/β-catenin, SHH, and transforming growth factor α/epidermal growth factor receptor (TGF-α/EGFR) signaling. Boundary formation of the HF involves Wnt/β-catenin, Notch, BMP2, and BMP4. During anagen, follicle formation is stimulated by Wnt/β-catenin, SHH, Notch, fibroblast growth factor 10 (FGF10), and fibroblast growth factor 12 (FGF12). The transition from anagen to catagen phase is induced by fibroblast growth factor 5 (FGF5), BMP, and transforming growth factor β (TGF-β). Finally, fibroblast growth factor 18 (FGF18) maintains the telogen phase and inhibits the transition of HFs into anagen.

The SHH signal is not an initiating factor for HF neogenesis but is involved in regulating HF development. During hair germ tissue neogenesis, the expression of SHH, Ptch, and Ptch2 is induced approximately six to tenfold [114]. When HF development is inhibited, these signals are also suppressed. Treatment of mice with SHH-blocking monoclonal antibodies during gestation resulted in abnormal follicular development and hair shaft deficiency in the offspring [115,116]. SHH and platelet-derived growth factor-A (PDGF-A) are vital signals for the precise formation of dermal papilla structures [117]. During wound repair, activation of SHH appropriately inhibits scar formation and promotes HF regeneration [118].

The SHH pathway maintains the HFSC population and regulates the hair cycle. During anagen, HFSCs generate transit-amplifying cells, producing SHH. SHH regulates HFSCs' proliferation and replenishes the stem cell ecological niche [28,119,120]. The dermal papilla triggers SHH expression in primed progenitor descendants. As the DP leaves the bulge, quiescent stem cells are briefly exposed to SHH, ensuring a short period of stem cell activation for regeneration [121]. Additionally, SHH can utilize the SHH-Noggin signaling loop and SCUBE3/Transforming growth factor β (TGF-β) mechanisms to regulate dermal papilla niche function [122,123]. Stimulating SHH activation is an effective method for promoting the regrowth of HF.

3.3. FGF signaling pathway

The fibroblast growth factor (FGF) family in mammals has over 20 members that influence organ development, wound repair, and angiogenesis by directly activating the FGF receptor. Currently known in HFs, FGF2, FGF9, FGF10, FGF12, and FGF20 promote hair growth, whereas FGF5 and FGF18 exert the opposite effect.

Multiple FGFs positively affect hair regeneration. For example, FGF2 can effectively increase the expression of versican and TGF-β2, two trichogen genes involved in hair follicle germs (HFGs) structure development, enhancing HF growth [82]. In a full-thickness wound healing model in mice, researchers found that FGF9, secreted by dermal γ-δ T cells that accumulated at the wound site, induced the expression of Wnt2 in dermal fibroblasts [124]. This activation of the Wnt pathway in dermal fibroblasts promotes hair regeneration. FGF10 enhances the proliferation and migration of outroot sheath (ORS) cells and DPCs by up-regulating β-catenin levels. Simultaneously, FGF10 antagonizes

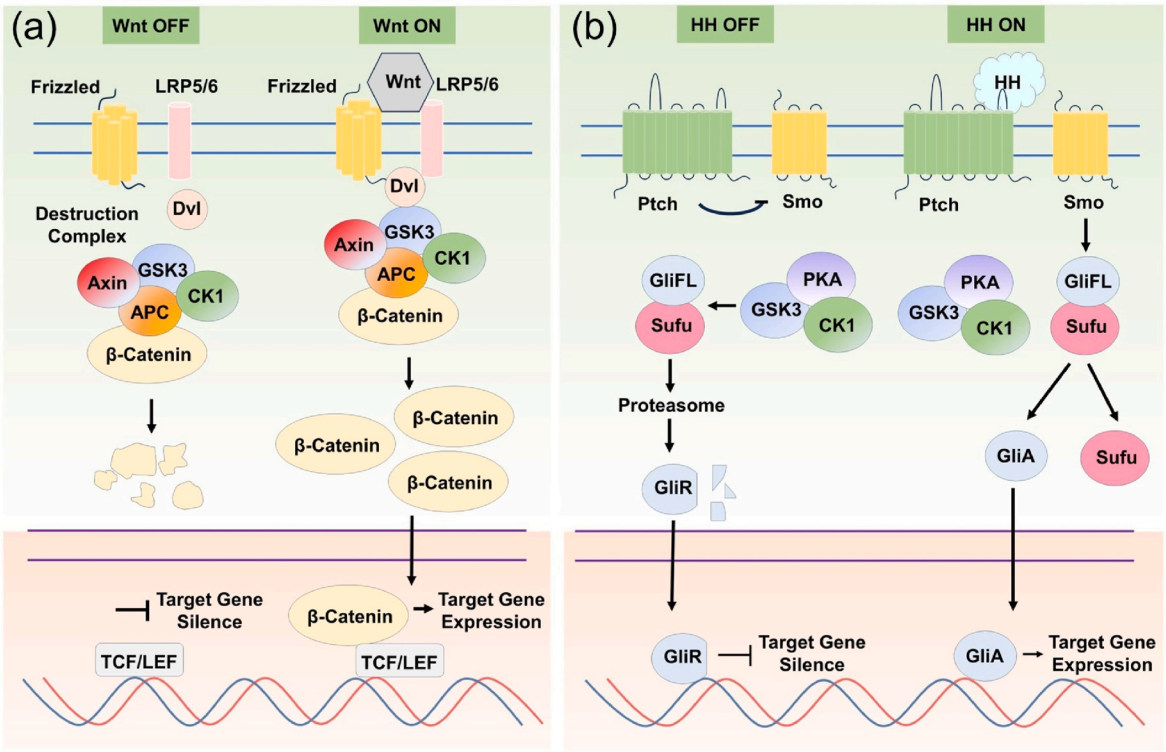

Fig. 4. Schematic depictions of the classic Wnt and Hedgehog (HH) signaling pathways. (a) The classic Wnt pathway. In the absence of Wnt, cellular β-catenin is targeted for degradation by a complex consisting of glycogen synthase 3 (GSK3), Axin, casein kinase 1 (CK1), and adenomatous polyposis coli tumor suppressor protein (APC), resulting in the silencing of targeted genes in the nucleus. In the presence of Wnt, the enzymatic complex fails, leading to the release of β-catenin. Subsequently, β-catenin translocates to the nucleus, where it interacts with the lymphoid enhancer factor/T cell factor (LEF/TCF) family, facilitating the normal transcription of the target genes. (b) The classic HH pathway. In the absence of HH (e.g., SHH), the Hh receptor Patch inhibits the smoothened (Smo) activity of protein kinases that includes protein kinase A (PKA), GSK3, and CK1. This inhibition leads to the cleavage of Gli into the truncated form GliR, acting as a deterrent to target gene expression. In the presence of HH, the HH ligand binds to Ptch and derepresses Smo. This action signals Sufu to release the Gli activator (GliA), which subsequently migrates to the nucleus and activates the expression of target genes.

secreted frizzled-related protein-1 (sFRP1), competitively regulating the β-catenin pathway and promoting follicular cycling [125]. Endogenous FGF12 is predominantly expressed in ORS cells during the anagen phase [126]. Elevated FGF12 levels enhance ORS cell migration and facilitate the transition of mice hair from the telogen to the anagen phase. FGF20 is involved in HF formation through its expression in the hair substrate during the initial stages of HF development [127,128]. It also can regulate the entire hair cycle and potentially induce hair growth.

FGF5 and FGF18 regulate the HF cycle by inhibiting hair growth. FGF5 is overexpressed in the late anagen phase, where it blocks the activation of DPCs and acts as a critical regulator in the HF cycle, promoting the transition from anagen to catagen [129,130]. FGF18 was overexpressed during the telogen phase and primarily regulates the HF cycle by sustaining the telogen phase and inhibiting the entry of HFs into anagen [129,131]. Inhibition of FGF5 can prolong the anagen phase, while inhibition of FGF18 promotes the transition of HFs from the telogen to the anagen phase [132]. In addition to FGF5, FGF18 and FGF13 are also involved in HF development and may play an inhibitory role. During morphogenesis in neonatal mice, the FGF13 protein was initially observed in the bulge region of the HF and keratin-forming cells of the basal lamina at 3 days postnatal [133]. Subsequently, FGF13 expression was mainly concentrated in the bulge region of the HF and peaked during the telogen phase of the mature HF [134].

3.4. NOTCH signaling pathway

The Notch signaling pathway is a highly conserved signal transduction mechanism evolution, mediating activating effects between neighboring cells [135,136] (Fig. 5a). In this pathway, the Notch ligand (Delta or Jagged) on the signal-sending cell binds to the Notch receptor on the signal-receiving cell. Subsequently, the receptor is cleaved by the γ-secretase complex located on the inner side of the cell membrane. This cleavage releases Notch protein fragments with transcriptional regulatory activity (NICD) into the nucleus. In the nucleus, NICD binds to other proteins (CBF-1/suppressor of hairless/Lag1 and mastermind-like) to regulate downstream target gene expression.

The Notch pathway promotes the differentiation of HFs, sebaceous glands, and the interfollicular epidermal spectrum during embryonic development, which is crucial in forming the boundaries of HFs [137–139]. Operating in the late stages of HF formation, the Notch pathway's activation accelerates the differentiation of HFSCs, thereby determining the fate of interfollicular cells [140,141]. Gradually decreasing the dose of Notch or in the absence of γ-secretase, the inner root sheath cells lose their fate maintenance capability [142,143]. At the end of the first growth phase, the epidermal differentiation program in the ORS cells is activated. As a result, the HF gradually transforms into an epidermal cyst, disintegrating the hair shaft structure and the inability to form a sebaceous gland. The presence of the Notch pathway is crucial for ensuring the correct differentiation of cells and forming a complete HF structure.

