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Review article

Advances and applications of biomimetic biomaterials for endogenous skin regeneration

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A B S T R A C T

Endogenous regeneration is becoming an increasingly important strategy for wound healing as it facilitates skin's own regenerative potential for self-healing, thereby avoiding the risks of immune rejection and exogenous infection. However, currently applied biomaterials for inducing endogenous skin regeneration are simplistic in their structure and function, lacking the ability to accurately mimic the intricate tissue structure and regulate the disordered microenvironment. Novel biomimetic biomaterials with precise structure, chemical composition, and biophysical properties offer a promising avenue for achieving perfect endogenous skin regeneration. Here, we outline the recent advances in biomimetic materials induced endogenous skin regeneration from the aspects of structural and functional mimicry, physiological process regulation, and biophysical property design. Furthermore, novel techniques including *in situ* reprograming, flexible electronic skin, artificial intelligence, single-cell sequencing, and spatial transcriptomics, which have potential to contribute to the development of biomimetic biomaterials are highlighted. Finally, the prospects and challenges of further research and application of biomimetic biomaterials are discussed. This review provides reference to address the clinical problems of rapid and high-quality skin regeneration.

1. Introduction

In response to injury, human body has pre-programmed endogenous regenerative processes to regenerate the normal skin structures. However, if injury exceeds the regenerative capacity such as large-area burns or diabetics with impaired regenerative capacity, skin will be forced to choose imperfect scarring repair or leave chronic wounds that is difficult to heal [1]. Clinically, the rapid and scar-free skin perfect regeneration has always been a coveted goal.

During the exploration of perfect wound healing, scientists proposed the concept of endogenous skin regeneration. The main idea of endogenous skin regeneration is to implant bioactive biomaterials to the wound sites and take advantage of *in vivo* microenvironment, guiding the endogenous cells to regenerate skin tissues *in situ* [2]. In this process, cell-free biomaterials act as tissue scaffolds or vehicles for the recruitment, attachment, migration and differentiation of host cells. Compared to traditional skin grafting and tissue engineering strategies, Endogenous regeneration strategies do not require exogenous cells and do not involve *in vitro* cell manipulation., avoids the risks of immune rejection and exogenous infection [3]. Furthermore, the cell-free biomaterial faces fewer ethical issues and regulatory hurdles. Therefore, the endogenous skin regeneration approaches are more suitable to be clinically applied. Several biomaterial artificial skins based on the principle of endogenous skin regeneration have been clinically tested and commercially produced now such as Biobrane® and Integra® [4]. However, clinically available biomaterial wound dressings and artificial skins have simplistic compositions and structures that make it difficult to achieve rapid scar-free healing and regeneration of the appendages [5].

Recently, deeper understanding of tissue regeneration and development of biomaterials science make it possible to precisely control the structure and properties of biomaterials. From macroscale to quantum scale, more and more biomimetic biomaterials have been designed and manufactured (Fig. 1). Biomimetic biomaterials are biomaterials that can precisely mimic the morphology, physical properties or biological

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functions of natural tissue [6]. Rely on the structural and functional customizability of biomimetic biomaterials, they can be designed to provide endogenous cells with a simulated space and biochemical microenvironment, thereby regulating cellular behaviors of specific cells, altering the healing process toward the right direction [7]. Based on the four stages of wound healing, novel biomimetic biomaterials can precisely mimic, replace, and regulate the wound tissue microenvironment to promote endogenous skin regeneration [8]. Therefore, biomimetic biomaterials are a viable therapeutic tool for endogenous skin regeneration that mitigates the shortcomings of current strategies.

According to the two lines of skin tissue simulation and biomimetic material design, this review outlines advances of biomimetic biomaterials for endogenous skin regeneration in recent five years. First, we review the recent advances of biomimetic biomaterials designed for rapid hemostasis, wound covering, dermal reconstruction, wound immunoregulation, and appendage regeneration by mimicking the skin structure and regulating the dynamic process of wound healing. Second, the physical and biological properties of biomimetic biomaterials that can be exploited to promote high-quality endogenous regeneration of skin are listed and discussed. Third, we list five novel techniques and future directions for perfect endogenous wound healing. Finally, we analyze the challenges that biomimetic biomaterials are still facing, as well as the direction of further research and the prospect of clinical applications. This review can provide references for the design and application of novel biomimetic biomaterials for solving the clinical challenges of endogenous perfect regeneration of deep large skin injuries and chronic hard-to-heal wounds.

2. Biomimetic biomaterials mimic morphological structure and tissue microenvironment for endogenous skin regeneration

The skin has a complex layered structure, with a variety of functional tissues inside, including appendages, capillaries, and nerve fibers. Rapid closing the skin wound and rebuilding normal tissue microenvironment after injury is essential for functional wound healing. A variety of biomimetic biomaterials, such as membrane biomaterials, hydrogel dressings, and immunoregulatory nano-vehicles are already available to mimic the structure and physical properties of the multi-layered skin (Fig. 2).

In this section, we have summarized the advances of biomimetic biomaterials from the standpoint of mimicking, rebuilding and regulating skin's layered structure and normal tissue microenvironments. Then dialectically analyzed the potential for clinical application of biomaterials as temporary skin substitutes, tissue scaffolds, signal pathway regulators, and drug-delivery vehicles. Through evaluation of the way these biomimetic biomaterials rebuild the structure and tissue microenvironment will contribute to their design and lead to therapeutic biomaterials that have the potential to achieve the aim of wound perfect healing.

2.1. Biomaterial tissue adhesives for endogenous skin regeneration

When skin wound happens and blood vessel ruptures, the original homeostasis of skin tissue is destroyed, then the hemostasis cascade reaction starts and hemostatic plug will form to close the wound in the first place. As the main structural component of hemostatic plug is fibrin which is cross-linked into network [9], hemostatic plug can be regarded as a kind of macromolecular polymer complex that encapsulates blood cells (Fig. 3b). Furthermore, after the hemostatic phase completes, hemostatic plug can be used as tissue scaffold for cell migration in the phase of proliferation. Biocompatible macromolecular tissue adhesive, which can mimic the structure of blood clots, can be a suitable alternative for or rapid wound closure and surgical sealants. Commercial fibrin-based adhesives such as Tisseel and Fibrin Glue fully mimic the composition of blood clots, but it has the disadvantage of low tissue adhesion strength (<20 kPa), potential immunogenicity, and brittle under cyclic stress [10]. For macromolecular polymer adhesives, there are mainly two ways to improve its adhesive strength and gluing speed: enhancing the matrix cohesion into adhesive, or enhancing the interfacial adhesion between adhesive and biological tissue (Fig. 3c).

The structural stability of skin cells is mainly maintained by the desmosomes and adhesion of ECM [11], so gluing the tissue is the most direct way to recover skin's structural injury and adhesiveness is the most important property of tissue adhesive. To achieve the goal of skin structural healing, tissue adhesion is the most important propriety of tissue adhesives. Due to the complex multi-layered structure of skin tissues, multifaceted requirements are need to be considered in the development of tissue adhesives. Now novel macromolecular tissue adhesives are developed based on molecular design theory of polymers, improve the adhesion strength by strengthening interfacial interaction or matrix cohesion. To accelerate the gluing speed of tissue adhesive, Yuk et al. proposed a double-sided tape (DST) adhesive hydrogel made of gelatin, chitosan and poly(acrylic acid) grafted with *N*-hydrosuccinimide ester. The DST tissue adhesive could quickly remove the interfacial water from the wet tissue surface and achieve strong adhesion (interfacial toughness greater than 710 J m^{-2}, between diverse tissues within 5 s that overcame the limitations of existing hydrogel tissue adhesives such as weak bonding to wet surface and slow adhesion formation [12].

In addition to the basic function of gluing the wound, tissue adhesives are evolving towards multi-functionalization and specialization. Many novel tissue adhesives have combined the features of antibacterial agent, hemostatic agents, wound dressings by chemically modified macromolecule polymers [13]. Some of them focus on the function of regeneration: A catechol and glucose modified poly(L-lysine) microporous hydrogel adhesive could achieve tunable adhesion, fast hemostasis, and full wound closure and regenerates thick dermis and epidermis with some hair follicles after 14 days to rat-skin defect model [14]. Interestingly, it was reported that a natural bioadhesive derived from skin secretion of *Andrias davidianus* could not only efficiently close

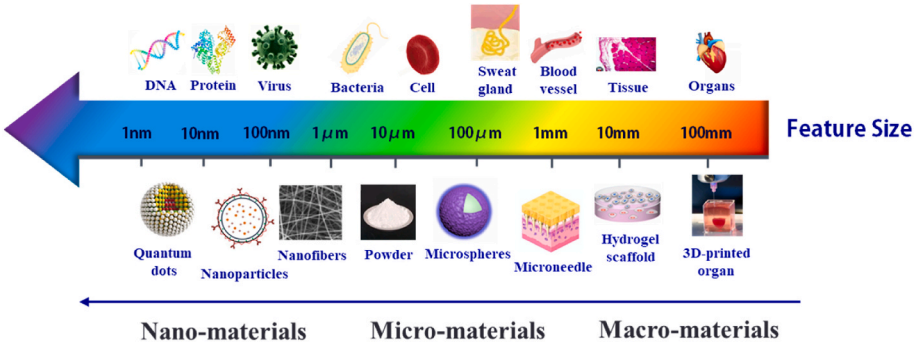

Fig. 1. Feature size of each biological structure in nature and its corresponding material on the same scale.

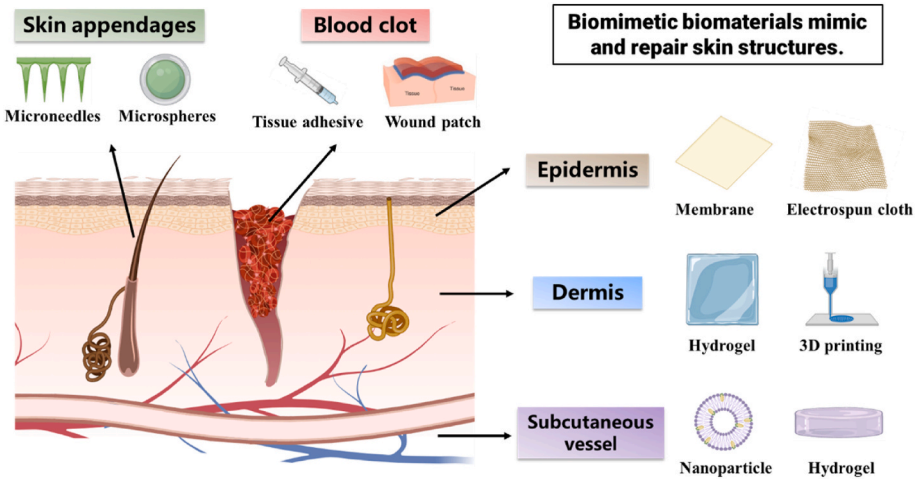

Fig. 2. The major tissue structures of the skin and their corresponding biomimetic biomaterials that promote structural and functional regeneration. Created with BioRender.com.

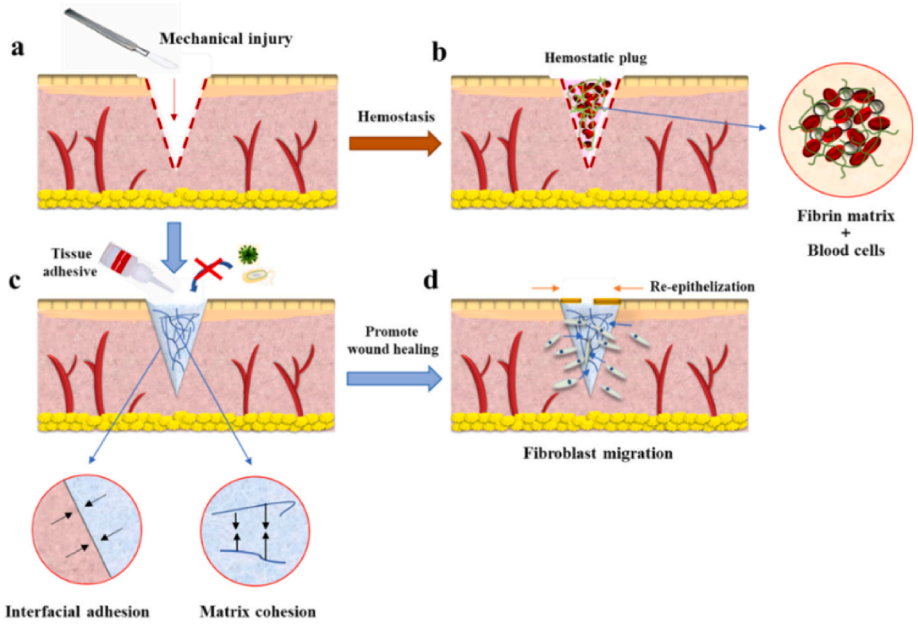

Fig. 3. Schematics of skin wound microenvironment by natural hemostasis (a, b); accelerated wound closure by tissue adhesives and two strategies to improve the adhesion of tissue adhesives (c).

the skin wound, but also promote wound scar-free healing and accelerate blood vessel regeneration [15].

Expanding the application scope is another way to improve tissue adhesives. Liu et al. developed the first-ever hydrophobic adhesive composed of polydimethylsiloxane, entangled macromolecular silicone fluid and a reactive silane, whose burst pressure on pigskin was 10 times higher than that of fibrin glue [16]. This adhesive could be used in wet environment and rapidly glue skin tissues under water. Moreover, extreme acid-tolerance tissue adhesive is also reported recently [17], expanded the application of tissue adhesives under special environment. Besides, researchers improve tissue adhesives by innovating the way of releasing adhesive as well. A novel approach was designed for wound closure: inserted the biocompatible and low melting point tissue adhesive into a hot melt glue gun, then melted and extruded it onto the wound directly. Releasing the adhesive by glue gun enables simple and accessible method to glue the wounds with minimal pain or distress [18].