The Notch pathway usually interacts with other signals, contributing to HF formation. Specifically, the Notch pathway acts downstream of the Wnt/β-catenin pathway [144]. Blocking Notch or deleting Jag1 accelerates HF growth and differentiation, thereby preventing β-catenin from inducing neo-follicle formation. Skin-resident regulatory immune T cells localized in HFs express high levels of Jagged1, a member of the Notch ligand family. This promotes HF regeneration by enhancing HFSC proliferation and differentiation [145]. Additionally, the Notch pathway

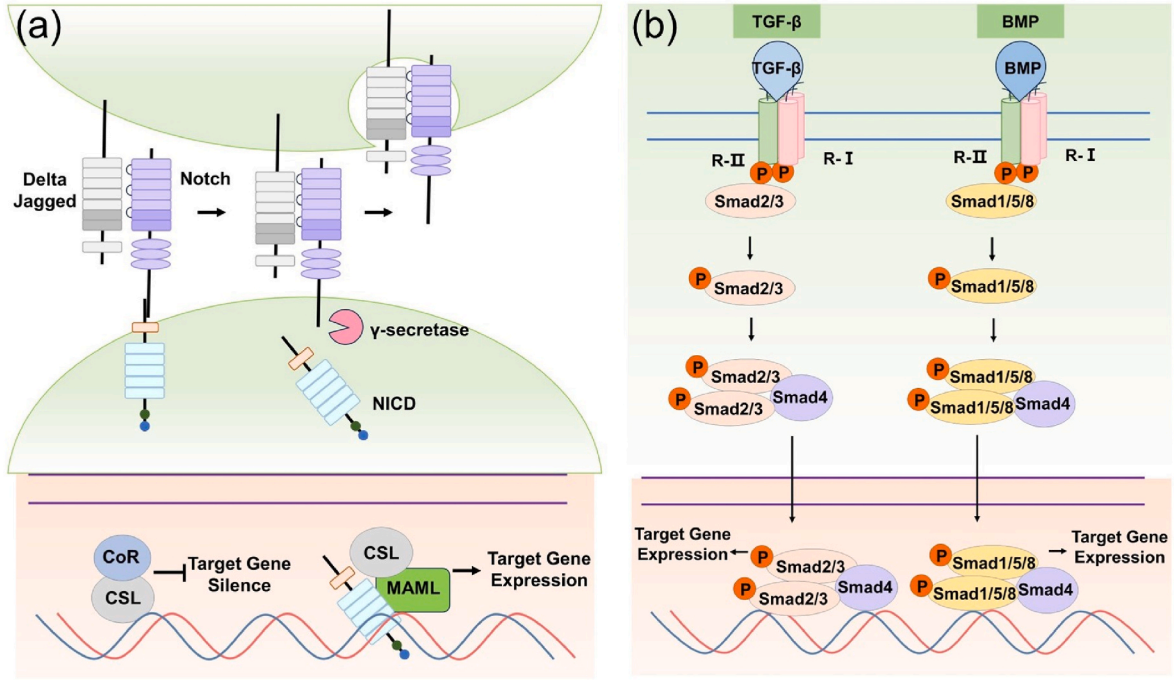

Fig. 5. Schematic depictions of the canonical Notch and transforming growth factor-β/bone morphogenetic protein (TGF-β/BMP) signaling pathways. (a) The Notch pathway. The receptor Notch binds to the ligand (Delta or Jagged) and then undergoes cleavage by the γ-secretase complex, releasing the active fragment of the Notch protein, NICD. NICD translocates to the nucleus and binds to the transcription factors CBF-1/suppressor of hairless/Lag1 (CSL) and mastermind-like (MAML) to regulate downstream gene expression. In the absence of NICD, the CSL co-inhibitor binds to silence target genes. (b) The TGF-β/BMP pathway. TGF-β or BMP binds to type I and II receptors, recruiting and phosphorylating downstream Smads (Smad2/3 in TGF-β, Smad1/5/8 in BMP). p-Smads form a trimeric complex with Smad4, which translocates to the nucleus to regulate the transcription of target genes.

maintains the development and stabilization of melanin stem cells and KCs, which enable environmental homeostasis around the HF [146, 147].

3.5. TGF-β/BMP signaling pathway

TGF-β superfamily consists of several subfamilies, including TGF-β, activins/inhibitors, growth and differentiation factors, and bone morphogenetic proteins (BMPs) [148]. This superfamily is involved in various events during epidermal/annexal development, with drosophila mothers against decapentaplegic proteins (smads) as the primary signal mediators from the membrane to the nucleus [149–151]. In the canonical TGF-β/BMP signaling pathway (Fig. 5b), upon ligand binding to its specific receptor complex, the type II receptor kinase is phosphorylated, activating the type I receptor kinase. The phosphorylated type I receptor then phosphorylates the R-Smads, forming a heterodimeric complex with Smad4. This complex translocates to the nucleus and regulates the expression of TGF-β target genes.

Deleting crucial proteins in the TGF-β/BMP pathway leads to structural and functional defects in HFs. For instance, in the absence of BMP receptor 1A activation, the differentiation of the inner root sheath is affected [152]. Moreover, deletion of the BMP receptor 1A gene leads to continuous activation of stem cells, resulting in HFSCs overactivation and niche expansion [153,154]. The loss of slow-cycling cells and the formation of tumor-like branches by follicular stem cells were observed. Smad4 knockout mice exhibit cutaneous follicular defects along with squamous cell carcinoma [155]. Noggin, acting as a negative regulator of the TGF-β superfamily and an antagonist of BMP, is typically expressed in the mesenchyme of HFs. The absence of Noggin expression delays neonatal follicle development and secondary follicle induction [156,157]. In contrast, in Noggin transgenic mice, HFs were formed but lacked hair shafts, suggesting that BMPs are pivotal in the genetic program controlling the differentiation of hair shafts in postnatal HFs [158]. Therefore, the TGF-β/BMP pathway can prevent the development of skin diseases caused by the failure to produce the correct follicular structure.

A competitive balance of endogenous BMP/Wnt signaling establishes a robust gene network that regulates the homeostasis of HFSCs activation and cycling [159–161]. The HF cycle initiates when the activation of Wnt in the HF surpasses the suppression of BMP. Notably, Wnt7b is a direct target of BMP signaling in HFSCs [162]. Competition between Wnt10b and Bmp6 regulates the activation of HFSCs, with their balance controlling the resting-anagen transition of the HF [163]. Secreted frizzled-related protein 1 (Sfrp1), acting as a Wnt antagonist, maintains tissue homeostasis in the HF through BMP-AKT-GSK3β signaling [164]. Additionally, Suzuki et al. [165] demonstrated that the SHH pathway is also involved in BMP/Wnt signaling dynamics as a downstream pathway of the Wnt pathway. Biological signals form a complex network and each stage of HF development results from the coordinated action of several biological signals.

HF cells develop and maintain the normal circulation of HFs under various positive and negative signals. In the hair loss area, there is an observed inhibition of positive regulatory signals for hair growth, promotion of negative regulatory signals, and disruption of the HF microenvironment. In our previous research, we developed a polydopamine-quercetin nanosystem that synergizes to restore the HF microenvironment and promote regeneration [12]. After treating the area of hair loss externally and restoring the function of the HFs, the hair returns to its normal growth cycle, and it could reach significant treatment when intervention begins in the early stages of hair loss. As hair loss progresses, damage to the HFs becomes irreparable. The limited quantity and non-renewability of HFs are currently the main challenges. Utilizing cells and matrix materials to fabricate HFs in vitro under the influence of biological signals represents a novel approach for future HF regeneration.

4. Materials-based hair follicle regeneration engineering

Advances in materials demonstrated great potential in therapeutics and regenerative medicine [166–169]. In hair follicle regeneration engineering, hair follicles can be generated in vivo exclusively by cells following transplantation. Simply implant the cultured and expanded human epidermal and dermal cells into the back wound of immunodeficient mice [170]. After approximately 12 weeks, distinct hair follicles can be observed. At present, the strategy for hair regeneration using cells without materials has been extensively studied. These researches involve investigating the combination of cell types capable of producing hair follicles and improving the hair induction ability of these cells through modifications in cell culture methods. In fact, during tissue repair, purely cellular strategies often face challenges in achieving efficient hair regeneration. Such typical studies currently highlight the positive effects of biomaterials on skin tissue engineering and hair regeneration [171–173]. The introduction of materials can play the function of inherent biological activity during hair regeneration. Moreover, the combination of materials and cells enhances the processability of the cells.

4.1. Extracellular matrix materials

The extracellular matrix, housing a complex network of numerous signaling molecules, is closely associated with cell division, differentiation, and intercellular information delivery. The main components of ECM in mammals are collagen, non-collagenous proteins, elastin, proteoglycans, and aminoglycans. The decellularized matrix (d-ECM) obtained by physically, chemically, or biologically removing cells from tissues serves as a promising scaffold biomaterial [174]. Girardeau-Hubert et al. [175] decellularized the pig skin by freeze-drying to produce dermal d-ECM and then processed it into a gel material for skin reconstruction (Fig. 6a). There is no denying that Matrigel is the most common 3D culture d-ECM used in current research, with its main component extracted from Engelbreth-Holm-Swarm mouse sarcomas.