Damaged red blood cells in blood clots can recruit immune cells, which can play an immunomodulatory role in inflammatory stage of wound healing [19]. Inspired by this phenomenon, an important development direction of next-generation tissue adhesives is combining it with other immunomodulatory active materials to regulate the local immune microenvironment to rebuild the previous steady-state environments and promoting high-quality wound healing.

2.2. *Membrane biomaterials for accelerated re-epithelialization*

When the skin is damaged, the original epidermal barrier is destroyed, skin tissue will be directly exposed to the external environment and microbial invasion. However, the normal process of wound closure and re-epithelialization of the skin takes time. Therefore, to avoid infections and chronic hard-to-heal wounds, is has an urgent need for more efficient smart biomaterial wound dressings and skin substitutes to cover and protect wounds in the first moments after injury and to regulate the wound microenvironment to accelerate endogenous regeneration. Because of the similarity in shape and properties to the

skin epidermis, membrane biomaterials are often the first choice for wound coverage and microenvironment management.

The commonly used wound dressing membranes are relatively simple in structure and function, such as transparent polymer membranes made of polyethylene, polyurethane, polylactic acid and other polymer materials. These isotropic polymer membranes are cost-effective and can provide basic functions of a wound dressing membrane: self-adhesive and shape-adaptive to cover wounds, retaining moisture, and blocking external microorganisms [20]. Now, reference to the structure and properties of the skin epidermis, researchers have taken the biomaterial membranes to further 3D structural and anisotropic design through new material molding techniques (electrostatic spinning, 3D printing, freeze-drying, etc.), allowing them to further functionalize and improve on the original bionic structure to promote wound healing [21]. The matrix of membrane biomaterials is generally selected from natural or synthetic polymeric materials with biocompatibility and biodegradability such as collagen, silk protein, chitosan, polycaprolactone, nanofibrillar cellulose, etc [22]. These polymer biomaterials endow the membranes with the basic properties of wound dressings such as adherence, water absorbency, and suitable mechanical properties, and at the same time, provide the basis for further functionalization and improvement.

As a typical example of structural and functional design of membrane biomaterials, Liu et al. developed a multifunctional Janus electrospinning nanofiber dressing with antibacterial and anti-inflammatory properties, and unidirectional water transport was prepared by depositing coaxial nanofibers on a hydrophilic poly(ε-caprolactone)@polydopamine-ε-polyl-lysine (PCL@PDA-ε-PL) nanofiber membrane. The coaxial nanofiber was loaded with the phase change material lauric acid in the shell layer and anti-inflammatory ibuprofen in the core layer. Due to the antibacterial ability of ε-PL, photothermal properties of PDA, and photothermal response released ibuprofen, the Janus membrane had antiseptic and anti-inflammatory properties. Moreover, that Janus membrane had asymmetric wettability that enabled directional water transport, thereby draining excessive wound exudate. All these properties coincide with the characteristics of the acute phase of the wound and help to maintain stable wound healing [23]. In addition, there have also been studies combining membrane biomaterials with responsive controlled-release vehicles to endow the membranes with the ability to smartly regulate the wound microenvironment: Du et al. reported a radial gradient nanofiber patch membrane inspired by the radial branching structure of the royal water lily leaf, with strong burst tolerance (4.6 N) and excellent mesenchymal stem cell recruitment are also impressive. The author precisely controlled the patterns on PCL/Col electrospinning membrane used programmable printed circuit in combination with needle soldering techniques. The membrane was covered with an MMP-9-responsive Gel-MA coating loading anti-inflammatory drug diclofenac sodium (DS) and stromal-cell-derived factor 1α (SDF1α), which had the ability of recruiting stem cells. This work opened a new pathway for development of smart fibrous membrane for stimulating endogenous skin regeneration [24].

In addition to common functions such as antimicrobial, anti-inflammatory, antioxidant, and scar inhibition [25], novel membrane biomaterials are now also developing in the direction of interactivity and intelligence. By loading pH-responsive dye in the mesoporous silica nanoparticles (MSNs), then encapsulating the nanoparticles into bacterial nanocellulose membrane, developed a membrane wound dressing for spatiotemporally continuous wound pH sensing, enable doctors to make timely adjustments to treatment strategies based on pH changes of the wound [26]. Wang et al. loaded aminobenzeneboronic acid modified gold nanoclusters (A-GNCs) on bacterial cellulose membranes as an antibacterial membrane wound dressing to display the amount of by *in situ* colorimetry. This self-monitoring membrane biomaterial could accurately show drug surplus in a simple, low-cost, and efficient way, [27].

There is already membrane wound dressing that have undergone clinical trials and proved its effectiveness. Zhang et al. developed a novel silk fibroin film used for wound healing. The randomized single-blind parallel controlled clinical trial with 71 patients shows that the group treated by silk fibroin film (n = 36) could significantly reduce the time of wound healing and incidence of adverse events compared to commercial dressing Sidaiyi (n = 35) [28]. The clinical evidence of membrane biomaterials establishing a foundation towards its application for skin repair and regeneration in the clinic.

Membrane biomaterial wound dressings can mimic the re-epithelialization process of wound healing, protect wounds and accelerate wound healing. Nevertheless, although many promising researches obtained with functionalized and structurally optimized membranes, some of the inherent disadvantages of membrane wound dressings remain, such as relatively poor absorbency, easy to peel off after drying, easy to damage surrounding tissues when dressing change and inapplicability to deep second-degree and deeper injuries [29]. However, if membrane biomaterials are used in conjunction with hydrogels or tissue-engineered skin, they can complement each other. I believe that as related researches continue, smart wound healing dressing based on membrane biomaterials will be fabricated soon.

2.3. Immunomodulatory biomaterials for biomimetic regulation of healing microenvironment

2.3.1. Functions and interactions of immune cells in the process of endogenous skin regeneration

The immune cells resident in each layer of skin coordinate to participate in repair the injured tissue. Cytokines secreted by immune cells are directly related to stem cell recruitment, therefore immune regulation during the inflammation phase is essential to promote endogenous wound regeneration [30]. From the perspective of cellular behavior, neutrophils arrive at the wound site first, followed by the transition from monocytes to macrophages [31]. These immune cells not only remove invading pathogens and release cytokines and chemokines to exacerbate inflammatory response, but also secret toxic mediators which may cause chronic wounds [32]. In the early stage of inflammation phase, neutrophils, monocytes and M1 macrophages are the main cell types in the wound area. Among these immune cells, macrophages play essential roles as sentry and scavenger, charged with the duty of killing pathogens, clearing the wound and establish a temporary inflammatory microenvironment [33]. Then anti-inflammatory M2 macrophage subtypes gradually dominate, triggering the proliferation phase.

Apart from directly initiating immune response to remove invading pathogens, the immune cells also interact with non-immune cells to modulate the healing process. Transcriptional space-time analysis provides a powerful genetic tool to explore the interactions between these immune-associated cells. Hu's research revealed the shared space-time patterns of cellular movement and gene enrichment between immune cells and non-immune cells, especially the spatiotemporal heterogeneity of macrophages-fibroblasts in wound healing. They functioned as "senders' and "receivers' of genetic programs, their pairing patterns demonstrated spatiotemporal heterogeneity during skin repair [34]. This research also confirmed some previously reported crosstalk between diverse cell types. For example, the subpopulation fibroblast_1 with high expression of inflammatory mediators emerged at the wound on day 1, and expressed chemokine Cxcl5 to recruit neutrophils into the wound [35]. Upon arriving at the wound, neutrophils expel extracellular traps (NETs) and release reactive oxygen species (ROS) [36], various cytokines and growth factors, such as TNF-α and VEGF, to regulate re-epithelialization through inducing keratinocytes migration [37]. Ma et a., performed single-cell RNA sequencing of $CD45^{+}$ immune cells within the diabetic wound and obtained 17 clusters of cells, described the differentiation profile of mononuclear macrophages on chronic wound [38]. Chen et al. performed single-cell RNA sequencing to the dermal cells from fibrotic and regenerative wounds, identified a series of

specifically expressed genes in fibrotic myofibroblasts or macrophages. The results suggested that the specific myofibroblast and macrophage subsets could change the skin wound healing fates by modulating critical signaling pathways [39]. The application of advanced genetic tools such as single-cell RNA sequencing in promoting skin regeneration will be further discussed in section 5.4.

Furthermore, mimicking the communication and interaction between immune cells and recruiting endogenous cells using bioactive materials to accelerate wound repair is also an important way to achieve endogenous skin regeneration [40].

2.3.2. *Macrophages polarization regulated by physical and chemical properties of biomaterial matrix*

Functional macrophages can be divided into two kinds: inflammatory promoting macrophages (phenotype I macrophages, M1) and inflammatory suppressing macrophages (phenotype II macrophages, M2), M2 macrophages can be further subdivided into four subtypes, each of which secretes different cytokines and performs different functions (Fig. 4a) [41]. In the early stages of wound healing (day 1–4), most of the macrophages are mostly pro-inflammatory M1 macrophages (about 85 %) and then transform into the anti-inflammatory M2 macrophages (about 80–85 %) on day 5 to day 7. The transition from M1 to M2 phase is critical to the wound healing process, with the function of inhibiting inflammation, promoting tissue regeneration, blood vessel formation and remodeling tissue ECM [42]. Disruption of this process will lead to abnormal increase of M1 macrophages and sustained release of inflammatory factors, causing persistent inflammation and infiltrating cell infiltration of the wound, and eventually leading to the formation of hard-healing chronic wound [43].

Regulating macrophage polarization through biomaterials, thereby recruiting cells and stimulating the skin's own regenerative potential is one of the ways to achieve endogenous skin regeneration (Fig. 4b). According to the mode of action, biomaterials that modulate macrophage polarization can be divided into two categories: endogenous immunomodulatory biomaterial scaffolds and immunomodulatory components biomaterial vehicles.

Biomaterial wound dressings are in direct contact with the wound, creating a temporary microenvironment on the wound. Therefore, the physical and chemical properties of the biomaterial matrix can directly influence macrophage polarization. Many physical properties can regulate the behavior and phenotype of macrophages, among which the stiffness of the matrix is one of the most studied physical factors. The molecular mechanism of biomaterials' stiffness for regulating macrophages is still unclear, but researchers found that macrophage cell's mechanically activated cation channel Piezo1 was the sensor to matrix stiffness, and the positive feedback between Piezo1 and actin drives macrophage activation [44]. Camarero-Espinosa et al., created two 3D-printed dual-porosity scaffolds with different mechanical feature, and evaluated their immunomodulatory properties to rat macrophages *in vitro* and *in vivo* in a rat subcutaneous model. The results revealed that soft scaffolds (<5 kPa) result in a pro-inflammatory M1 phenotype in contrast to stiffer scaffolds (>40 kPa) supporting a pro-healing M2 phenotype [45]. Sridharan et al. reported that on softer collagen-coated poly-acrylamide hydrogels, the expression level of TNF-α decreased and IL10 increased, showing the polarization toward M2 macrophages [46]. Another report also proved softer hydrogel matrix could enhance the polarization of M2/M1 macrophages and promoting angiogenesis [47]. These contradictory results may require more mechanistic studies to explain.

Except the stiffness of the matrix, surface properties of the polymer biomaterial (e.g., surface structure, pore size, surface roughness) also have an effect on macrophage polarization. Tylek et al. fabricated a series of fibrous scaffolds with different inter-fiber spacing (from 40 to 100 μm). They found that the elongation of macrophages is accompanied by a tendency to polarize to M2 type, the most obvious effect was observed in the scaffold with smallest pores (40 μm), suggested that the

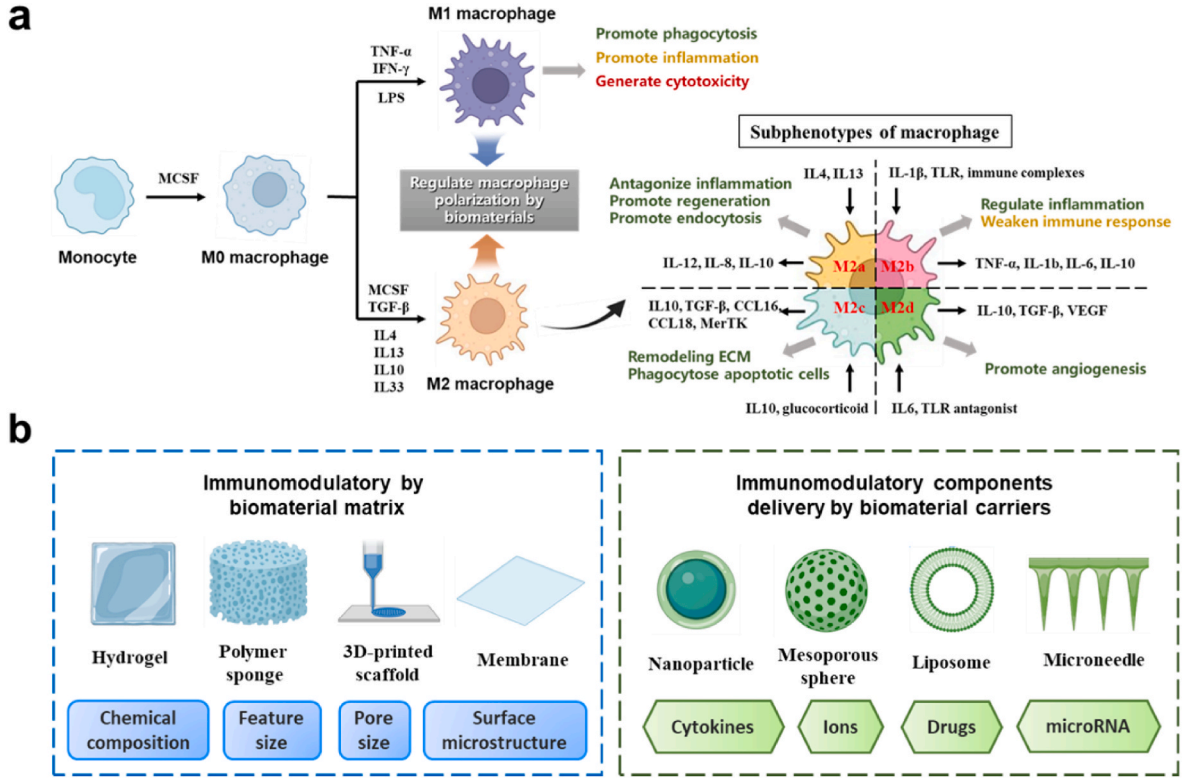

Fig. 4. Schematics of polarization, classification and function of macrophages (a); Two main strategies of regulating macrophage polarization by biomaterials, and their main influence factors and loaded bioactive components (b). MCSF, macrophage colony-stimulating factor; LPS, lipopolysaccharide; MerTK, c-Mer proto-oncogene tyrosine kinase; TLR, toll-like receptors. Created with BioRender.com.