Regeneration of bioengineered HFs necessitates providing seed cells with an extracellular environment akin to that in vivo. There seems to be a consensus to include Matrigel in the culture conditions of HF seed cells [35,176,177]. The addition of Matrigel enhanced the self-organization of EpSCs and MSCs, leading to improved activity and the formation of superior spatial structures compared to ultra-low attachment cultures [178–180]. Additionally, it preserved the hair-inducing capability of high-passage DPCs. Kageyama et al. [82] found that after 2 days of culture with Matrigel, EpSCs and MSCs form a specific spatial arrangement termed hair follicloids (Fig. 6b–c). After testing, approximately half of the gene expression related to ECM and adhesive proteins in the hair follicloids showed a significant increase (Fig. 6d–e). Havlickova et al. [181] formed another "folliculoid sandwich" system using DPCs, ORS keratinocytes, and Matrigel as a tool for testing in vitro. Matrigel not only promotes polymerization between cells but also enhances printability. When a mixture of EpSCs, SKPs, and Matrigel was printed directly onto the injured area, mice could completely heal their wounds, resulting in a structure similar to native skin [182].

Based on decellularized extracellular matrices have been developed for use in research of over 15 tissue types or organs [183]. Apart from Matrigel, other d-ECM may also become potential biomaterials for HF regeneration research. However, elucidating decellularized stromal components and in vivo biological safety still requires long-term basic research.

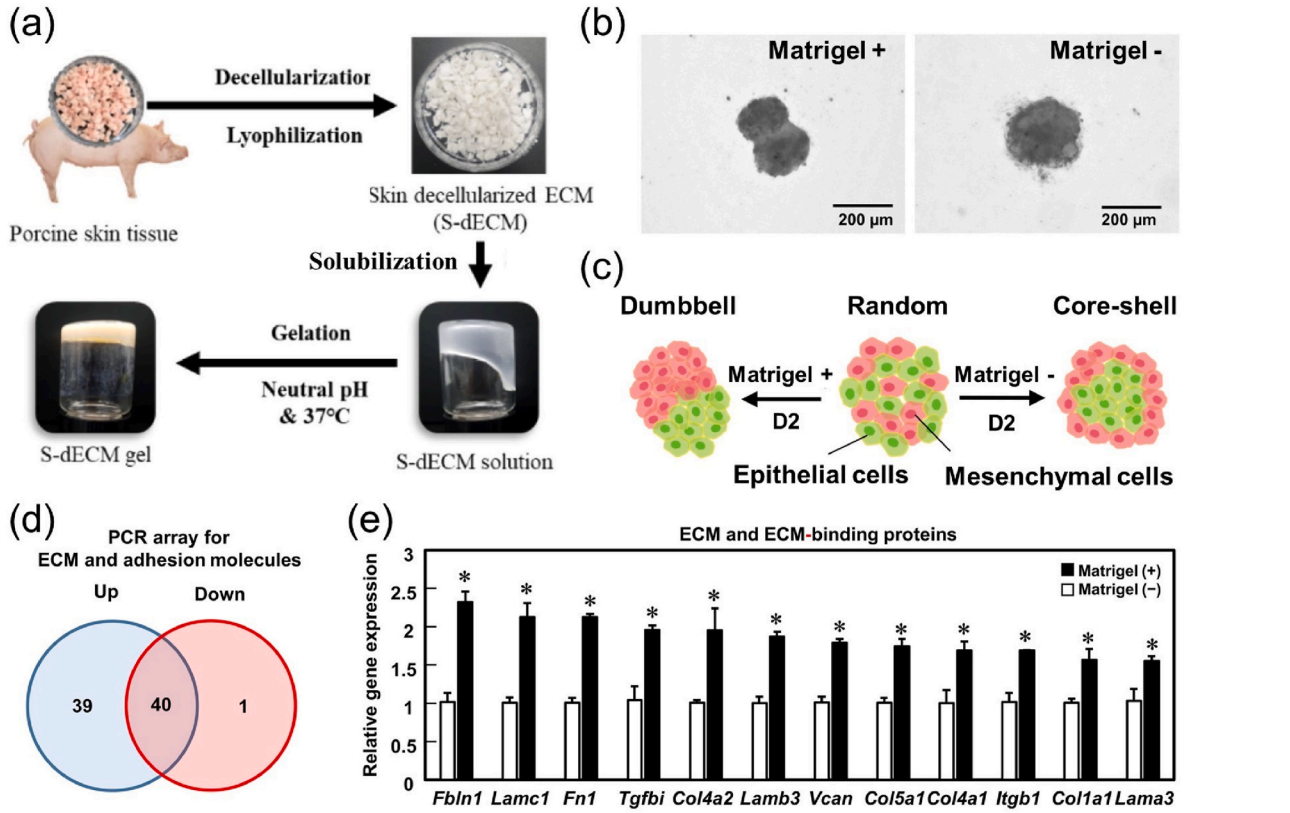

Fig. 6. Acquisition and application of decellularized matrix. (a) Process for the decellularization and solubilization of porcine skin extracellular matrix. Reproduced with permission [175]. Copyright 2022, Elsevier. (b) Localization of EpSCs and MSCs cultured with or without Matrigel supplementation after 2 days of culture. (c) Schematic of different structures formed by EpSCs and MSCs in the presence or absence of Matrigel. (d) In hair follicloids constructed from epithelial cells and mesenchymal cells, the number of genes up- and down-regulated due to Matrigel supplementation. (e) In hair follicloids, the changes in gene expression of ECM and ECM binding related proteins. (b–e) reproduced with permission [82]. Copyright 2022, The American Association for the Advancement of Science.

4.2. Natural polymers

Natural polymers, characterized by their biocompatibility and degradability, have garnered attention in tissue regeneration research. Polysaccharides and proteins are currently the most widely studied in tissue engineering of HFs [184,185]. The applications of various natural polymers for HF regeneration are listed in Table 1.

Various proteins from animal sources have positive effects on skin repair and hair follicular structure formation. Among them, collagen is the most abundant functional protein in animals and the main component of ECM. Abreu et al. [186] employed microscopy-guided laser ablation (MGLA) to fabricate a subcompartment in rat tail collagen I, which effectively guided the aggregation of DPCs and KCs to recreate follicular structures. Unlike this, Kageyama et al. [187] directly mixed collagen I with mouse embryonic MSCs or human DPCs to form dumbbell-shaped hair beads. When transplanted intradermally on the back of nude mice, these beads effectively generate HFs. The hydrogel derived from collagen I can mimic the natural ECM structure and interact with cells for more intricate designs. Zhang et al. [198] developed bilayer tissue-engineered skin substitutes (TESSs) by combining type I collagen with adult scalp progenitor cells and epidermal stem cells in vitro. This early double-layer TESS was transplanted onto the full-thickness skin wounds of nude mice, where hair follicle formation was observed after 8 weeks. Gelatin is a collagen hydrolysis product. Gupta et al. [173] prepared silk-gelatin (SG) by mixing gelatin and silk fibroin solution and crosslinking with tyrosinase. They used SG hydrogel to form DPC spheres as the 3D organoid model for drug screening. Silk fibroin has been extensively researched and utilized in the field of biomedicine because of its exceptional biocompatibility [199,200]. In addition, silk fibroin hydrogel containing MSCs has demonstrated the ability to facilitate scar-free skin healing and promote HF regeneration [188]. Chantre et al. [189] prepared another ECM protein Fn scaffold using rotary jet spinning. The structure of the Fn scaffold is similar to that of the native ECM (Fig. 7a). In animal models of wound repair, Fn demonstrates superior wound healing capabilities, and the morphology after repair closely resembles the natural skin (Fig. 7b). Fibrin hydrogel derived from human plasma is also being studied in cultivating HF seed cells. Fibrin microgels to encapsulate human DPC spheres have been found to enhance cell viability, restore cells' intrinsic properties, and induce epidermal invaginations [190]. Chen et al. [191] prepared fibrin-based hydrogels with SKPs to induce HF genesis. These hydrogels possess a porous structure that aids in preserving the stemness of SKPs in vitro and enhances the efficiency of HF induction in vivo (Fig. 7c–f).

Natural polysaccharides and their derivatives are a class of macromolecules with significant biological activities. Glycosaminoglycans are primarily found in animal connective tissues. Fernandez-Martos et al. [192] reported that glycosaminoglycan hydrogel can promote the survival of isolated human HFs, resulting in a highly proliferative phenotype in both the hair bulb and supra bulbar regions. Hyaluronic acid (HA) and chondroitin sulfate are both types of glycosaminoglycans. HA can stimulate the proliferation of DPCs and promote the formation of a more extensive hair germ model [193]. Similarly, chondroitin sulfate disaccharides and L-mannose promote the proliferation of dermal fibroblasts and DPCs by mediating the Wnt signaling pathway and inducing the cellular production of ECM molecules such as collagen and elastin [194]. Unlike glycosaminoglycans, sodium alginate is a natural polysaccharide extracted from algae. The lyophilization scaffold composed of silk fibroin and sodium alginate demonstrated excellent cytocompatibility and retained the ability to induce HF differentiation [195,201]. In the wound repair model, this scaffold facilitated the regeneration of HF structures. Lim et al. [196] developed a fibrous hydrogel scaffold using sodium alginate combined with chitin. DPCs and KC self-assemble in this scaffold, forming a structure similar to that of the native hair bulb. Sodium alginate is a negatively charged polymer.

Table 1
Summary of natural polymer applications in hair follicle engineering.

Material	Concentration	Form	Cell type	Spheres size/cell number	Applications	Ref
Rat tail collagen I	0.03 mg/mL	Hydrogel 3D microchannel	Human DPCs, Human KCs	258.5 ± 2.5 μm	Build a skin model bearing folliculoid structures.	[186]
Collagen type I-A	2.4 mg/mL	Solution	Mouse EpSCs, Mouse MSCs, Human DPCs	10×10^3 cells/bead	Hair generation assays in nude mouse back transplantation.	[187]
Silk fibroin/Gelatin	5 wt%	Hydrogel	Human DPCs, Human KCs, Human HFSCs	5×10^3 cells each	Modulation of the DP spheroids model toward the development of the HF organoid.	[173]
Silk fibroin	2 wt%	Hydrogel	Mouse MSCs	–	Silk material system for scarless skin regeneration with HFs.	[188]
Human ECM protein fibronectin	20 mg/mL	Nanofiber	–	–	Nanofibers restore dermal papilla and recruit basal epithelial cells in full-thickness wound repair.	[189]
Fibrin from human blood	2.4 mg/mL	Microgel	Human DPCs	280 μm	The fibrin microgels system induces epidermal invaginations while culturing DP spheroids.	[190]
Fibrinogen	40 mg/mL	Hydrogel	Mouse EpSCs, Mouse SKPs	–	Fibrinogen hydrogel-loaded cells in nude mouse wounds HF reconstruction.	[191]
Glycosaminoglycans	0.225 mg/mL	Hydrogel	–	–	Promoting the maintenance of a highly proliferative phenotype in the hair bulb and supra bulbar regions.	[192]
Hyaluronic acid	0.05 mg/cm^2	–	Human DPCs, Human LFs, Human KCs	3.5×10^3 cells each	Build a hair germ-like organoid for HF biology research.	[193]
L-fucose, chondroitin sulfate disaccharide	–	Solution	HDFa, iDPCs	–	These support and promote the proliferation of dermal fibroblasts and DPCs.	[194]
Silk fibroin/Sodium alginate	2 wt %	Lyophilisation scaffold	Human UC-MSCs	–	Scaffold delivered hUC-MSCs to enhance skin scarless healing and HF regeneration.	[195]
Chitin/Sodium alginate	10 mg/mL	Hydrogel	Human DPCs, NHEK	~100 μm	Scaffold delivered hDPCs, and NHEK a suitable model for studying HF interactions, with possible application for in vitro drug testing assays.	[196]
$(Gelatin)_2$/Alginate	0.1 wt %	Solution	Mouse DPCs, Mouse EpSCs	mDPCs: 1×10^6 cells, mEpSCs: 5×10^5 cells	LBL nano-coating with $(Gelatin)_2$/Alginate on the cell surface included FGF-2 for spot-by-spot HF regeneration.	[197]

Abbreviations: hLFs: human lung fibroblasts; HDFa: human dermal fibroblasts cell line; iDPCs: immortalized human dermal papilla cells; hUC-MSCs: human umbilical mesenchymal stem cells; NHEK: normal human epidermal keratinocytes.

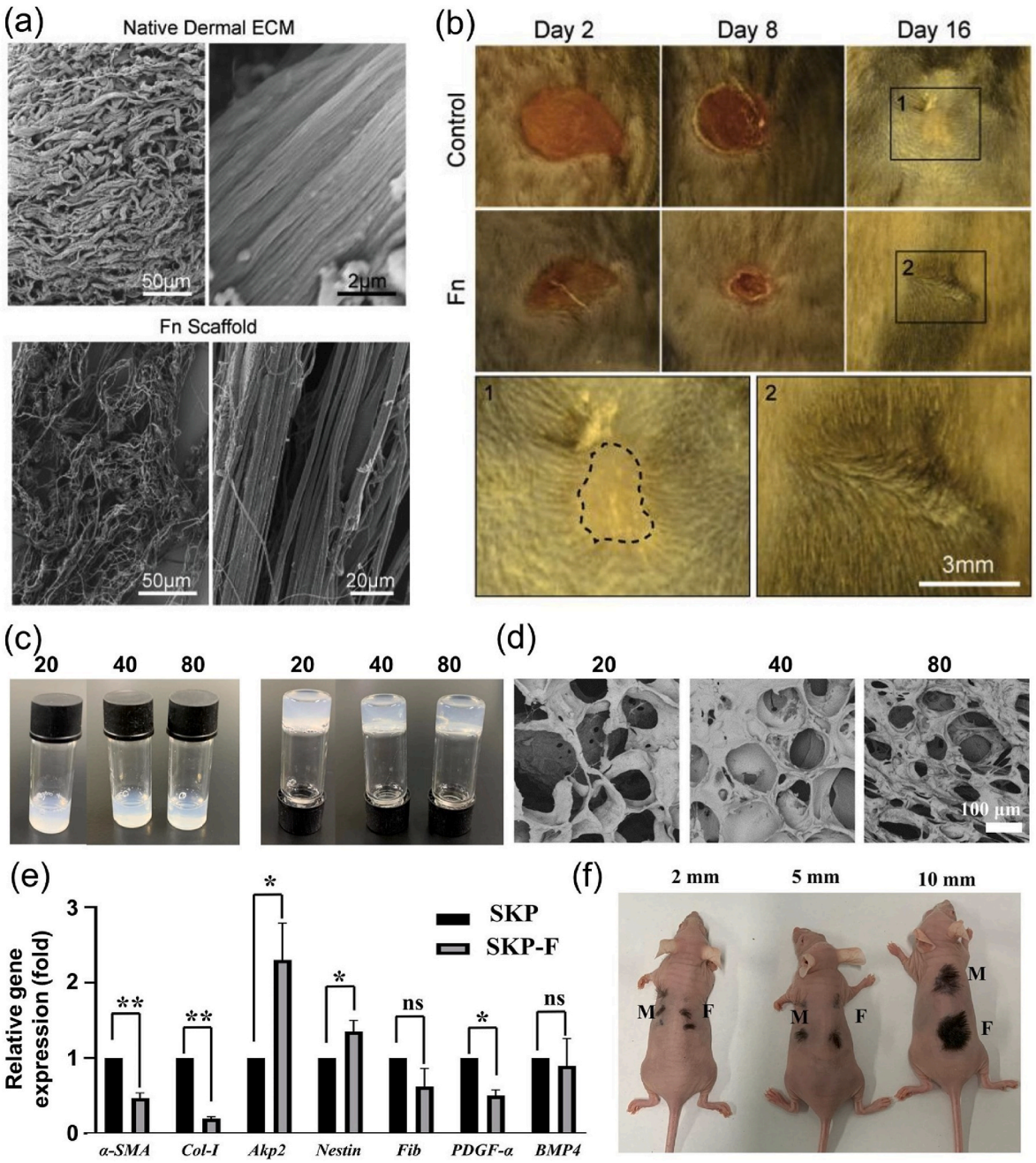

Fig. 7. Natural polymer applications in skin repair and HF regeneration. (a) SEM images of the native dermal ECM and fibronectin (Fn) scaffolds. (b) Representative images of the untreated group (Control) and Fn nanofiber-treated group on days 2, 8, and 16 in wound repair experiments. The insets below are shown in the enlarged image, showing that the FN treatment group has a better wound healing effect (highlighted with the dashed line). (a–b) reproduced with permission [189]. Copyright 2018, Elsevier. (c) Gross appearance of fibrin solution (left) and hydrogel (right) at concentrations of 20, 40, and 80 mg/mL (d) SEM images of fibrin hydrogels at concentrations of 20, 40, and 80 mg/mL. (e) Real-time PCR analysis of SKPs cultured with fibrin hydrogels for 3 days and the expression of HF induction-associated genes. (f) Representative back images of nude mice after 4 weeks of transplantation. (c–f) reproduced with permission [191]. Copyright 2022, The Authors.

Lin et al. [197] loaded sodium alginate and positively charged gelatin layer-by-layer (LBL), forming nano-scale ECM on the surface of DPCs. It has been found that LBL packaging does not damage cell viability and biological characteristics, which can further effectively encapsulate active ingredients.

4.3. Synthetic polymers

Synthetic polymers refer to materials obtained through polymerization reactions of monomers. Several synthetic polymers show promising applications in promoting the culture of HF cells and regeneration of HFs, including polyethylene glycol diacrylate (PEGDA), gelatin methacryloyl (GelMA), polyvinyl alcohol (PVA), and their derivatives. The synthetic polymers used in HF fabrication and regeneration are detailed in Table 2.

PEGDA is a polyethylene glycol derivative with adjustable mechanical properties. Pan et al. [212] fabricated hydrogel microwells using PEGDA with center islets using soft lithography. The PEGDA microwells had different compartments to culture dermal and epithelial cells separately. These microwells can support cell proliferation and cell

Table 2
Summary of synthetic polymer applications in hair follicle engineering.