scaffold with smaller pore sizes could promote the polarization of macrophages to M2 phenotype and accelerate wound healing [48]. Similarly, Zhu et al. also found that the smallest scale of TiO_2 honeycomb-like structure (90 nm) could activate of the RhoA/Rho-associated protein kinase signaling pathway, thus significantly activate the anti-inflammatory macrophage phenotype (M2), and induced higher expression level of CD206, IL-4, and IL-10 [49]. Previous study also found that the surface roughness of biomaterials could regulate macrophage polarization. On the rough surface of hydrogel, more macrophages exhibited M1 phenotype and high-level secretion of inflammatory factor (TNF-α and IL-6), while smoother surface induced M2 phenotype [50,51]. In addition, the form of the biomaterial also regulates the immune response. It has been reported that compared to fibers and membranes, hydrogels are more capable of shortening the inflammatory period and accelerating wound healing due to their ability to mimic the structure and function of the skin's ECM [52].

The chemical composition of the matrix material likewise plays an important role in regulating macrophage polarization. Many naturally sourced macromolecular biomaterials such as chitosan, alginate, and hyaluronic acid have been reported to have immunomodulatory properties [53–55]. Chitosan is a natural cationic polysaccharide biomaterial with excellent biocompatibility, antimicrobial and anti-inflammatory properties. However, it has been reported that chitosan can induce macrophages to secrete TNF-α and IL-1β, causing chronic inflammation in wounds [56]. By chemically modifying the side-chain groups of chitosan and compositing it with other materials, it is possible to exploit the strengths and avoid the weaknesses of chitosan. Yu et al. developed a multifunctional CS/Poly[2-(methacryloyloxy)ethyl] trimethyl ammonium chloride (PMETAC) hydrogel crosslinked by covalent bonds and van der Waals forces. The PMETAC hydrogel had excellent antibacterial activity, self-healing ability and biocompatibility *in vitro*. Moreover, it could promote macrophage polarization to M2 direction, and shifting the balance of T helper type 17 (Th17) cells towards anti-inflammatory regulatory T (Treg) cells to regulate the immune microenvironment and promotes rapid wound healing [57]. Feng et al. proposed a drug-free biomimetic glycopeptide hydrogel (GPgel) established by the self-assembly β-sheet Q11 peptide-grafted glucomannan which could mimic the composition and structure of the skin ECM. GPgel was able to activate the mannose receptors via the ERK/STAT6 pathway, while significantly polarizing M0 macrophages to M2 macrophages [58]. These results provide numerous inspirations for the development of biomaterials for the treatment of both acute wounds and chronic wounds.

Because of the similarity of the structural and physical properties of biomaterial scaffolds to real skin, biomimetic scaffolds with immunomodulatory functions through material design will have a broad application prospect in biomedicine field.

2.3.3. Macrophages polarization induced by smart biomaterial delivery vehicles

Traditional biomaterial scaffolds can only release drugs by physical diffusion. However, with the gradual emphasis on the concept of precise medicine, more and more biomaterial vehicles with the ability to precisely control the release of drugs according to the changes in the wound microenvironment have been designed for the intelligent regulation of macrophage polarization and acceleration of wound healing.

As reviewed in section 4.2, smart controlled release vehicles are generally based on responsive biomaterial designs. The main vehicle-loaded bioactive components with immunomodulatory effects are cytokines, metal or non-metal ions, and commercialized drugs. Peng et al. produced a poly(lactic acid glycol)/filamentous cellulose membranes loading artemisinin by electrospinning technique. This membranes material was able to decrease the secretion level of IL-1β and TNF-α of macrophages, shorten the inflammatory period and promote wound healing [59]. Chen et al. reported an electrospinning poly(lactic acid) fibers which could control release of IL-10. At early stage, IL-10 prevented the excessive inflammatory response, and then the subsequent release maintained high levels of IL-10 induced macrophage polarization toward M2 phenotype to promote wound healing [60]. Gauthier et al. developed PEG liposomes loaded with dexamethasone phosphate and surface-modified phosphatidylserine for topical delivery to macrophages to promote the polarization toward M2 macrophages [61]. Precise delivery using nanomaterials not only reduces drug loss, but also reduces systemic side effects of drugs. It is also worth noting that Huang et al. grafted superparamagnetic nanoparticles on collagen nanofibers, successfully constructed a superparamagnetic hydrogel which could efficiently polarize macrophages to M2 phenotype through the podosome/Rho/ROCK mechanical pathway under the control of external static magnetic field [62]. Due to the controllability and no side effects on the human body, utilizing external energy fields (e.g. electric field, magnetic field, photothermal effect and ultrasound) to act on responsive biomaterials to regulate macrophage polarization will also be a major development trend of immunomodulatory materials in the future.

Currently, although a lot of researches have successfully developed biomaterials to regulate the polarization of macrophages, but they still have a long way to be clinically applied and commercial produced due to the common problems like production costs, reproducibility, immune rejection, etc. [63]. In addition, the development of immunomodulation-related biomaterials is also encountering some challenges. For example, some researchers have argued that the simple classification of functional macrophages into M1 and M2 is not rigorous enough. The characteristics of M1 and M2 macrophages are not necessarily mutually exclusive, but often coexist, and it could be more reasonable to differentiate them based on the expression of their surface markers [64]. Several studies have also found that M1-type macrophage-induced inflammation is associated with the quality of wound healing, and therefore one-sided radical induction of macrophage polarization toward the M2 phenotype is unreasonable [65]. Therefore, the dynamic complexity of the immune process must be taken into consideration in the development of novel immunomodulatory biomaterials.

2.4. Biomimetic biomaterials for dermal ECM rebuilding

The skin ECM is not only a support structure for tissue and cells, but also the direct microenvironment for tissue cell survival, and it has an extremely close relationship with the regeneration, repair and immunity of tissue cells [66]. The composition and structure of the ECM is dynamic, constantly changing, and always in a status of dynamic balance. However, skin deep injuries can destroy the structural integrity of the skin's layered structure and impede subsequent cell migration and tissue regeneration. However, traditional wound dressings such as gauze don not have the ability to replace and reconstruct ECM. In this case, biomimetic biomaterial is a viable therapeutic tool that can temporarily replace dermal ECM and accelerate wound healing.

2.4.1. Biomimetic hydrogels for endogenous dermal reconstruction

Developments in biomaterials have provided us more options for wound repair materials such as nanofibers, membranes, foams, powders and hydrogels. Among these, hydrogels have high hydrophilicity, good biocompatibility and biodegradability, ion transport ability, and similar structures to the ECM, make hydrogels have great application potential as wound management materials [67]. In addition, the main chain molecules of polymer hydrogels can be chemically modified to endow the hydrogel with injectability, self-healing properties, antibacterial activity, antioxidant activity and other properties which can give benefit to wound healing. Due to their structural similarity to skin ECM, hydrogel materials can be used as a scaffold for cell migration and proliferation. Currently, many novel hydrogel biomaterials enhance their function in promoting wound healing through improving the cytocompatibility of hydrogels as cell scaffolds [68]. Despite the biological macromolecular, some bioactive polypeptides also can be

fabricated into the main chain of polymer hydrogels and reveal its biological function. Chen et al. fabricated a bioactive polypeptide hydrogel constituted by silk fibroin and a vascular endothelial growth factor mimetic peptide QK through hydrogen bonding and hydrophilic/hydrophobic interactions between silk fibroin and QK. With the help of QK, the QK-SF hydrogel could significantly improve the endothelial growth, migration and angiogenesis through up-regulating the expression of angiogenesis-related genes in HUVECs. Furthermore, The QK-SF hydrogel revealed the ability of promoting macrophages M2 polarization, keratinocyte differentiation, and collagen deposition, so it can play dual functional roles in promoting angiogenesis and immunoregulation for tissue regeneration [69]. In addition, hydrogel can also load cell derivatives like platelet lysate and exosomes, making the hydrogel material more similar in structure and biological function to real skin ECM and providing the hydrogel with better performance in promoting wound healing [70,71].

Lots of novel hydrogel skin substitutes have been reported composited with different forms of nano-materials with improved properties. However, just few clinical trials of cell-free biomaterial wound dressings that mimic extracellular matrix have been conducted. Driver et al. evaluated the safety and efficacy of Integra hydrogel artificial skin for the clinical trial of nonhealing diabetic foot ulcers. Randomized 307 subjects from 32 sites with nonhealing diabetic foot were tested. The results showed that patients treated by Integra (n = 154) had significant decreased time to complete wound closure, increased the rate of wound closure, improved components of quality of life and had less adverse events compared with the standard of care treatment (treated by 0.9 % sodium chloride gel, n = 153) [72]. Moreover, Glat et al. also presented a clinical trial comparing SilvaSorb (an alginate hydrogel wound dressing loading silver ions) with traditional drug Silvadene (a silver sulfadiazine cream), demonstrated the efficacy of SilvaSorb in the treatment of partial-thickness burns [73]. A double-blind phase III clinical study investigated the efficacy of chitosan hydrogel (10 %) loading isosorbide dinitrate to accelerate the healing of skin ulcer [74]. The reported hydrogel skin substitutes still need to be clinically tested, and how to translate the scientific research achievements into clinical application is an urgent problem to be solved, which is also the direction of our efforts.

2.4.2. *Biomimetic biomaterials for scar-free wound healing*

Properly wound healing is a complex and well-organized process, both spatially and temporally. Sometimes, wound's tissue microenvironment can be disrupted which is characterized by chronic inflammation, aberrant ECM deposition, myofibroblast accumulation, can cause the formation of hypertrophic scar. Current researchers have found out a series of factors contributed to scar formation, such as external force, growth factors, cytokines, cells (especially myofibroblasts), and the ECM [75]. The mechanochemical feedback between cells and ECM mediated by transmembrane integrin is important for maintaining normal physiological conditions and regulating wound healing cascade. Directly receive the stimulus of mechanical signals (stiffness and tension), then fibroblasts differentiate into myofibroblasts with a higher contractile capacity [76]. Excessive deposition of ECM further stimulated myofibroblasts to generate more Collagen-I, which results in scar formation [77]. This explains why scar is rich in non-functional excessive deposition of ECM and replacement of aligned collagenous fiber. Hence, breaking this vicious cycle becomes a new target for the treatment of pathological scar diseases.

The traditional methods of treating scar include medication (i.e., corticosteroids and fluorouracil), cryotherapy, surgical excision, and perioperative therapies and laser therapy. Although some of them have proven to be effective, many patients undergoing these treatments suffer from a lot of pain and high risk of recurrence. Recent reports on the molecular mechanism of scar formation and novel nano materials may help provide a promising future in scar-free wound healing. These strategies mainly through reducing wound's tension, inhibition of inflammation, inhibition of relevant growth factors, inhibition of myofibroblast differentiation, and promotion of degradation of excess ECM [78].

The first strategy is utilizing biomaterials to deliver growth factor s or small-molecule inhibitors to inhibit the expression of scar related genes. Recent work showed that inhibition of Yes-associated protein (YAP) signal pathway in fibroblasts could achieve skin wound scar-free regeneration [79]. YAP play a key role in mechanical signal transduction, YAP-mediated mechanotransduction induced En-1 activation which leads to scar formation. En-1 gene are switched off permanently in postnatal stage, but it will be activated in response to injury, which leads to fibrotic outcome. In the early stages of wound healing, YAP can be inhibited by reducing the tensile effect at the wound or by using a YAP inhibitor (verteporfin), thereby inhibiting the transformation of myofibroblasts and preventing scar formation [80]. Zhang et al. constructed a verteporfin-loaded biodegradable hydrogel (VP-gel) using hyaluronic acid and PEG. Sustained released verteporfin from VP-gel could regulate TGF-β family-induced cellular responses and the downstream signaling molecule Smad2 in fibroblasts to reduce myofibroblast differentiation, promoting ECM reconstruction and significantly prevent scar formation [81]. In addition, several key proteins associated with the fibrosis signal pathway, such as TGF-β, α-SMA and Wingless (Wnt), are also important targets for scar-free regeneration. Especially TGF-β family, TGF-β1 has been proven to induce fibroblast differentiation to myofibroblasts [82]. Recent report by Zhang et al. used a drug-free silk fibroin microneedle patch (SF MNs) directly regulated the expression of the mechanical sensitive gene ANKRD1 and consequently down-regulated the expression of scar related gens like TGF-β1, α-SMA and collagen I (Fig. 5f and g). Therefore, the SF MNs could generate a low-stress microenvironment that significantly decreased the scar elevation index in the rabbit ear hypertrophic scar model (Fig. 7c–e) [83]. Recent clinic trial assessed the performance of EGF-loaded chitosan for scar-free wound healing in 60-subjects. The study suggested EGF-loaded chitosan as a potential treatment with better wound healing and scar prevention [84].