Material	Form	Pore size	Mechanical property	Cell type	Spheres size/cell number	Applications	Ref
PEGDA	Microgel array	–		Human DPCs, HaCaT, HDFs	hDPCs: 36×10^4 cells, HaCaT& HDFs: 72×10^4 cells	PEGDA microgel array constructs cell spheres to probe cellular interactions.	[202]
GelMA	Hydrogel bio-ink	–	–	SKPs, Mouse EpSCs,	–	In situ, bioprinting of GelMA hydrogels containing EpSCs and SKPs onto skin wounds showed complete wound healing and functional tissue skin regeneration.	[203]
GelMA/ HAMA	Hydrogel bio-ink	118.40 ± 12.32 μm	Young's modulus: 15.72 ± 3.9 kPa	HDFs, Human DPCs, HaCaT	–	3D-printed skin equivalents containing HF structures and epidermal/papillary dermis were fabricated using GelMA/HAMA bioink.	[204]
GelMA/Nano-cellulose	Hydrogel bio-ink	Dermis: 76.98 ± 2.26 μm basal: 31.44 ± 2.09 μm	Compressive modulus: 16.4 ± 0.9 kPa-73.0 ± 10.6 kPa	HaCaT, HDFs	–	Heterogeneous tissue-engineered skin repaired wounds with HFs and early dentate ridge structures.	[205]
GelMA-Zn/Si	Hydrogel bio-ink	~100 μm	–	HaCaT, HUVECs	–	GelMA-zinc/silicon-printed hydrogel bioprint in situ for treating excisional wounds with HF regeneration.	[206]
GelMA/ Catechol-grafted HA	Core-shell microsphere	–	–	Mouse MSCs, Mouse EpSCs,	~217.5 μm	G/HAD microspheres are capable of HFs generation upon transplantation into the dorsal dermis of nude mice.	[21]
Chitosan/ PVA	Nanofiber sponge	21−25 μm	–	Mouse DPCs, Mouse EpSCs	1×10^7 cells each	DPC spheres formed on Chitosan/PVA nanofiber sponge are HF-inducible under the skin of nude mice.	[207]
PVA	Surface coating	–	–	Human DPCs, Rat DPCs	0.5×10^4-5×10^4 cells	Aggregates formed by cell inoculation in PVA-coated well plates induce HF neogenesis subcutaneously in nude mice.	[208]
EVAL	Membrane	–	–	Rat DPCs	125–150 μm	EVAL membranes facilitate DP self-assembly into many compact spheroidal microtissues that can induce new HFs.	[209]
EVAL/ECM protein	Membrane	–	–	Rat DPCs	–	DPC spheres are formed on EVAL or fibronectin-coated EVAL membranes.	[210]
EVAL	Membrane	–	–	Rat DPCs Rat KCs	50–200 μm	A method for high-throughput generation of organoid hybrid microtissues by biomaterial-facilitated self-assembly.	[211]

survival for up to 14 days. On this foundation, Justin et al. [213] investigated the effect of PEDGA microwell matrix hardness on the aggregation of DPCs. DPC spheres exhibit higher expression of HF markers on soft matrices than on stiff matrices. Compared with two-dimensional cell models and individual types of cell spheres, 3D cell spheres formed by multiple HF-related cells can better simulate real HF situations. Therefore, Tan et al. [202] sequentially inoculated DPCs, HDFs, and HaCaT into PEDGA microwells for cultivation. DP-HaCaT forms a core-shell structure, where DPCs gather in the core, and HDFs polarize and migrate out of the DP-HaCaT region (Fig. 8a–b). PEGDA micropores can facilitate the formation of diverse HF cell spheres, enhancing the efficiency of standardized cell sphere production.

GelMA is a polymer material extensively employed in tissue regeneration that can be cured into a gel through photocrosslinking with the aid of a photoinitiator. GelMA has been used in research to construct various 3D skin models because of its adjustable mechanical properties and printability [214–216]. As a high-performance bioink, GelMA hydrogels containing EpSCs and SKPs in situ bioprinting for skin wound repair have showcased complex skin regeneration, encompassing the epidermis, dermis, blood vessels, HFs, and sebaceous glands [203]. Different from in-situ printing, Kang et al. [204] created 3D-printed skin equivalents in vitro using GelMA/hyaluronic acid methacrylate (HAMA) bioink (Fig. 8c–d). The skin equivalents had a remarkable microporous structure, which is suitable for cell adhesion and growth (Fig. 8-e). After testing, the cells carried in the skin equivalent exhibit good cell viability (Fig. 8f–g), demonstrating its potential as a model for skin tissue engineering and HF regeneration. Moreover, the introduction of nanoparticles into GelMA to augment hydrogel properties and facilitate HF neogenesis was observed in a skin damage model [205,206]. In addition to 3D printing, GelMA can be combined with microfluidics to prepare cells-loaded microspheres [21].

PVA and its derivative, ethylene vinyl alcohol (EVAL), exhibit low cell adhesion. Therefore, the nanofibers and membrane coating prepared from these materials can effectively promote the formation of HF cell spheres. Zhang et al. [207] prepared a chitosan/PVA nanofiber sponge for HFs regeneration (Fig. 8h–i). After three days of cultivation, the formation of cell spheres in 3D nanofiber sponges resulted in a larger microstructure size than in 2D nanofiber membranes (Fig. 8j). In animal experiments, nanofiber sponges loaded with cell spheres demonstrated effective hair induction efficiency. When cells were inoculated in PVA-coated well plates, DPCs swiftly aggregated into individual spheres [208]. Similarly, membrane materials derived from EVAL facilitated the self-assembly of DPCs into spherical microstructures measuring 125–150 μm, which also could induce new HFs [209]. However, it was found in the experiment that cell growth was slower, and cell loss was more significant after cell inoculation in EVAL. Young et al. [210] selected multiple ECM components and found that FN-coated EVAL can enhance cell aggregation and keep cells highly mobile. Considering the diversity of cells in HFs, single-cell types of cell spheres cannot reproduce the structure of HFs. Yen et al. [211] used DPCs and KCs to establish folliculoid microtissues on EVAL surfaces and explored the potential tissue formations of heterologous cells. The aggregation exhibited a core-shell structure, with DPCs located at the center, and high expression of DPCs characteristic genes was detected.

5. Novel engineered strategy for hair follicle engineering

The close arrangement of cells within tissues is essential for

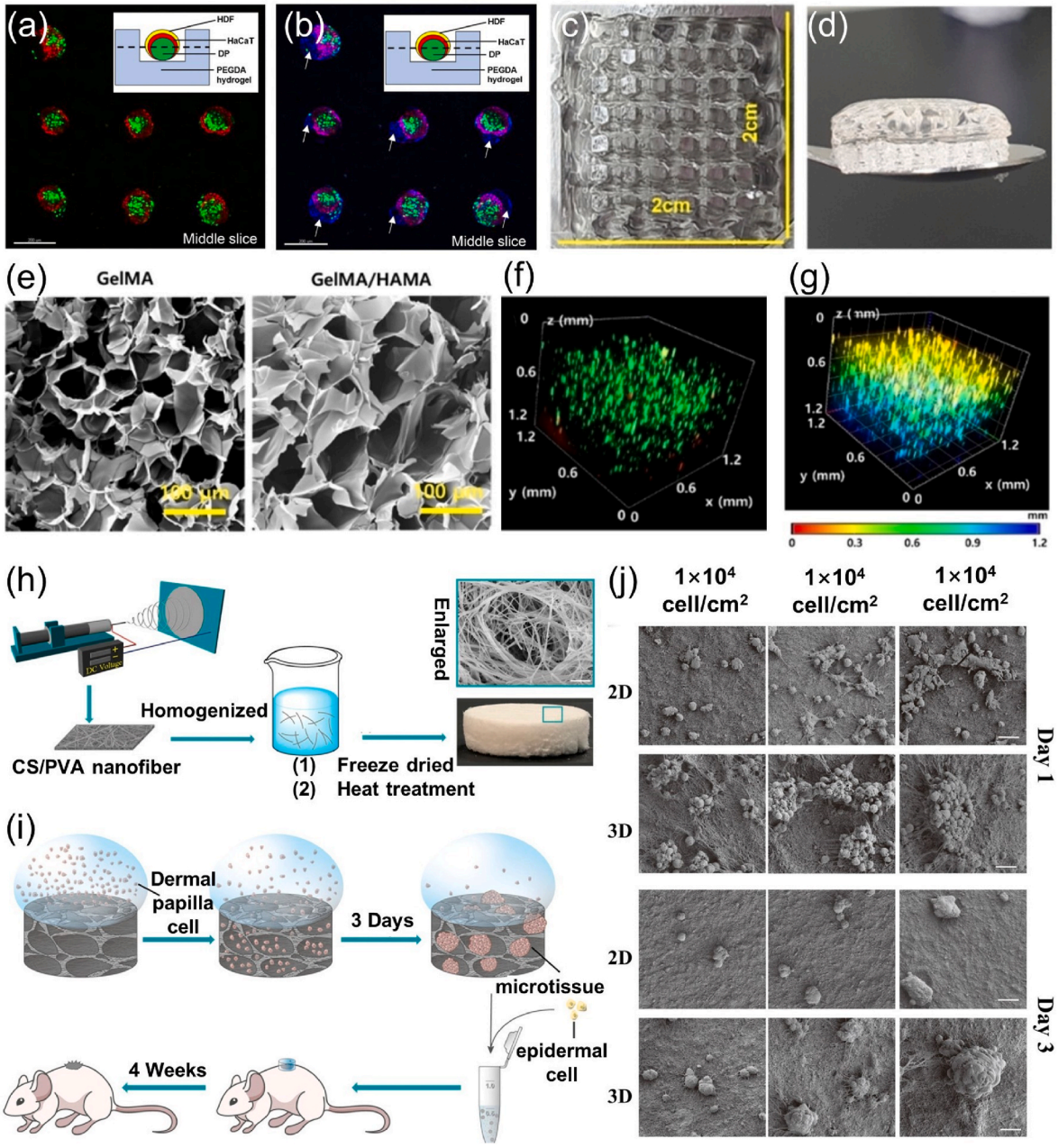

Fig. 8. Synthetic polymer applications in HF regeneration. (a) The confocal image of RFP-expressing HaCaT surrounding GFP-expressing DP in the middle slice. Scale bar: 200 μm. (b) The confocal image of 3D tri-cultured aggregates. The white arrows indicate the position of HDFs that have polarized and migrated around with DP-HaCaT aggregates in the middle slice. Scale bar: 200 μm. (a–b) reproduced with permission [202]. Copyright 2019, The Authors. (c–d) Digital images of the 3D printed dermis. (c) Top and (d) lateral views of the 3D printed skin equivalent. (e) Scanning electron microscopy (SEM) images of cryo-sectioned GelMA and GelMA/HAMA. (f) 3D projection of the live/dead assay in skin equivalent. (g) Depth coding of the live cell signal in skin equivalent. (c–g) reproduced with permission [204]. Copyright 2022, Wiley-VCH GmbH. (h) Preparation process of the Chitosan/PVA nanofiber sponge. Scale bar: 5 μm. (i) After 3 days of culture, DP microtissues can form within the internal structure of the nanofiber sponge. DP microtissues were mixed with epidermal cells and transplanted into the back of nude mice. After 4 weeks, HFs can be observed to regenerate. (j) SEM images of the cell morphological change in the 2D and 3D after 1 and 3 days of culture. Scale bar: 25 μm. (h–j) reproduced with permission [207]. Copyright 2020, American Chemical Society.

facilitating intricate interactions among cells and the ECM. Moreover, the functions of HF development, perception, and participation in skin regulation cannot be achieved by a single cell type. When attempting to replicate the structure and function of HFs, we endeavored to combine seed cells into a functional microstructure using various methods. Here, we introduce three commonly used methods for preparing HF microstructures in current research: cellular self-assembly, microfluidics, and 3D printing.