The second strategy is to construct bioactive composite vehicles of biomaterials that transport drugs or exosomes. Recently, collagen and amnion in the form of a blended hydrogel have been developed for burn wound dressings. The rat model treated with the blended hydrogel on a chitosan-collagen membrane showed significant wound healing and fewer scar formation. Histology results reported faster re-epithelialization and higher wound contraction [85]. Fibronectin nanofiber scaffolds in murine fullthickness skin wounds showed significant skin tissue restoration. The grafts accelerated wound closure with reduced scar severity. Histological analysis further confirmed the fibronectin-treated group had ECM fiber alignment similar to native morphology [86]. Jiang et al. studied the cell regeneration effects and its underlying mechanism of human bone marrow mesenchymal stem cell-derived exosomes (hBM-MSC-Ex) on cutaneous wound healing in rats. Their results proved that hBM-MSC-Ex could effectively promote the wound healing and inhibit the formation of scar through inhibiting the TGF-β/Smad signal pathway [87].

Besides, some other influencing factors such as chronic inflammation of wound, oxidative stress and excessive angiogenesis have been reported to be associated with scar formation [88–90]. Novel multifunctional biomaterials with antibacterial activity, anti-inflammatory action, antioxidant activity and regulating angiogenesis are developed target to these causes. Thus, it is the trend in the future to design biomimetic hydrogel biomaterials according to different clinical symptoms of patients.

3. Biomimetic biomaterials for skin appendage regeneration

The skin appendages, including the hair follicles, sebaceous glands, sweat glands and nails, play an important role in maintaining normal skin function. Due to the presence of skin stem cells, skin appendages can generally regenerate naturally after superficial skin damage [91].

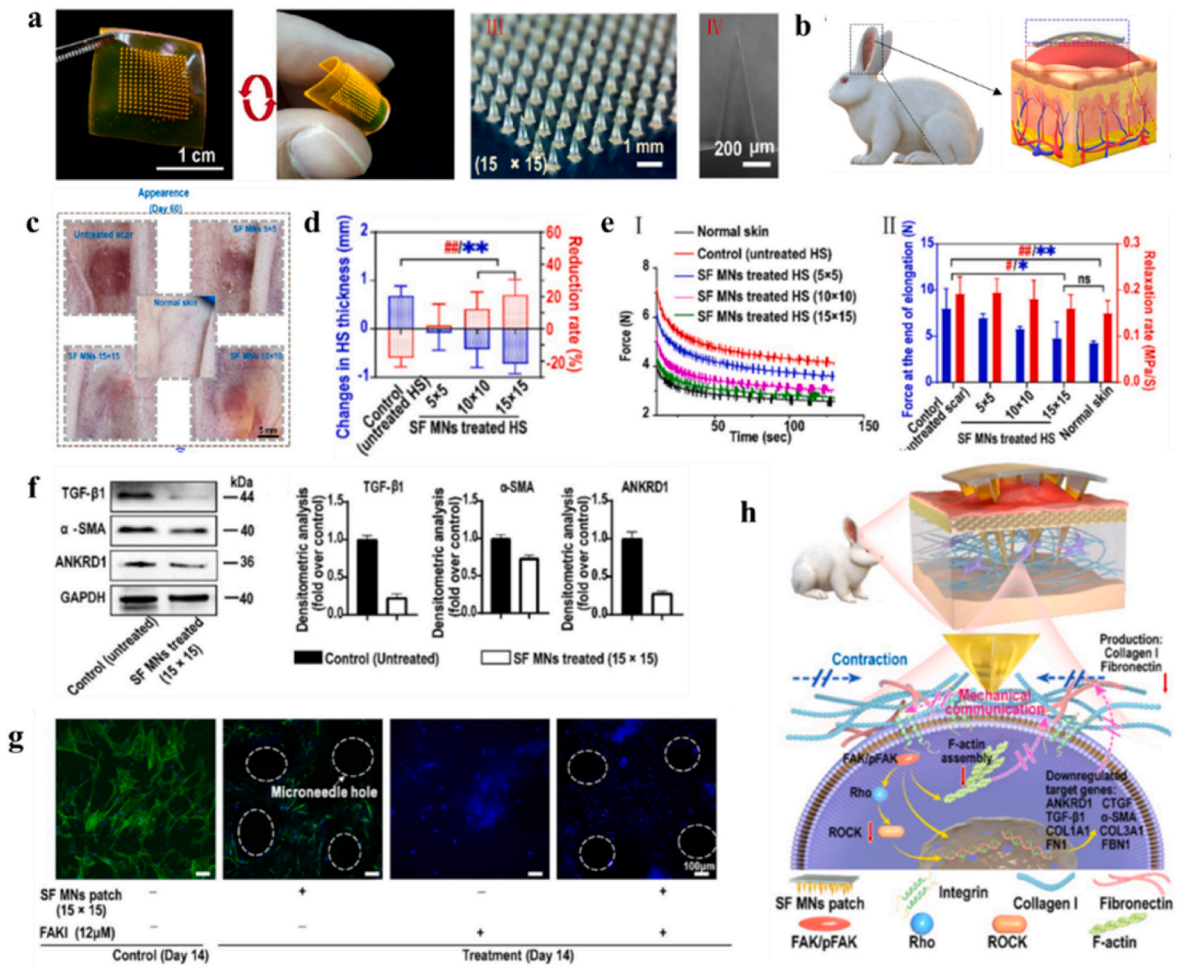

Fig. 5. Array of silk fibroin microneedle patch (a); Schematic diagram of rabbit ear scar models and the position SF MN patches treat rabbit ear scar (b); Photos of post-treated scar tissues. (c); Changes in thickness of scar tissues before and post-treatment (d); Dumbbell-shaped mechanical test specimens of uninjured skin and scars in the direction of the axial axis (e); Western blotting and semiquantitative statistics of protein levels of TGF-β1, α-SMA, and ANKRD1 (f); CLSM of the intracellular F-actin meshwork of fibroblasts under different treatments (g); Illustration of SF MN interrupting the mechanical communication between fibroblasts and the ECM (h). Reprinted from Ref. [83].

But after skin deep injuries such as deep burns, skin ulcers with loss of deep dermal tissue or imperfect healing of pathological scarring can result in the inability of skin appendages regeneration. The loss of hair and the inability to produce sweat and sebum can cause impaired thermoregulation, skin barrier and protection, causing great pain and inconvenience to the patient's life. After deep skin damage, due to the destruction of skin stem cells, the regeneration of the skin appendages often faces the problem of the lack of both "seeds' and suitable "soil'. Researches on appendage regeneration have centered on transplanting seed cells with regenerative potential and reconstructing the microenvironment for skin appendages regeneration [92]. In this section, we will review current biomaterial strategies to achieve endogenous appendage regeneration by recruiting seed cells and rebuilding suitable tissue microenvironment.

3.1. Biomimetic biomaterials for hair follicle regeneration

The hair follicle (HF) is a skin appendage consisting of multiple layers of keratin-forming cells and hair papilla cells. It originates from ectoderm and is regulated by a multiple of signaling such as Wnt and Notch [93]. Hair follicles and hairs not only provide the function of protection to skin, but also provide a channel for sweat secretion by sweat glands. Hair follicle stem cells demonstrate surprising plasticity and regeneration ability. They can promote wound healing through mediating re-epithelization, wound closure, transdifferentiating to endothelial cells and sweat gland cells to promote neovascularization and skin appendages regeneration [94]. In a word, regeneration of HF seems to have every advantage and no drawback.

Irreversible damage to the hair follicle may occur in some people due to endogenous endocrine disorders or deep skin injury, and some medications and treatments can also disrupt the normal hair follicle regeneration cycle, leading to hair loss [95]. The main treatment options for hair loss are hair transplantation and medication. However, medications for hair loss such as minoxidil or finasteride often have significant side effects; hair transplantation cannot address the root cause of the lack of hair follicles and have a high recurrence rate [96]. Therefore, researchers have focused on the multi-directional researches by novel drugs, exosome therapy and biomimetic biomaterial scaffolds in an attempt to achieve HF regeneration (Fig. 6).

3.1.1. Tissue engineering strategies for hair follicle regeneration

Tissue engineering techniques are one of the common strategies for regeneration of skin appendages. Compared to drug therapy and hair follicle transplantation, tissue engineered hair follicle tissue can provide a suitable microenvironment for hair follicle regeneration and always has a higher survival rate [97]. In terms of tissue engineering matrix, different 3D-culture hydrogels composed of silk-gelatin, hyaluronic acid, and collagen were proved to improve the stem cell differentiation

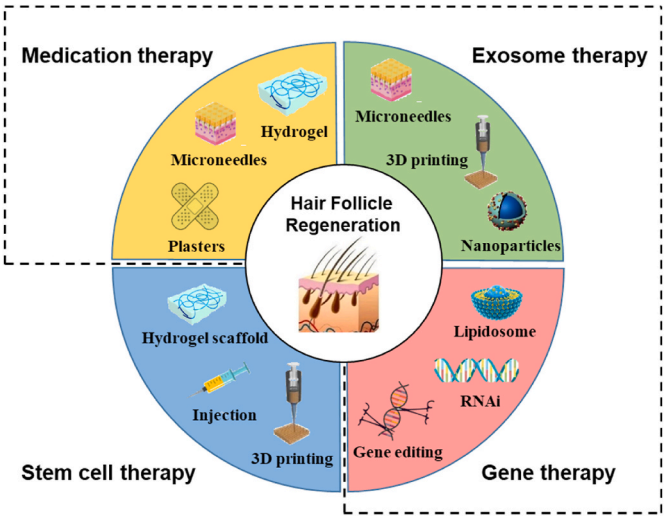

Fig. 6. Schematic diagram of current therapeutic strategies for hair follicle regeneration and their corresponding biomaterial in recent reports. The strategies of endogenous regeneration of hair follicle are marked with the dashed box.

to hair germs for HF regeneration [98]. Chen et al. reported a tissue engineering hydrogel that combined the injectable fibrin hydrogel, epidermal stem cells and dermal progenitor cells. That fibrin hydrogels were biocompatible and could provide a microenvironment for the survival of skin stem cells, and that the combination of the two can achieve hair follicle-containing skin regeneration [99].

Novel technologies such as bio-3D printing and microneedles also have been used for tissue engineered HF regeneration studies. *In vitro* 3D printing can precisely introduce complex adnexal structures within biomaterial tissue engineering matrix, and arrange cells into a biomimetic micropattern that simulated the tissue structures of dermis and hair follicles [100]. Zheng et al. developed an HF organoid-loaded methacrylated gelatin-cryomicroneedles which could easily delivery the HF organoids under the skin [101]. Bio-3D printing and microneedle technologies have the advantages of high structural accuracy and precise customization of microstructures, and proving a promising strategy for HF regeneration. However, the complexity of preparation, difficulty of preservation, and immune rejection have been the problems that have been difficult to be completely solved for *in vitro* tissue-engineered strategies compared with other strategies of endogenous regeneration strategies [102].

3.1.2. *Exosome therapy for endogenous hair follicle regeneration*

In recent studies, exosomes, which is a kind of cell-derived vesicles containing various bioactive molecules secreted by cells, have become a new therapy with significant efficacy in HF regeneration. Exosome's double membrane vesicular structure can protect drugs, proteins and nucleic acids from rapid degradation [103]. Compared with cell therapy, exosomes have lower immunogenicity and higher biocompatibility, which can avoid graft failure due to immune rejection [104]. In addition, exosomes can be prepared quickly and in large quantities *in vitro*, therefore have more potential for application than stem cell therapies. Now several commercial exosome products for alopecia treatment are in clinical use [105].

In exosomes from a variety of sources, the exosomes derived from dermal papilla cells (DPCs) is directly related to HF regeneration. The exact mechanism of exosomes promoting HF regeneration is still not clear. Recent report suggested that the paracrine signaling, which can mediate the crosstalk between epithelial cells and mesenchymal cells during the hair growth cycle, was the main target of DPCs derived exosome (DPC-Exos). DPC-Exos could regulate the Wnt/β-catenin and Sonic hedgehog (Shh) signaling in outer root sheath cells, resulting in producing longer hair shafts in mice [106]. Injection of DPC-Exos has been shown to upregulate the β-catenin and Shh levels, which are important regulators of the hair cycle, and accelerate the onset of HF anagen in mice [107]. Kwack et al. used dermal papilla cell exosomes to induce prolonged anagen of HF in mice after subcutaneous injection [108]. DPC-Exos are shown to decrease hair loss and reduced inflammation around hair follicles in alopecia areata mouse model as well [109]. However, DPC cells have a limited capacity for proliferation and continuous culture, stem cell-derived exosomes are easier to be mass prepared and extracted. Adipose-derived stem cells exosomes can promote DPC proliferation via upregulating the Wnt/β-catenin and TNF-α signaling pathways, and further promote hair regeneration [110]. Stem cells derived exosomes have more functions than DPC-Exos, but less target ability for HF regeneration than DPC-Exos. Further engineered and modified of natural exosomes to combine their advantages and endowed them with the function of targeting specific tissue cells are the future trends of exosome therapies [111]. In addition, exosomes from various cells like human dermal fibroblasts, macrophages, neural progenitor cells and keratinocytes also can promote hair growth [112–115]. Both of them work by activating the Wnt/β-catenin signaling pathway and increasing the secretion of VEGF, thus promoting the proliferation of DPCs [116]. Interestingly, some exosomes from non-animal cells like bacteria [117] and bovine colostrum [118], have also been shown to have positive effects on HF regeneration, which provides new ideas for preparing exosomes in large quantities.