5.1. Cellular self-assembly

Under low adsorption culture conditions, DPCs can self-assemble to form cell spheres. Compared to DPCs cultured in 2D, DPC spheres more closely mimic the in vivo environment and demonstrate a partial restoration of hair-inducing properties [58,217–219]. DPC spheres can be used as an in vitro model for drug screening and mechanism research [220]. It is challenging for cells and cell spheres to develop a complete hair follicle structure in vitro. Subcutaneously injecting cells into nude mice for the patch assay can effectively validate their hair induction

capability [221]. Furthermore, Lin et al. [18] induce high-passage DPC spheroid formation in 3D hanging-drop array plates (Fig. 9a). Compared with 2D culture, the expression of hair-induced biomarkers is significantly increased in 3D cell spheres. Significant hair neogenesis was observed by implanting DP microtissues and newborn mouse EpSCs subcutaneously in nude mice.

Due to a single type of cell not providing the EMI required for hair regeneration, the efficiency of HF formation is lower when DPC spheres transfer to subcutaneous tissue. To address this limitation, DPCs and KCs are combined to form 3D KC-DPC spheres [2]. Further, Fukuyama et al. [177] assembled DPC spheres and KCs into a cylindrical structure with a guiding nylon wire. After two weeks of cultivation, they obtained a

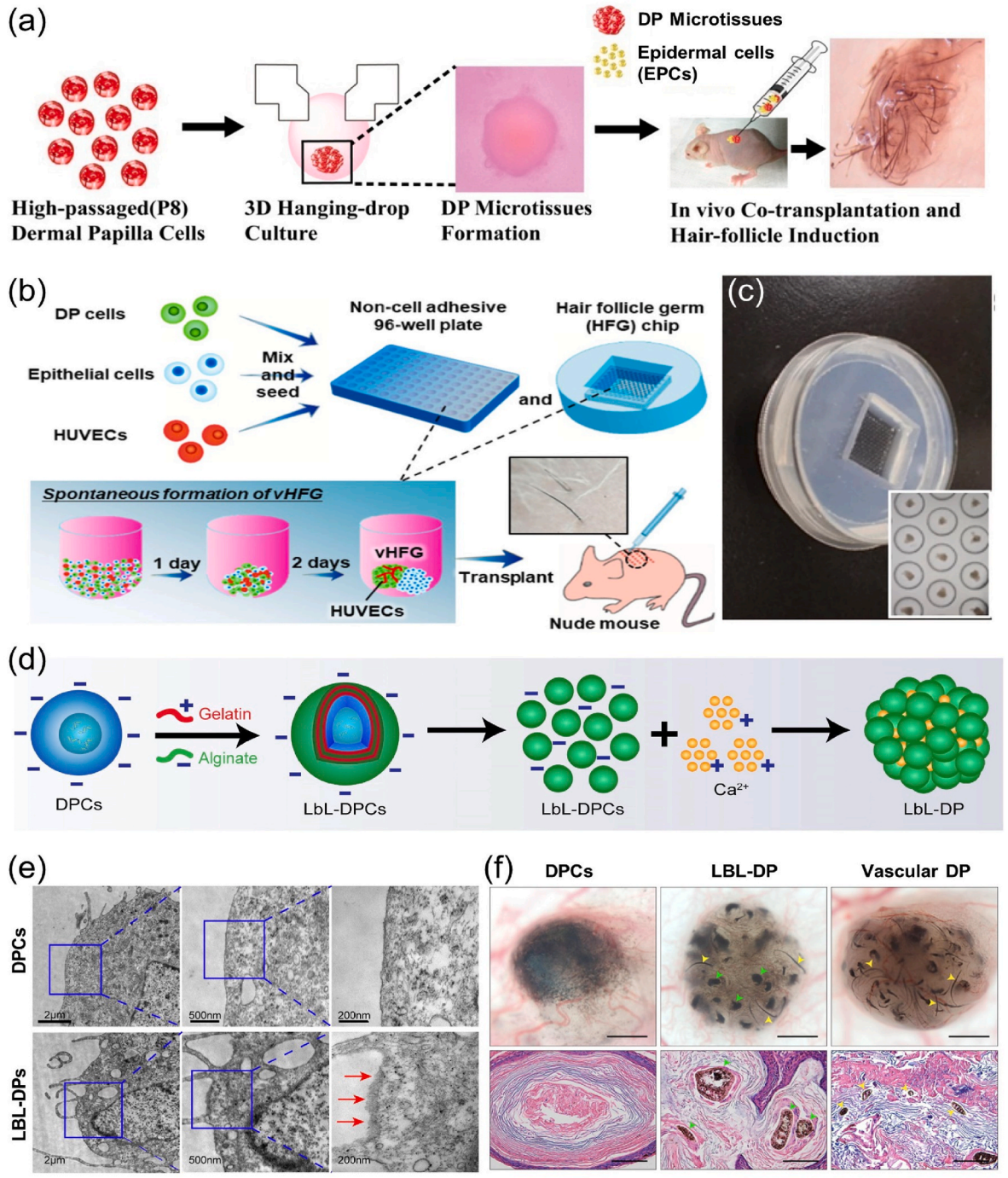

Fig. 9. Fabrication of self-assembled spheres of HF cells. (a) Formation of microtissues from highly passaged DPC cells using the hanging-drop approach. Reproduced with permission [18]. Copyright 2016, American Chemical Society. (b) Preparation of vHFGs using DPCs, epithelial cells, and HUVECs after 2 days of self-organization using HFG chip. Transplanting vHFGs to the back of nude mice can achieve hair regeneration. (c) Digital image of HFG chip. The inset shows cultured vHFGs in microwells. (b–c) reproduced with permission [19]. Copyright 2021, The Authors. (d) Schematic illustration of LBL-DP preparation. DPCs coated with gelatin (red) and alginate (green), and then LBL-DPCs were crosslinked with calcium ions to prepare LBL-DP. (e) TEM images of DPCs and LBL-DPs. Red arrows indicate the nano-scale ultrathin ECM. (f) Subcutaneous images and HE staining of transplant sites after three weeks post-injection. There is no hair regeneration in the DPCs group; in contrast, green arrows indicate LBL-DP can induce a large number of HF-like structures, and yellow arrows indicate numerous de novo hairs were generated in vascular DP. Scale bars: 100 μm (HE images) and 500 μm (stereoscopic images). (d–f) reproduced with permission [222]. Copyright 2022, The Authors.

structure resembling natural HFs. The involvement of DPCs is not essential for constructing HFs in vitro, as other cell combinations can also induce HF regeneration. According to the research conducted by Su et al. [95], hair follicle-like organoids were formed when scalp-derived dermal progenitor cells were combined with foreskin-derived epidermal stem cells in a 2:1 ratio. Moreover, in vivo transplantation experiments have confirmed its potential for inducing hair growth. Kageyama et al. [223] developed a method for the large-scale in vitro preparation of HFGs using mouse EpSCs and MSCs self-organization. These HFGs efficiently generated HFs when transplanted intradermally onto the backs of nude mice. Using similar approaches, Kageyama et al. [19] added HUVECs to DPCs and mouse EpSCs to form HFGs in the HFG chip (Fig. 9b–c). HUVECs, DPCs, and EpSCs spontaneously form dumbbell-shaped HFGs from homogeneous aggregates after cultivation, with HUVECs located in the papillary area. After testing, HFGs containing HUVECs showed a higher expression of hair marker-related genes. Additionally, significantly increased levels of hair regeneration were observed when transplanted subcutaneously into nude mice.

The absence of cellular matrix involvement in cellular self-assembly can impact the efficiency of HF induction. LBL nanocoating technology involves coating sodium alginate and gelatin layer by layer on the surface of cells under the action of charges and cross-linking with calcium ions. This process utilizes biomaterials to mimic ECM components, creating a nano-scale ultrathin ECM. DPC spheres formed using LBL-DPCs are implanted subcutaneously with EpSCs in nude mice, forming HFs renew [224]. Furthermore, Chen et al. [222] co-cultured LBL-DPCs with LBL-coated HUVECs to construct vascularized DP spheroids similarly, resulting in a threefold increase in hair induction efficiency (Fig. 9d-f).

5.2. Microfluidic technology

Microfluidics, a fabrication technology at the microscale, allows for the creation of precise microscale structures and biomimetic microenvironments for engineered tissues [225]. Microfluidics has been applied in skin simulation, HF culture, and the basic unit construction of HFs [226–228]. Especially, microfluidic technology can combine seed cells and matrix materials, making it a promising tool for the standardized preparation of HF precursors.

Traditional 2D cultivation is far from the real in vivo environment, and microfluidic technology offers flexible design capabilities, enabling the construction of in vitro models that closely mimic the in vivo environment for experimental research. For instance, Ahn et al. [229] developed a three-dimensional innervated epidermal keratinocyte layer as a co-culture model for sensory neurons and epidermal KCs on a microfluidic chip. Especially in the cultivation of HFs, Atac et al. [230]

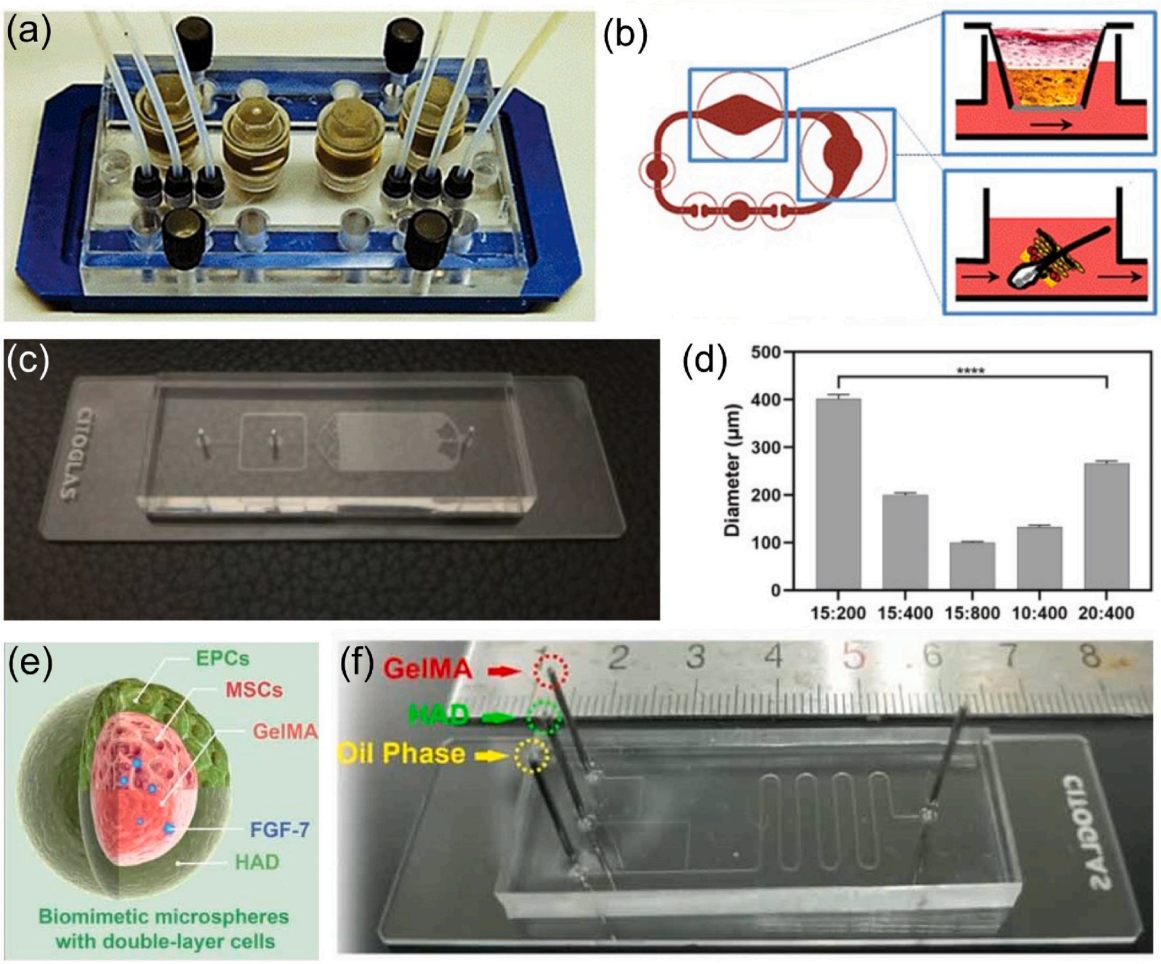

Fig. 10. Applications of microfluidics in hair culture and cell spheres preparation. (a) Digital image of multi-organ-chip with built-in micropumps to provide a pulsatile flow of the medium. (b) Schematic diagram of labeled areas for culturing in vitro skin models, ex vitro skin, and hair follicular units in transwells. (a–b) reproduced with permission [230]. Copyright 2013, Royal Society of Chemistry. (c) Digital image of the T-junction microfluidic chip. (d) The diameters of IGMs vary with the oil and aqueous phase flow rates (Flow rate of aqueous phase: flow rate of oil phase). (c–d) reproduced with permission [20]. Copyright 2022, The Authors. (e) The GelMA/HAD microspheres encapsulate MSCs and EPCs using the microfluidic method. (f) Picture of the microfluidic chip. (e–f) reproduced with permission [21]. Copyright 2009, IOP Publishing.

described a dynamic microfluidic perfusion bioreactor platform (Fig. 10a). The multi-organic chip with a micro pump pumps flow culture medium to achieve in vitro HF cultivation in transwell (Fig. 10b). Besides microfluidic chips, microfluidic air-jet spinning technology can fabricate large-area, high-strength nanofiber artificial skin, facilitating HF regeneration during wound repair [231]. The high efficiency, integrated miniaturization, and automation capabilities of microfluidics are well-aligned with the requirements of HF engineering.

Microfluidics is a potential tool for fabricating basic units with integrated and high-throughput features. Ji et al. [232] prepared artificial HF seeding microspheres containing tideglusib and tamibarotene, which can convert fibroblasts into cells with DPC fate. This type of microsphere can promote in situ HF regeneration while enhancing wound repair. In addition to drug-loaded microspheres, microfluidic technology can also be used for high-throughput preparation of microspheres containing cells. Zhang et al. [20] prepared GelMA/chitosan microcarriers (IGMs) loaded with PRP and inoculated with DPCs on high-throughput microfluidic microarrays to efficiently induce the production of HFs. They explored the production of IGMs with various diameters by adjusting water and oil flow rates using microfluidic chips (Fig. 10c–d). Even when loaded with PRP, the induction efficiency of HFs in microspheres containing single-cell types is still not high. Huang et al. [21] prepared core-shell microspheres containing multiple cell types using microfluidic-assisted technology for HF regeneration (Fig. 10e–f). The future direction of microfluidics is moving towards modularity and deep integration with other technologies, presenting novel opportunities for engineered HF.

5.3. 3D printing technology

3D printing is an emerging technology in recent years that constructs objects by adding materials layer by layer, also known as additive manufacturing. 3D printing in the medical field can be divided into biological 3D printing and non-biological 3D printing based on the presence of biological components. 3D bioprinting, which enables the printing of bio-inks loaded with seed cells in specific shapes and structures, represents one of the most promising emerging technologies for the in vitro production of engineered HFs. Selecting bio-inks suitable for cell growth is crucial in 3D bioprinting to create an adjustable microenvironment [233,234]. This technology offers advantages in both skin repair and hair regeneration [235–237].

3D bioprinting can be used to construct regenerative tissues in situ on wounds or manufacture scaffold materials that carry cells for hair regeneration at wound repair sites. Chen et al. [238] mixed EpSCs, SKPs,