Safe and effective delivery of exosomes into subcutaneous and target tissues is the basis of exosome therapy. Exosomes are natural delivery vehicles, they can be modified (chemical surface modification and genetic engineering modification) and confer they cell/tissue targeting specificity to further enhance their safety [119]. In order to maintain the integrity and bioactivity of exosomes, exosomes are best suited for compositing with hydrogels and hydrogel-based microneedles (Fig. 7a). After entering the body, exosomes can be released through dissolution and degradation of the hydrogel. We can choose the most appropriate exosome delivery method according to the actual situation of the patient. These hydrogel scaffolds can not only help maintain the biological activity of exosomes, but also deliver them more accurately to their target sites compared to traditional injections. For non-traumatic hair loss, microneedle-based exosomes transdermal delivery system has been reported to have better efficacy and safety [120]. It was shown that combination therapy of microneedle patches containing human amniotic mesenchymal stem cell exosomes combined with low-color-temperature yellow light had better therapeutic effect in promoting hair regrowth compared to monotherapy [121]. As an alternative to drug treatment, Shi et al. fabricated a drug-free separable microneedle patch comprised of chitosan lactate (CL) and adipose-derived stem cell exosomes for promoting hair regeneration (Fig. 7b). The exosomes could be sustainably released from needles after insertion into the skin, then the exosomes would be endocytosed by dermal papilla cells and promote cell proliferation via the activation of the Wnt/β-catenin signaling pathway. Compared with monotherapy of minoxidil, the microneedle patches could more significantly promote mice's hair regeneration within 7 days (Fig. 7c) [122]. As a painless, minimally invasive and side-effect free delivery vehicle for exosomes, microneedles are well suited for HF regeneration.

Although preliminary clinical data have shown their effectiveness in promoting HF regeneration and some phase I and phase II clinical trials are underway, but no exosome products have been formally approved by the FDA for therapeutic use [123]. And there are no complete clinical studies on the optimal source and dose of exosomes for the treatment of hair loss, more clinical trials are needed to demonstrate the safety and efficacy of exosome therapy. In addition, how to prepare clinical-grade exosomes on an industrial scale is also a limitation for the clinical application of exosome therapy. The techniques of exosome donor cell modification, culture, and exosome extraction and characterization are

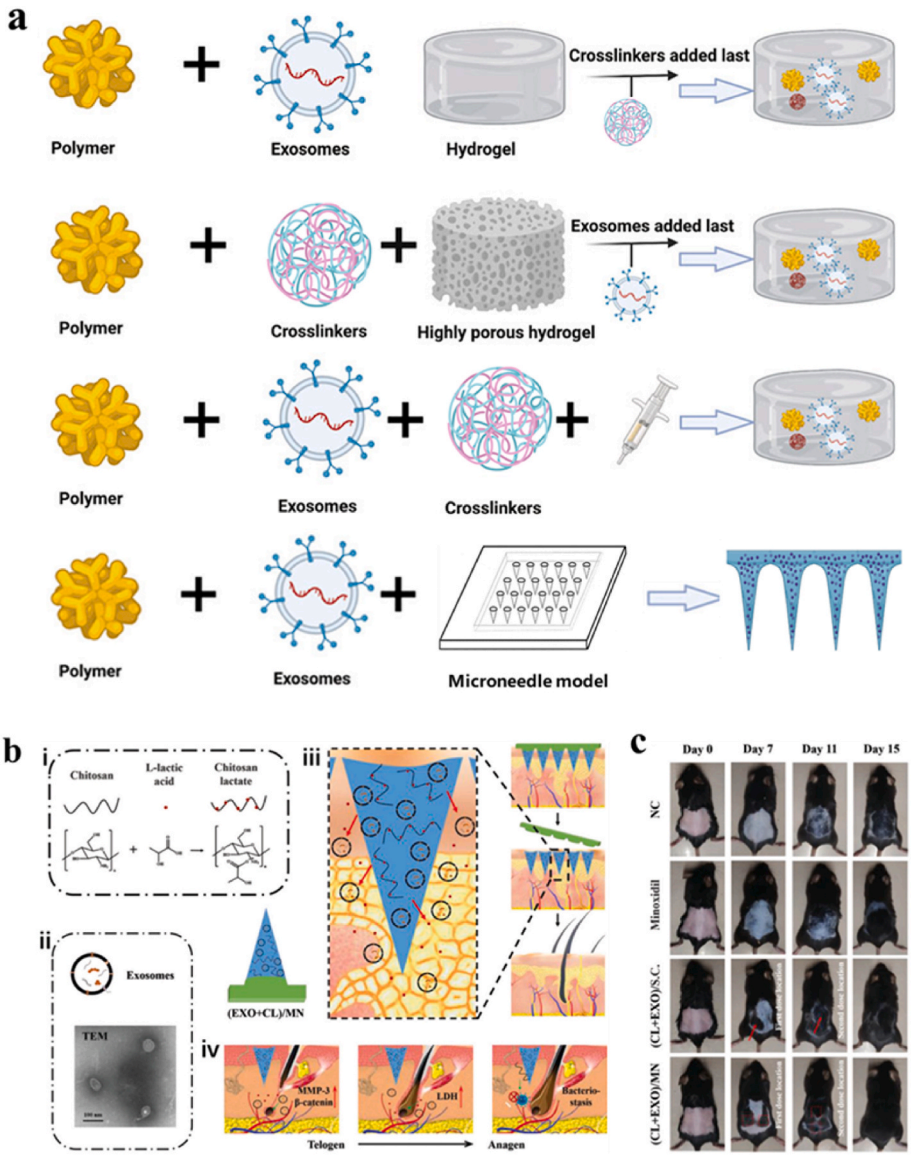

Fig. 7. Schematic diagram of exosomes composited with biomaterial vehicles (a); Schematic of composition (i, ii) and skin insertion (iii) of microneedle patch as applied for hair regeneration (b); Photographs of mice treated with microneedle patch or minoxidil respectively. Reprinted from Refs. [122,124].

also need to be further developed.

3.1.3. Biomimetic biomaterial scaffolds for endogenous hair follicle regeneration

The mammalian hair follicle is a complex microscopic organ, and hair follicles were once thought to be formed only during embryonic development, and complete damage of HF in adulthood was considered as permanent loss. But now researchers have developed a variety of wound dressings aim to achieve HF endogenous regeneration on the wound through multiple mechanisms such as microenvironment regulation, inflammation control and stem cell recruitment.

A recent article revealed the mechanism of biomaterial scaffold to promote re-epithelialization of wounds and facilitate HF regeneration: Yang et al. developed an electrospinning poly(lactide-*co*-glycolide) (PLGA)/fish collagen (FC) aligned extracellular matrix scaffold. That scaffold could accelerate wound coverage and suppress type 2 inflammation by modulating regulatory T cells, thereby reducing fibrosis and promoting HF regeneration [125]. Zhang et al. fabricated a sandwich-structured wound dressing using hydrophilic zinc silicate bioceramics (ZnCS) and hydrophobic polylactic acid (PLA) by the technique of hot compression molding. This bioactive bioceramic with unique organic/inorganic membrane structure shown excellent exudate absorption ability and effectively created a dry wound environment. Furthermore, the synergistic effect of Zn^{2+} and SiO_3^{2-} release by ZnCS could promote the recruitment, viability, and differentiation of hair follicle cells and promote HF regeneration [126]. Similarly using the bioactive effects of inorganic ions, a new type of nano-composited Cur-Fe-mesoporous silica nanoparticles, was reported that the released curcumin and biologically active SiO_3^{2-} and Fe^{3+} from nanoparticles had synergistic activity in both inhibiting scar formation and promoting HF regeneration [127]. Through electrostatic interaction, Ca^{2+} cross-linking, and lyophilization processes, Kang et al. demonstrate an alginate/chitosan/fucoidan (ACF) sponges as wound dressing, and the ACF sponges could promote HF regeneration by reducing inflammation and enhancing vascularization [128]. In addition, the physical structure like microscopic dimensions of the wound dressing material have recently been reported to determine its effect on HF regeneration. Wang et al. prepared aligned electrospinning membranes with different fiber diameters, compared with diameters of 588 ± 132 nm and 1048 ± 130 nm, membranes with diameter of 319 ± 100 nm could significantly

improve wound healing with the regeneration of immature hair follicles [129]. Due to the biophysical properties of biomaterial scaffold, it is more suitable for being used as wound dressing or artificial skin in cases of skin damage, to ensures normal regeneration of hair follicles while promoting wound healing.

3.1.4. Summary and prospects of biomaterial induced hair follicle regeneration

Because hair is closely related to the physical beauty of human, hair regeneration is the most clinically demanded and researched among the skin appendages in these years. But the hair follicle is a multicellular complex skin appendage, traditional hair repair methods such as drug therapy and hair transplantation have limitations and are prone to recurrence [130]. The development of biomaterial has provided the basis for novel HF regeneration strategies. Numerous cellular and animal experiments have demonstrated the effectiveness of biomaterials for HF regeneration [131]. Among these biomaterials, because microneedles can build inner tissue microenvironments through prick and dissolve into the skin and then release loaded bioactive components, that method is natural fit for hair regeneration. Therefore, in my opinion, delivering novel drugs or exosomes into the skin using microneedles is currently the best way to achieve HF regeneration safely and efficiently.

In addition, research on the molecular mechanisms of HF regeneration has brought many new insights. For example, skin-resident bacteria were proved to be the key modulators of keratinocyte metabolism, and bacterially induced hypoxia could improve the glutamine metabolism in keratinocytes with attendant enhancement of skin and HF regeneration [132]. Yin et al. found a micromolecular hexasaccharide OG6, which was able to promote regulatory T cells mobilization around HFs and stimulate the regeneration of robust hairs [133]. Psychological stress can lead to the increasing production of stress hormones (glucocorticoids) that cause defective activation of hair follicle stem cells, leading to hair loss [134]. These studies provide new ideas for hair regeneration through biomaterials. Novel technologies and methodologies will hopefully lead to new progress in HF neogenesis. For instance, combining reprogramming technique, organoid technology and nano-vehicle system, create and culture transplantable hair follicles as an alternative to HF transplantation is promising.

From the clinical perspective, it is still a long way to achieve HF endogenous regeneration using biomaterials in the clinic. First, safety testing of most synthetic biomaterials is limited to cellular and animal experiments, and no systematic clinical trials have been conducted [135]. Second, the physiological structures and signaling pathways of model animals' hair follicle are different from those of humans, and the results of related experiments may be difficult to be validated in humans. Third, the molecular mechanisms associated with hair loss and HF regeneration have not been fully clarified, and there are no drugs that can cure hair loss absolutely until now, so biomaterials are also limited [136]. But with the emergence of new drugs and treatments, combined with biomaterials with different properties, the challenge of HF regeneration will be overcome in the near future.

3.2. Biomimetic biomaterials for sweat glands regeneration

As one of the important skin appendages, the sweat glands are essential for maintaining internal environmental homeostasis by secreting sweat, regulating body temperature and excreting waste. Due to the existence of skin stem cells, injured sweat gland is usually able to renew and repair itself. Sweat glands may be another reservoir of progenitors maintaining homeostasis and promoting wound repair. Mouse sweat buds emerge before birth, K14+ multiple progenitors from the epidermis grow downward into dermis and differentiate to myoepithelial cells and luminal cells, once sweat glands get mature, the entire glands demonstrate few signs of cellular turnover. Besides, stem cells within sweat glands remain quiescent during wound repair. Surprisingly, Fuchs et al. revealed the unipotency of progenitors in the organ. Once glandular injury happens, neighboring myoepithelial cells and luminal cells can proliferate to replenish damaged cells respectively. While during epidermal injury, only basal cells in sweat duct accompanying cells in epidermis partake wound repair [137].

However, after a deep injury to the skin and scar tissue forms, the normal tissue microenvironment that would induce sweat gland regeneration is disrupted, making it difficult for sweat glands to regenerate naturally [138]. Similar to sweat gland regeneration strategies, transplanting seed cells to regenerate sweat glands and inducing endogenous sweat glands regeneration by biomaterials are the two main ideas to achieve structural and functional regeneration of sweat glands. Now various strategies such as stem cell therapy, bioactive factor induction and small molecule reprogramming have been applied to sweat gland regeneration studies [139].

3.2.1. Sweat gland regeneration: from cell transplantation to endogenous regeneration

Sweat gland stem cells are the direct source cells for sweat glands and are important for maintaining sweat gland homeostasis and repairing localized epidermis damage [140]. However, when the skin is deeply damaged, the sweat gland stem cells in the dermis are destroyed and are unable to proliferate and differentiate effectively to compensate for the missing sweat glands. In addition, sweat gland stem cells will lose their morphological properties when cultured *in vitro* [141]. Therefore, researchers have attempted to use stem cells with the potential to differentiate into sweat glands for sweat gland regeneration therapy. In the year of 2007, our team transplanted human sweat-like cells induced by bone marrow mesenchymal stem cells into the skin of a burn patient, first regenerated sweat-like tissue with normal sweat cell phenotype and sweating function [142]. Then our team used the CRISPR/dCas9 system upregulated the expression of Ectodysplasin-A, successfully used the reprogrammed sweat-like organs to regenerate sweat glands with sweating function in the mouse foot burn model, expanded the source of sweat glands cells [143].

Since cell transplantation cannot re-establish the suitable tissue microenvironment for sweat glands, and the activity and phenotype of the transplanted stem cells cannot be guaranteed in the long term [144]. Together with the potential risk of immune rejection and tumorigenesis, sweat gland endogenous regeneration with the help of biomaterials is becoming increasingly attractive.

3.2.2. Inducing endogenous sweat glands regeneration by biomaterials

Functionally designed biomaterial artificial skin can cover the wound and promote healing while also providing a suitable tissue microenvironment for the regeneration of artificial appendages such as sweat glands. Typical example: Kolakshyapati et al. developed a novel scaffold material for endogenous regeneration of sweat glands. They combined the collagen-chitosan porous scaffold with Lipofectamine 2000/pDNA-EGF complexes, and the BMSCs were seeded on the scaffold copplex. The seeded BMSCs were transfected endogenously by the released complexes and specially differentiated into sweat gland cells *in vitro* under the induction of the expressed EGF. Transplanting the scaffold complex onto the full-thickness skin defects of SD rat model, confirmed that GAS/BM-MSCs could accelerate wound healing and induce the regeneration of sweat gland-like structures by upregulating the expression of carcino-embryonic antigen (CEA), cytokeratin 8 (CK8) and cytokeratin 14 (CK14) [145]. In accordance with the tiny and subtle structure of sweat glands, 3D bio-printed biomaterial matrix makes it possible to precisely control the tissue microenvironment within biological materials. Three 3D bio-printed scaffold materials were constructed using 210, 340 and 420 μm diameter nozzles, the results showed that the 340 μm group of 3D bio-printed scaffold was the best choice for promoting the proliferation of mouse epidermal stem cells, maintaining cell activity and inducing the targeted differentiation of mouse epidermal stem cells into sweat gland cells [146]. Huang et al.

added the homogenate of mouse paw pad, epidermal stem cells (ESCs) and EGF into the gelatin/sodium alginate bioink, constructed the tissue microenvironment of sweat gland regeneration by 3D printing scaffold model. Results of cellular and animal experiments showed that the 3D printing models could accurately induce directional differentiation of ESCs to sweat gland like cells, and transplanting the sweat gland like cells into a burn model could partially regenerate mice's sweat gland [147]. That group has also reported that increased stiffness of hydrogel bioink can improve the differentiation efficiency of MSCs to sweat glands. The potential reason is that increased hardness promotes the activation of the Yes-associated protein mediated mechanotransduction signaling pathway in MSCs, thereby upregulating the expression of genes related to sweat gland differentiation [148].

As sweat glands endogenous regeneration is highly dependent on their local microenvironment, biomaterials can be designed to recruit endogenous stem cells and repair the tissue microenvironment that is unsuitable for sweat gland neogenesis by delivering bioactive molecules. Engineered exosomes are a highly promising strategy for endogenous regeneration of sweat glands. It was reported that biomimetic exosomes loading TGF-β1 were obtained from human umbilical cord mesenchymal stem cells (HUMSCs) could endow the epidermal keratinocytes with stem cell-like properties and enhanced the migration of keratinocytes to accelerate endogenous regeneration of sweat glands [149]. In addition, scarless healing through biomimetic biomaterials is another ideal way to achieve sweat glands *in situ* regeneration, just as reviewed in section 2.5.

Compared to hair follicle regeneration studies, fewer relevant studies have focused on sweat gland regeneration, but sweat glands are equally important in maintaining homeostasis in the body. Stem cell, tissue engineering and other repair techniques have promoted the progress of sweat gland regeneration technology, and provided references for related researches. However, there are still some challenges that need to be addressed: (1) Signaling pathways associated with sweat gland regeneration need to be further clarified to provide targets for biomaterial-based therapy; (2) Novel biomaterials have to be further developed and combined with new technologies, such as 4D printing, *in vivo* reprogramming, omics techniques, and smart responsive nanovehicles; (3) Reported biomaterials need further clinical trials to ensure their safety and efficacy of these therapies before they are used in clinical treatment in the future.

3.3. Biomaterial based strategies for endogenous regeneration of multiple appendages

Advances in biomaterials and stem cell technology have made it possible to create more complex skin tissue structures, but skin epidermis and dermis contain different cell populations, matrix compositions, as well as blood vessels and nerve endings, and the tissue microenvironments and activated signal molecules required for the regeneration of different skin appendages are various. For example, During the development of the mammalian ectodermal appendages, the Bone morphogenetic protein (BMP) and Sonic hedgehog (SHH) signals are the deciders of cell differentiation, leading to a completely different fate switch between hair follicles and sweat glands [150]. Therefore, the simultaneous regeneration of multiple skin appendages is still a challenge, and the construction of a differentiated microenvironment for the regeneration of different appendages in the same biomaterial system is a major bottleneck at present. At present, there are two main ideas to achieve simultaneous regeneration of multiple skin appendages: one is to construct artificial skin with multiple appendages for transplantation *in vitro*; the another is to induce multiple appendages endogenous regeneration by inhibiting the formation of scar tissue on the wound.

Lee et al. stepwise modulated the TGF-β and fibroblast growth factor (FGF) signaling pathways of human pluripotent stem cells (hPSCs), developed an organoid culture system that can generate complex skin organoid with pigmented hair follicles and sebaceous glands. Grafting the skin organoid onto nude mice, it could form skin tissue with mature hair follicles and hairs. This skin organoid will provide a foundation skin appendant development and reconstructive treatment [151]. In order to develop a skin model with both hair follicle and sweat gland structures, Zhang et al. seeded the hair follicle spheroids on 3D printed gelatin/sodium alginate/sweat gland cells scaffolds, successfully established a three-dimensional bio-printed skin model with sweat glands and hair follicles [152].

On the other hand, as described in section 2.4, important progress has been made in recent years in the study of the molecular mechanisms of scar formation. Mechanical force signals to the wound would activate the YAP signaling pathway and translocate YAP to the nucleus, thereby activating the Engrailed-1 gene, which in turn leads to fibroblast overexpression of type I collagen and ultimately to proliferative scar tissue formation. Knockout of the *YAP* gene or using Verteporfin, which is the inhibitor of the YAP protein, could effectively inhibit the formation of scar tissue and promote endogenous regenerate of hair follicles and sebaceous glands [79].

Several studies have finished the regeneration of two skin appendages, but there is still no report of successful regeneration of three skin appendages together. It is worth mentioning that our group has now achieved reprogramming regeneration of sebaceous glands by lentiviral transfection and small molecule induction [153]. In our ongoing researches, we will attempt to induce simultaneous endogenous regeneration of three skin appendages using *in vivo* small molecule reprogramming techniques. We believe that in the near future it will be possible to achieve skin perfect regeneration with the feature of rapid, scar-free and appendages intact.

4. Property and function design of biomimetic biomaterials for endogenous skin regeneration

To achieve the goal of fast and high-quality endogenous skin regeneration, a series of biomimetic biomaterials are developed to repair, replace, and regulate the dysfunctional tissues to restore the homeostasis of skin. The molecular structure of biomaterials determines their physical and biological properties, and the properties of biomaterials are inseparable from their application in wound healing. In this section, the requirement of physical and biological functions of novel biomimetic biomaterials for wound healing have been summarized, and then revealed how the physical properties and external stimulus-responsiveness of materials modified through molecular design according to clinical needs, so as to intervene and promote the dynamic process of wound healing through biomaterial-based skin structure reconstruction and microenvironment regulation.

4.1. Physical property design of biomaterials for endogenous skin regeneration

4.1.1. Mechanical properties

The mechanical signals play an important role in regulating stem cell proliferation, stemness maintenance, and differentiation [154]. The major mechanical properties of biomaterials used in wound regeneration include stiffness, elastic modulus, tensile strength, viscoelasticity and so on. Among these, cell fates regulated by matrix stiffness has been widely studied. To skin cells, epithelial cells cultured on stiff matrixes exhibited higher activity of migration and adhesion, and the higher activity of cells can maintain for a long time after transfer on the softer matrix [155]. Matrix with too hard stiffness will lead to differentiation of fibroblasts to myofibroblasts, which is the key pathological process causing the formation of hypertrophic scars [156]. In addition, the mechanical signals were also reported to regulate immune responses by influencing the behavior of human monocyte-derived macrophages [157], which can further affect the inflammatory phase of wound healing.

Most commonly used medical hydrogels are made of natural macromolecule polymers such as fibrin, chitosan, collagen, hyaluronic

acid and alginate, that can mimic the structure of natural tissue. However, the mechanical strength of natural hydrogel is essentially poor. On the other hand, synthetic polymer hydrogels such as poly(ethylene glycol) (PEG), poly(acrylamide) (PAAM) and poly(vinyl alcohol) (PVA) possess controllable chemical and mechanical features, but they are weak in bioactivity. Polymer hydrogel's mechanical property is closely related to its molecular chain structure (molecular weight, way of cross-linking, degree of crystallinity, etc.), lots of physical and chemical modified methods are developed referring to clinical need.

According to the requirements, there are generally two approaches to controlling the mechanical properties of polymeric polymers. The first is to change the cross-linked structure of the hydrogel by chemical modification. Increasing the crosslink density by enhancing molecular interactions (physical entanglements, hydrogen bonds, hydrophobic interactions, coordination interactions, etc.) between molecular chains through molecular design is the most commonly used way to enhance the mechanical properties of hydrogels [158]. Novel hydrogels whose Young's modulus range from a few Pa to a few GPa [159] and reversible tensile strain rate reach 10,200 % [160] have been reported. They can fully meet the mechanical performance requirements of simulating human skin (Young's modulus between 0.5 and 1.95 MPa, tensile strain rate between 140% and 180 %). Hydrogel crosslinked by non-covalent bonds like hydrogen bonds and Schiff base reaction showed excellent self-healing capability, demonstrating great potential in wound healing [161]. Moreover, building dual cross-linked network hydrogels and composite-formed supramolecular networks are two effective ways to improve the mechanical properties of hydrogels as well. Several recent studies have achieved variable mechanical properties of hydrogel materials, providing a reference for mimicking the dynamic changes of mechanical properties of ECM in wound healing [162]. The chemical composition, mechanical property and their potential applications of reported hydrogel materials for wound healing in recent two years are summarized in Table 1.

4.1.2. *Surface topography*

Surface topographies of biomaterials mainly include surface

Table 1
Chemical composition, mechanical properties, and functions of recently reported hydrogel biomaterials.

Monomers of polymer	Reinforcing phase	Cross-linking bonds	Elasticity modulus	Storage modulus	Tensile strength	Physical property	Biological property	Application	Reference
aldehyde group modified HA + gelatin	Silver nanoparticles	amidation reaction	/	about 200 Pa	1500 kPa	wet adhesion	antibacterial ability	treating abdominal wall injury	[163]
Pluronic F-68 + Pluronic F-127	glucose oxidase	micellization	/	about 300 Pa	/	thermo-sensitivity; injectability	antibacterial ability	skin wound healing	[164]
tea polyphenols + polydopamine + polyvinyl alcohol	/	cyclic freeze-thaw	20.65 ± 0.52 Mpa	/	3.32 ± 0.10 Mpa	photo-thermal conversion	antibacterial and antioxidant ability	inhibit resistant bacteria; skin wound healing	[165]
glycol monomethyl ether modified glycidyl methacrylate functionalized chitosan + methacrylamide dopamine	zinc ion	photo-polymerization and zinc ion coordination	/	283 Pa	37 kPa	tissue adhesion	antibacterial ability; hemostatic ability	hemostatic material; healing of infected wounds	[166]
protocatechualdehyde + quaternized chitosan	ferric iron ion	coordinate bond and Schiff base bonds	/	1980 Pa	19.1 MPa	injectability; autonomous healing; NIR responsiveness	antibacterial ability; hemostatic ability	wound closure; infected full-thickness skin wound healing	[167]
gelatin methacryloyl	cerium oxide nanoparticles and antimicrobial peptide	free radical crosslinking	/	/	25.3 + 1.5 kPa	sprayable property; ROS scavenging	antibacterial ability	skin-remodeling material	[168]
polyacrylamide + chitosan quaternary ammnonium salt	litmus	covalent bond crosslinking	/	/	30 kPa	adhesion; intelligent wound monitoring	antibacterial ability; hemostatic ability	accelerate wound healing; smart chronic wound management	[169]
guar gum based hydrogel	dopamine modified gelatin Ag nanoparticles	borate/diol bonds	/	about 150 Pa	/	injectable; self-healing; antioxidant activity	NIR synergistic antibacterial ability	prevent bacteria-derived wound infection; accelerate wound healing	[170]
adipic dihydrazide modified hyaluronic acid + benzaldehyde group functionalized poly(ethylene glycol)-co-poly(glycerol sebacate)	cuttlefish melanin nanoparticles	Schiff base reaction	/	about 220 Pa	/	tissue adhesion; stretchability; self-healing; anti-oxidation	photothermal antibacterial ability; hemostasis; exudate absorption	treat motion wound infections; promote wound healing	[171]
Silk fbroin + acryloyl-β. cyelodextrin + 2-hydroxyethyl aerylate	curcumin	photo-polymerization by host-guest interaction and hydrophobic β-sheet conformation	/	/	/	rapid self-healing; injectability; drug delivery ability	antioxidant and anti-inflammatory activity; boosting wound healing	boost better wound healing performance wound dressings	[172]

geometrical shape and orientation, surface pore size and surface roughness. More and more studies reveal that the microenvironment constructed by the surface topography of biomaterials has a great influence on the adhesion, migration, proliferation, and differentiation of cells in the skin regeneration process [173]. Typically, the natural biological tissues have specific topological structures which are closely related to their physiological functions. The surface topology structure in different tissues is one of the factors that regulate the biological behavior of cells. According to the natural structure of physiological tissues, tissue scaffolds with various types and sizes of porous and topography structure for regulating cell or tissue growth have been designed and fabricated [174].