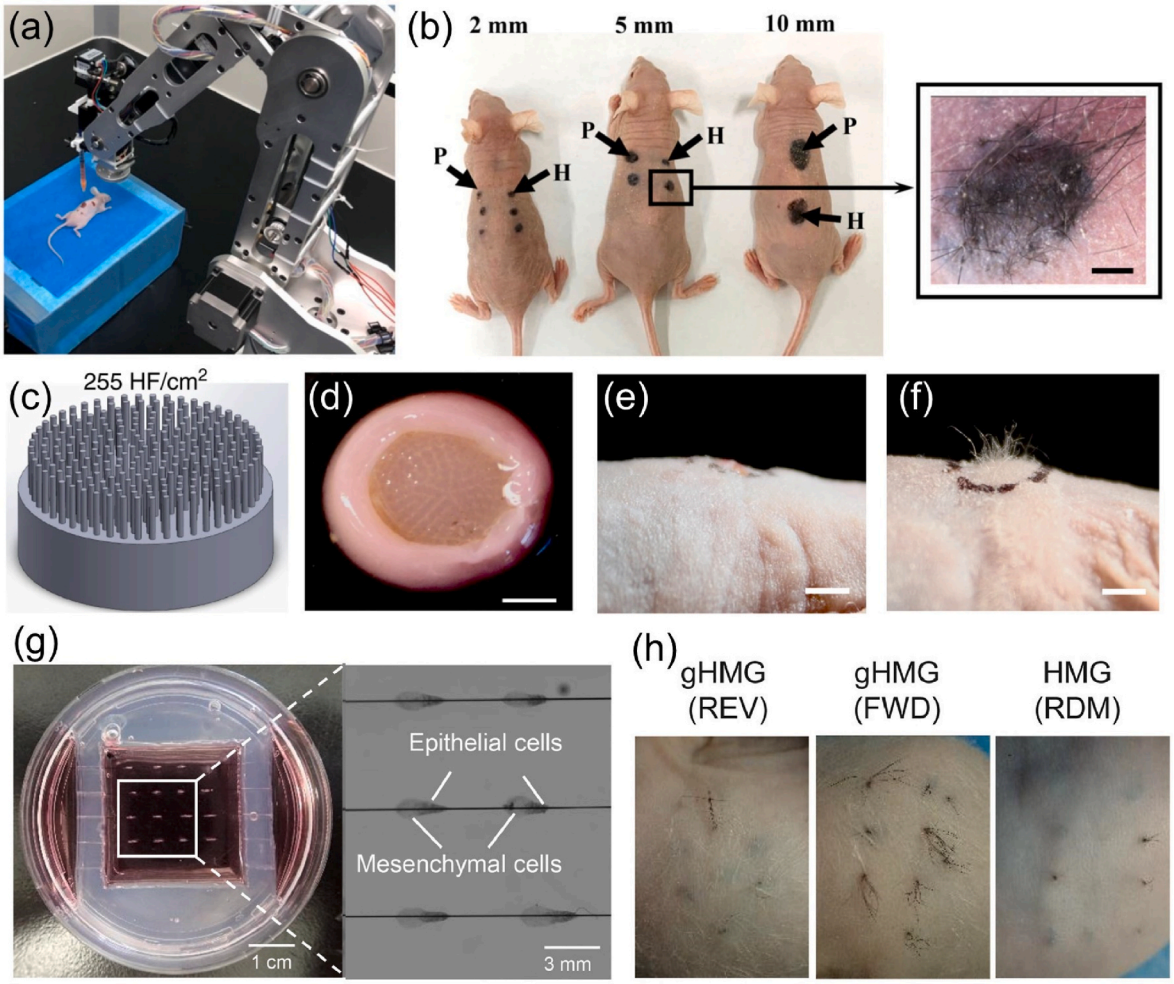

Fig. 11. Applications of 3D bioprinting in HF regeneration. (a) Bioprinting robot performs printing work on the back of nude mice. (b) After 4 weeks, HFs were generated after robotic bioprinting (P) and hand implantation (H). Scale bar: 2 mm. (a–b) reproduced with permission [182]. Copyright 2022, The Authors. (c–d) The mold generated by 3D printing has 255 HF per cm^2 in grafts. Scale bar: 4 mm. (e–f) Within 4–6 weeks of grafting high follicle-density HSCs onto immune-deficient nude mice, hair grew in the grafts. Scale bar: 2 mm. (c–f) reproduced with permission [22]. Copyright 2018, The Authors. (g) The printed hair microgels (HMG) in both macro and micro views. (h) The three separate tissue grafts produce hair shafts. gHMG: guide- HMG, RVE: upper side, mesenchymal bead; bottom side: epithelial bead, FWD: upper side, epithelial bead; bottom side: mesenchymal bead, RDM: random directions. Three weeks following the transplant, the dorsal skin of the nude mice was examined in the transplanted areas. (g–h) reproduced with permission [23]. Copyright 2023, The Authors.

and Matrigel and printed in situ onto the defect area of the full-layer skin of nude mice to achieve hair regeneration at the wound site. To enable personalized in-situ printing based on the wound, Zhao et al. [182] described an adaptive multi-DoF in situ bioprinting robot (Fig. 11a). Similarly, after 4 weeks of cultivation, the wounds healed to natural skin, exhibiting a complete skin structure including HFs (Fig. 11b). In-situ printing can meet personalized needs, while 3D-printed cell-loaded composite scaffolds can meet standardization requirements. Kang et al. [239] printed gelatin and alginate saline gel containing fibroblasts, HUVECs, DPCs, and EpSCs into composite scaffolds in sequence. Due to the appropriate layered structure of the scaffold and the dot bioprinting of DPCs, the HF regeneration at the wound site of nude mice shows the correct directionality. The above studies focus on HF regeneration through wound repair using 3D bioprinting. However, creating HFs in the laboratory is still a daunting challenge.

3D printing technology can mimic the structure of HFs, fabricate biomimetic HFGs, and provide a foundation for HF transplantation. 3D bioprinted HFs are generally in a semi-mature state that needs to be transferred to the subcutaneous area for further development. Embedded 3D printing can simulate forming HF-like structures by printing seed cells into matrix materials and cultivating them [240]. Similarly, Motter et al. [241] printed DPC and HUVEC spheres in the dermis gel layer and cultured them to form HF-like structure closely resembling natural skin tissue. Moreover, Abaci et al. [22] used 3D printing to prepare plastic molds for creating a density-adjustable microporous array in gel (Fig. 11c–d). When transplanted into nude mice, human skin constructs could be formed by DPCs, fibroblasts, KCs, and HUVECs in gel micropores could induce hair growth (Fig. 11e–f). 3D bioprinting can also be used to prepare HF grafts in specific directions. Nanmo et al. [23] employed 3D bioprinting to fabricate ordered millimeter-sized HFG-like grafts. They utilized two collagen droplets containing MSCs and EpSCs, positioned next to each other and printed on surgical suture guides for culturing. These grafts were then transplanted into the skin of nude mice, resulting in the correct hair direction (Fig. 11g–h). 3D printing has the characteristics of high precision and repeatability, making it very suitable for HF engineering.

6. Conclusion and prospect

The constraint of hair follicles is attributed to their predetermined quantity during embryonic development. Developing tissue-engineered hair follicles to overcome constraints on the necessary follicle count serves two significant objectives: 1) establishing a model for fundamental research on hair follicles, and 2) mitigating the scarcity of follicles for hair restoration in populations affected by hair loss.

The primary method for obtaining initial seed cells is still the extraction from HF tissue [242–244]. However, these cells gradually lose their hair growth-inducing ability during in vitro culture. Optimizing the culture environment and using 3D techniques can improve that, but restoring their hair-inducing ability remains challenging. On the other hand, the current research primarily focuses on animal models. The positive regeneration effects observed in animal models remain unpredictable in humans. Leng et al. [245] transplanted cell mixtures into punch biopsy wounds on the backs of nude mice. They found that the efficiency of hair follicle formation using human cells was significantly lower than that observed with mouse cells. HF acts as a regenerative system with self-renewal capacity, where cells respond to biological signals [246]. Various signals play a role in either promoting or inhibiting hair growth and regeneration cycles. Targeting regulating the signals could trigger compensatory signals to collaborate and maintain HF formation and balance. Proper signals could drive the seed cells to form the HF structures, while signal dysregulation would lead to disease [247,248]. It is worth considering that research on various biological signals remains relatively independent; however, the biological signals involved in hair follicle regeneration form a complex network centered around the Wnt signaling pathway. How to precisely regulate the behavior of stem cells through alterations in biological signals is an area where research remains unclear.

Biomaterials fulfill diverse roles in HF rebuilding, such as developing microgel arrays, hydrogel bioinks, cell-loaded microspheres, membrane materials, and surface coating. Optimal materials aim to promote seeded cell proliferation ex vivo and enhance HF induction efficacy in vivo [249]. The components found in dECM are highly suitable for hair follicle regeneration. Compared to synthetic polymers, dECMs consist of structural proteins and glycosaminoglycans, which enhance intercellular interactions and signal transmission within three-dimensional structures [250]. Presently, Matrigel is extensively utilized in HF research in laboratory settings. Nonetheless, its application and transplantation in vivo raise concerns about heterogeneity. Screening or designing safer and more effective biomaterials represents a current research direction. Among these, natural polymers with well-defined compositions, particularly collagen, hold significant potential as substitutes for the extracellular matrix in the future. Depending on specific requirements, functional groups can be introduced into natural polymers through doping or grafting techniques to enhance the biological activity of the material and establish a robust foundation for stem cell regeneration within hair follicles.

The commonly used method for assessing the potential of hair follicles is transplanting constructed HFGs into subcutaneous or full-thickness wounds in animals for further development. This approach presents several challenges, including a low survival rate of hair follicles, invasive trauma, and complex procedures. The current engineering methods also concentrate on effectively preparing HFGs and improving the hair follicle regeneration process. Self-assembled cell spheres have shown insufficient homogeneity and low production efficiency. Integrating microfluidics and 3D bioprinting holds promise for enhancing the fabrication of HFGs, posing new opportunities in this field [251]. However, constructing mature hair follicles with full life activity ex vivo remains a significant challenge. Under optimal in vitro culture conditions, mature hair follicles can grow to a maximum length of 3 mm, which is still significantly less than the growth potential of hair follicles in the organism itself [82]. It would be an alternative strategy that integrating the micromachining, including microfluidics with 3D printing, will boost hair follicle regeneration.

This review summarizes a basic description of stem cells, signaling regulation, materials and methods in HF engineering, and further reviews the accelerated regeneration strategies of tissue-engineered HFs by considering these components. It is believed that through further research on the process of HF regeneration and circulation, the advancement of diverse techniques for acquiring seed cells, the identification of biocompatible and bioeffective materials supported by advanced technology, and the simulation of in vivo regeneration patterns, the creation of customized HFs will soon be achievable.

CRediT authorship contribution statement

Yudie Lv: Writing – review & editing, Writing – original draft, Formal analysis. **Weili Yang:** Writing – review & editing, Writing – original draft. **Perumal Ramesh Kannan:** Writing – review & editing. **Han Zhang:** Writing – review & editing, Visualization. **Rui Zhang:** Writing – review & editing, Visualization. **Ruibo Zhao:** Writing – review & editing, Project administration, Funding acquisition. **Xiangdong Kong:** Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

All authors declared that they have no conflicts of interest to this work.

Acknowledgments

The authors acknowledge the support of the key project of the Natural Science Foundation of Zhejiang Province (LZ24E020002), the National Natural Science Foundation of China (51672250), the Key Research & Development Program of Zhejiang Province (2024C03075, 2024C03019, 2021C01180, 2019C04020), and the discipline construction funding of biomedical materials in ZSTU.

Data availability

No data was used for the research described in the article.

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