Based on the clinical requirements and inherent properties of biomaterial, several technologies such as soft lithography [175], electrospinning [176], 3D-printing [177] and nanoimprinting [178] have been used to produce specific micro/nanoscale topographies on biomaterial surfaces. Nanoimprinted patterned PVA hydrogels with different isotropic and anisotropic topographies could significantly promote vascular endothelial cells attachment on it both *in vitro* and *in vivo* compared with non-patterned PVA hydrogel [179]. Vicente et al. found the orientation of migration of fibroblasts could be faster and more well-organized on polyurethane-amide hydrogels with variable groove width of 1–9 μm prepared by UV-assisted capillary molding [180]. Micrometer level hexagonal topography on poly(dimethylsiloxane) (PDMS) was reported to have the function of accelerating epithelial cell proliferation [181].

Surface nanostructures have been also reported to affect macrophage phenotype. Hu et al. fabricated electrospun membranes with three types of surface topography (random, aligned and latticed, Fig. 8a). The experimental results showed that the surface microstructure of wound dressings could form different immune microenvironments, and further affected wound healing (Fig. 8c–e) [182]. In addition to fiber arrangement, diameter of electrospun PLA nanofibers has been shown to increase the anti-inflammatory phenotype of macrophages compared with flat or micron fibers [183]. Additionally, constructing microscopic surface topography on polymer materials could provide antibacterial and antifouling properties to the materials, which is helpful to ensure the long-term stability of biomaterial implants [184].

The correct design and fabrication of appropriate topographical features on the surface of biomaterial scaffolds will be helpful for the development of wound dressing with excellent physical and biological performance in regenerative medicine.

4.1.3. Tissue adhesion

Adhesion of biomaterial is also one of the key properties for fast closure and long-term wound coverage. Polymer tissue adhesive with strong adhesion is an essential application of biomaterials in skin injury repair. Sutures, staples and clips are the most commonly used method for skin wound closure in current surgical procedures, but using these devices may cause secondary damage and induce hypertrophic scar [185]. Polymer adhesive materials have been widely used to seal and repair the skin wound. Traditional adhesive like cyanoacrylate has strong adhesiveness, but its serious biological toxicity severely limits its application in biomedical field.

Through noncovalent interactions (such as hydrogen bonds, hydrophobic interactions, Van der Waals' force and cation-π interactions) and covalent bonds (e.g., coordination bonds, Michal addition, and Schiff base reactions) between biomacromolecules, a series of novel tissue adhesives with strong adhesion, excellent mechanical properties and multiple advanced functionalities have been developed. Cintron-Cruz et al. combined pH-responsive bridging chitosan chains and polyacrylamide-alginate hydrogel dissipative matrix, its adhesion to tissues could arrive staggering 2000 J m^{-2} within 10 min through covalent bond with the functional groups of skin (such as –COOH and $–NH_2$ groups in collagen) [186]. Based on similar mechanism of enhancing interfacial interaction, a hemostatic paste was developed inspired by the barnacle glue, the paste consists of a blood-repelling hydrophobic oil matrix containing embedded microparticles that can covalently crosslink with tissue surfaces, enables fast and coagulation-independent hemostasis [187]. Tannic acid is a potential natural biological glue due to its pyrogallol group which is similar to the catechol groups of dopamine, Li et al. reported a ternary tissue adhesive by simple mixing of tannic acid (TA), polyethylene glycol (PEG) and gelatin. The covalent bond between TA and gelatin, and the hydrogen bonds between TA and PEG together lead to the excellent adhesion of the ternary adhesive and enabled the complex to dissipate energy upon deformation. Moreover, this ternary adhesive showed significant antibacterial activity, biocompatibility, degradability and wound repairing ability on rat skin wound model [188].

4.1.4. Conductivity

Skin is one of the electroactive tissues of the human body, and

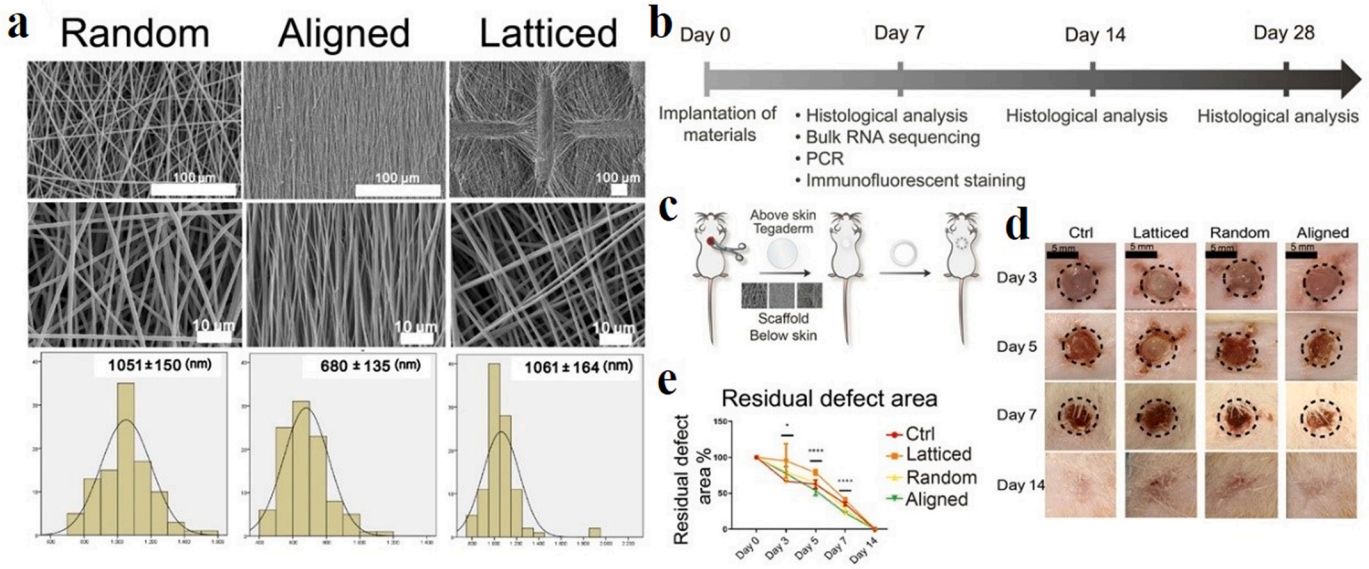

Fig. 8. (A) Surface topography of random, aligned, and latticed electrospun membranes. (B) Workflow for evaluating rat skin wound healing. PCR, polymerase chain reaction. (C) Surgical processes for the rat skin excisional wound model. (D and E) Residual wound area at 3, 5, 7, and 14 days. Reprinted from Ref. [182].

endogenous skin bioelectric field plays an important role in skin wound healing [189]. Through ion transport between the epithelium and the epidermis, the epidermis maintains a potential of 10–60 mV [190]. Once skin injury happens, endogenous electric fields ranging from 40 to 200 mV/mm will generate and mediate the beginning of wound healing [191]. The positive effects of bioelectricity on the regeneration of bioelectrically active tissues have been well recognized through promoting cell proliferation, differentiation and migration.

However, most macromolecule biomaterials are non-conductive because their molecular chains lack free electrons. At present, there are three main ideas to prepare conductive polymer materials: the first is to construct intrinsic conducting polymers such as polyaniline (PANI) and polypyrrole (PPV); the second is to add conductive inorganic materials (metal powder, carbon black or graphene) in polymers; the third is to physically composite other types of conductive nanomaterials with polymers. So far, a series of conductive wound dressings in different forms such as hydrogel, film, membrane and electrospun nanofiber have been developed by the mechanism of facilitating the transmission of endogenous bioelectricity or electrical stimulation to electroactive cells and tissues.

The conductivity of wound dressing, as one of the physical properties of multifunctional wound repair materials, has been shown to have the function of promoting the healing of chronic wounds [192]. On the other hand, conductive hydrogel wound dressings can transmit the skin's endogenous electrical signals and increasing intracellular Ca^{2+} concentration, and then promoting the regeneration of skin's blood and nerves by promoting phosphorylation of proteins in the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway and mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway [193]. Moreover, another application of conductive biomaterials is as wound sensors, which can perceive the changes of physical and biological microenvironments of wound in real-time. Fan et al. developed a conductive tetrabenzaldehyde-functionalized pentaerythritol/chitosan hydrogel (CPT) via dynamic hydrogen bonds and Schiff base cross-linking bonds. The CPT hydrogel also had the properties of injectability, self-healing, broad-spectrum antibacterial activity and promoting wound healing. Meanwhile, the movement and strain of the hydrogel would lead to changes of resistance value, and then changing the current inside the hydrogel, thereby it could act as a real-time monitoring sensor [194].

4.2. Stimulus responsive biomaterials for endogenous skin regeneration

Skin wound healing is a multi-stage dynamic process. During this process, the physical, chemical and biological microenvironment of wound will undergo continuous dynamic changes. Target to the changes of wound microenvironment, dynamic stimulus-responsive biomaterials are designed and developed. Stimulus-responsive biomaterials, as a new type of smart biomaterial, have more advantages in sensing external physical (light, temperature, pressure, electric field, magnetic field, etc.), chemical (pH, reactive oxygen, ions, etc.) and biochemical (enzymes, etc.) stimuli. Stimulus-responsive biomaterials can receive specific signals, and then respond with a specific physical or chemical reaction (shape change, mechanical property change, release of content, etc.). Therefore, stimulus-responsive biomaterials are becoming a series of ideal materials for skin wound healing.

4.2.1. Piezoelectric material

In the process of wound healing, external microcurrent can increase blood flow, promote fibroblast cell migration, angiogenesis and collagen deposition, thereby accelerating wound healing [195]. However, the source of the external charge is a problem. One solution is to use wound dressings with piezoelectric properties on wounds. When piezoelectric material receives mechanical forces such as stretching, compression and bending, charges and electric potential difference will be generated on two opposing surfaces of the material. It is worth mentioning that some biological molecular such as collagen and hydroxyapatite also have piezoelectric effect caused by the movement of asymmetrical structure derived dipole moment [196]. Skin, bones, ligaments and tendons tissues also exhibit the piezoelectric effect as a result of the piezoelectric collagen and protein molecules.

Recently, with the development of surface modification and tissue engineering, many novel biocompatible piezoelectric materials which are able to connect and interact with human tissues (skin, muscles, bones, nerves, etc.) have potential for further application in regenerative medicine. Compared with traditional treatment strategies, bio-piezoelectric materials can dynamically supply controlled electric field to accelerate wound healing [197]. PVDF and its copolymers are the most commonly used bio-piezoelectric polymers. In addition, poly--L-lactic acid, polyacrylonitrile, polyvinyl chloride, and nylon-11 are also reported to be used as piezoelectric material of wound dressing. Liang et., reported a 3D-printed ZnO nanoparticles modified PVDF/sodium alginate (SA) piezoelectric hydrogel scaffold (ZPFSA) as wound dressing. The ZPFSA scaffold had dual piezoelectric response models, which can be used to simulate and amplify endogenous bioelectricity to promote wound healing and prevent scar formation [198]. Piezoelectric materials can also be used in combination with sonodynamic therapy, Wu et al. developed a piezoelectric barium titanate ($BaTiO_3$) nano-cubes with Schottky junction modified by Au nanoparticles (Au@BTO) as a new kind of sonosensitizer for high-efficient sonodynamic therapy for wound healing. Ultrasound as an exogenous source of mechanical energy, can trigger the piezoelectric effect of Au@BTO, promote wound healing by generating free charges. Besides, this piezoelectric nanocomposite also had enhanced antibacterial activity by promoting ROS generation via redox reaction, had great potential for bioelectric and sonodynamic therapy for wound healing [199].

4.2.2. Magnetic materials

Previous studies have shown that external magnetic field has the effect of improving blood circulation and thus improving the quality of wound healing. Magnetic field and electromagnetic field have positive effects on skin regeneration, regulating the disorders of the central nervous [200]. There are several hypotheses about the mechanism of the therapeutic effect of external magnetic field: (1) external magnetic can control the movement and transfer of unpaired electrons in free radicals and regulate the generation of reactive oxygen species (ROS), and then accelerate tissue regeneration by resisting oxidative stress; (2) The magnetic field causes changes the permeability and membrane potential of cell membranes that affects sodium content and potassium-efflux or the transmembrane voltage; (3) magnetic field may affect the enzymatic activities of some metal ions-related enzymes; (4) external magnetic fields may affect the transport and distribution of Ca^{2+}, which is an important transduction second messenger of cell signal transduction [201].

It was reported that static magnetic field (SMF) generated from neodymium permanent magnets was able to reduce ROS, oxidative stress and promote diabetic mice wound healing [202]. However, human keratinocytes cultured under the rotating magnetic field (RMF, f = 50 Hz, B = 28.4 mT) showed lower ROS levels, lower intracellular Ca^{2+} concentration and lower viability than control group, which is not conducive to wound healing [203]. So, more studies should be conducted to further evaluate the effect of external magnetic field on skin regeneration.

At present, the magnetic materials used for wound healing are mostly used as reinforcing phases that endow composite biomaterials with special physical properties. For example, adding silica coated magnetic nanoparticles (Fe_3O_4@SiO_2) into agarose/hyaluronic acid methacrylate (HAMA) microspheres, can make it easily and flexibly to capture and remove the microspheres from the solution by a magnet [204]. Moreover, adding magnetic material into nanoparticles with high surface energy and cohesiveness can significantly enhance their dispersity into water and protect them from aggregation [205].

4.2.3. Shape-memory biomaterials

Shape-memory materials are a class of smart materials that can recover its definite permanent shape from variable temporary shape in response to external physical stimuli like heat, light, pressure, etc. Nitinol is the first material discovered to have shape memory effect, and the most of the early discovered shape memory materials are metal alloys. Now researchers have discovered that some polymeric materials also have shape memory effects. The permanent shape of shape-memory polymers is the thermodynamically favorable shape. When the polymer molecular system receives external energy, the molecular conformation is changed and some chemical bonds formed at that time as a "trigger", fix the molecular chain to its temporary shape and storing the energy related to the deformation. When the trigger gets a certain stimulating signal, the polymer chains will be unfrozen, then recover its permanent shape [206]. This unique property of shape-memory polymers allows them to be used as sharp memory stitch or controlled release drug vehicles.

For biomedical applications, shape-memory polymers are well suited as self-degrading surgical sutures due to their excellent biocompatibility and biodegradability. Gong et al. reported a thermo-sensitivity sharp memory stitch composed of polyurethane and polycaprolactone. When the proportion of polyurethane reached 30 %, the stitch reveled best shape memory effect and self-knotted after heating [207]. Herting et al. found that a coil coated with a porous shape-memory foam could promote neointima formation in the aneurysm neck, which in turn led to a full recovery [208].

The property of stimuli-responsive structural change provides the ability of encapsulating and releasing the drugs to shape memory polymers. Wischke et al. developed a shape-memory polymer matrix as drug release system. Enoxacin, nitrofurantoin, and ethacridine lactate could be well encapsulated and released by structural change of the polymer. Besides, encapsulating drugs into the polymer network would not affect the mechanical properties of the polymer [209]. The drug delivery system based on shape-memory polymers have potential to be applied as drug vehicle composited with other matrix polymers for skin regeneration.

4.2.4. Photothermal biomaterials

Photothermal materials, which are able to absorb photon energy and convert it into heat energy, are the basis of photothermal therapy. Now novel photothermal materials enables controlled localized and quantitative heating through changing the distribution and proportion of photothermal agents, irradiation time, and laser intensity. The current applications of photothermal materials in the field of skin regeneration are mainly in the following two areas:

The first is the photothermal antibacterial effect. The high temperature generated by the photothermal effect (>50 °C) can cause irreversible protein denaturation, which affects the activity of enzymes inside the bacteria, as well as affecting the permeability of the cell membrane, thus killing the bacteria [210]. As physical antimicrobial materials, photothermal materials is one of the best strategies to avoid drug resistance of bacteria. Ma et al. developed a molybdenum disulfide-ceria (MoS_2–CeO_2) nanocomposite material that had both photothermal antibacterial capability of polyethylene glycol modified molybdenum disulfide nanosheets and the antioxidant activity of cerium dioxide nanoparticles. The MoS_2–CeO_2 nanocomposite revealed excellent photothermal antibacterial activity under 808 nm laser, as well as sustained antioxidant activity through reversible transformation of Ce^{3+} and Ce^{4+}. It is a promising material for chronic wounds treatment especially the infected diabetic wounds [211]. With the help of the Local Surface Plasmon Resonance (LSPR), metal ions like Cu^{2+} and Ag^{+} can synergistically enhance the photothermal antibacterial ability of photothermal materials [212,213]. By sustained release of metal ions and controlled light treatment, can achieve stable and controllable antibacterial effect. Luo et al. reported a photo-responsive metal–heterojunction composed of two organic framework (MOF) materials Prussian blue (PB) and PCN-224. Due to the accelerated separation of photogenerated electron-hole pairs and releasing of iron and zirconium ions, after irradiation of 660 nm light for 15 min, the PB-PCN-224 heterojunction showed high antibacterial rates (99.84 %) against *Staphylococcus aureus*. Besides, this junction material also revealed the ability of accelerating wound healing (Fig. 9) [214]. In order to enhance the sustained antibacterial ability of photothermal antibacterial materials, they can be compounded with antibiotic drugs as well. Deng et al. developed a polysaccharide hydrogel compounded with ferric tannate (TA-Fe) nanoparticles and vancomycin. The vancomycin could be controlled released by NIR irradiation treatment, and the vancomycin could be released continuously after the NIR was removed. After 5 days of treatment, the wound covered by the TA-Fe/vancomycin composite hydrogel showed the highest wound closure rate (80 %) and no bacterial infections occurred [215].

The second is promoting the proliferation and migration of skin cells through light derived thermal effect. Previous report has proved that the mild local heat (41°C–43 °C) can promote cell proliferation and angiogenesis, accelerating wound healing and skin regeneration [216]. By simply physical mixing of thiolated HA and CuS nanoparticles, Zhou et al. successfully prepared the photothermal CuS/HA hydrogel as wound healing. After laser irradiation (808 nm, 1 W/cm^{-2}) for 10 min, the temperature of the CuS/HA hydrogel injected on the wound could rise to 50.3 °C gradually, and it could effectively up-regulate the expression of vascular endothelial growth factor (VEGF) and promote the formation of new blood vessels in the process of wound healing [217].

However, the photothermal materials cannot work in a situation without NIR equipment, and the low tissue penetration rate of NIR limit the application of photothermal materials in deep tissue diseases. To solve this problem, some researchers combined photothermal property with magnetothermal ability or external electrical stimulation. Du et al. designed a conductive and photothermal electronic skin (e-skin) patch using polypyrrole/Pluronic F127 hydrogels as the electrolytes. By synergistically utilizing electrical stimulation and photothermal heating effect, this E-skin patch could significantly promote wound closure, angiogenesis, collagen deposition and re-epithelization. Moreover, the E-skin patch had revealed the potential as a sensor to monitor human activities for patients with anaphia diseases [218]. In conclusion, photothermal materials should further incorporate with new drugs and other forms of materials to broaden their applications for wound healing and tissue regeneration.

4.2.5. pH-responsive biomaterials for promoting skin regeneration

The process of wound healing is accompanied by a significant change in wound pH value, and the pH value of wound is closely related to the successful healing of the wound. For example, changing the wound microenvironment from alkaline to acidic is necessary for the hemostasis and inflammatory stage of rapid healing in order to inhibit microbial reproduction, prevent infection, and promote oxygen release and angiogenesis. For the proliferative and remodeling phases, an alkaline environment is required to promote the migration and accretion of fibroblasts and keratinocytes [219]. However, the microenvironmental disturbances marked by long-term alkaline wound microenvironment can cause chronic non-healing wounds [220]. Taking advantage of this phenomenon, pH responsive materials are designed based on the pH-triggered release mechanisms.

pH-responsive drug delivery biomaterials are generally designed through two strategies. One is releasing drugs through pH-induced swelling or dissolving of the polymeric biomaterials, another is conjugating the drugs in to the vehicle material with pH-responsive fractured chemical bonds. Eudragit S100 is a pH-sensitive polymer, which only dissolves in the solution of alkaline condition. Coating thin Eudragit S100 film can provide pH responsive drug-delivery ability to PLGA/gelatin microneedle. At normal skin (pH 4.5), the drug loaded in the microneedle was released at low level. But at pH 7.5 which is equal to

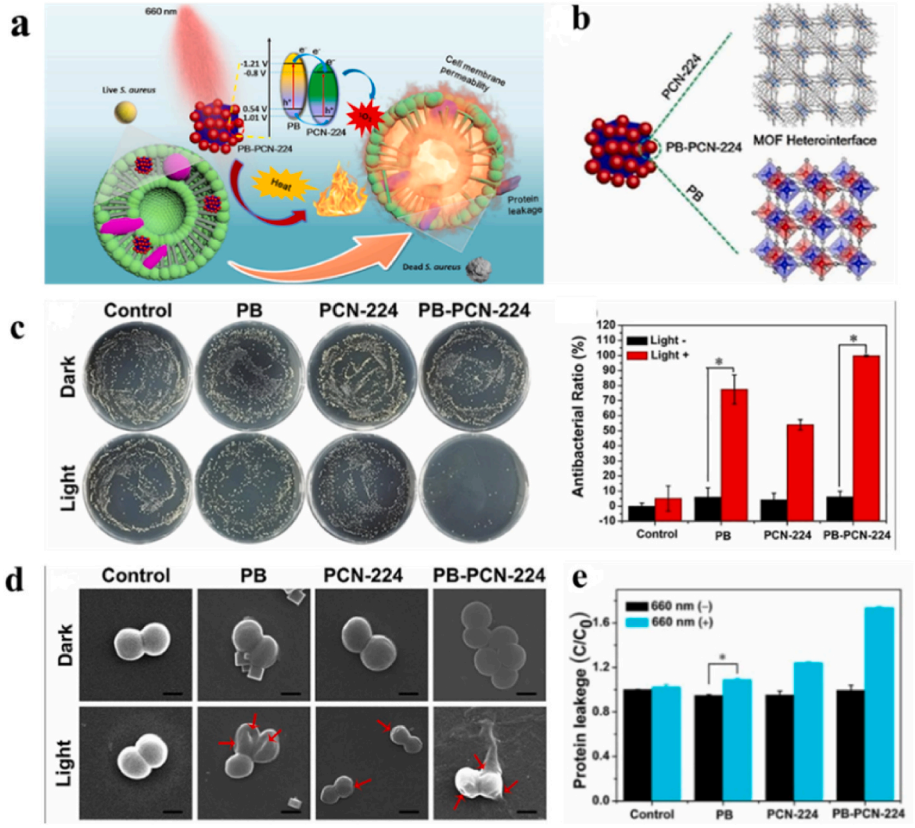

Fig. 9. Schema of the synergy of the ROS and photothermal effects in the germ-killing response of PB-PCN-224 (a); The crystal structure diagram of PB-PCN-224 (b); The spread plate images and antibacterial rate of PB-PCN-224 against *S. aureus* (c); SEM pictures of the morphology of *S. aureus* treated with or without 660 nm light irradiation (d); The protein leakage concentration of *S. aureus* treated or not treated with 660 nm light irradiation (e). Reprinted from Ref. [214].

wound pH conditions, the drug releasing was significantly increased, thereby achieved controlled release of encapsulated drugs in response to wound pH levels to accelerate wound healing [221]. Cai et al. developed a multilayer film composited by titania nanotubes (TNT) and alginate dialdehyde (ADA), BMP-2 was physically loaded in the multilayer film and gentamicin (Gen) was chemical bonded with ADA through the imine double bonds. As the imine double bond is easily broken in acidic environment, once the multilayer film was degraded in acidic infected tissue, BMP2 and Gen would be released. Thus, this TNT-ADA/BMP-2/Gen film revealed excellent antibacterial activity and anti-infection ability [222]. Zha et al. prepared Cu–HAs nanoparticles with dual responsiveness to photothermal effects and pH, then loaded these nanoparticles into PVA films containing the macrophage recruitment agent SEW2871. This PVA@Cu–HAs NPs@SEW film could improve wound healing by NIR-induced local hyperthermia and promoting M2 macrophage polarization [223].

4.2.6. *Enzyme-responsive biomaterials for promoting skin regeneration*

Enzymes play a vital role in chemical and biological processes of wound healing, so enzymes can be used as triggers to change the structure and properties of biomaterials to create smart responsive materials. Enzymes have a high selectivity for a certain substrate, so that it has much higher accuracy of controlled release than pH triggers.

Matrix metalloproteinases (MMPs) and serine proteases, which play an important role in promoting wound healing, are two main targets of enzyme responsive wound dressing materials. Members of the MMP protein family are significantly differentially expressed at different times of wound healing. For example, MMP-1 and MMP-9 are mainly expressed in the first three days after wound formation. The peak of MMP-2 and MMP-8 expression is on day 5, then it decreases rapidly thereafter. And MMP-7 consistently maintained a high expression after the third day. In contrast, MMP overexpressed on pathological chronic wounds such as diabetic wounds [224]. So, it is an ideal method to control the delivery of drug by using the transient expression of MMPs. Through a boronic ester-based reaction between the phenylboronic acid groups of the 3-carboxyl-4-fluorophenylboronic acid-grafted quaternized chitosan and the hydroxyl groups of the polyvinyl alcohol, Shao et al. developed DFO@G gelatin microspheres that loading a pro-angiogenic drug of desferrioxamine (DFO). The DFO@G microspheres could sustain release the DFO by responding to the overexpressed MMPs, and then accelerated angiogenesis by upregulating expression of hypoxia-inducible factor-1 and angiogenic growth factors, resulting in collagen deposition and rapid wound closure [225].

Some enzymes produced by the reproduction of wound bacteria can also be used as targets for the antibacterial enzyme-responsive biomaterials. Wang et al. reported a series of quaternized triblock copolymers (QP-*b*-PCL-*b*-QPs), and synthesized them into reverse micelles (RMs) in tetrahydrofuran. The shell of RMs contained bacterial lipase-responsive poly(ε-caprolactone) (PCL). In the presence of bacterial lipase, the biodegradable PCL blocks were hydrolyzed, resulting in the responsive release of quaternary biocidal agents (QBAs), and then revealed its antibacterial activity and control the infection of the wound [226].

With the deepening research on wound healing mechanism and the application of new biomaterials, new responsive targets and multi-responsive materials will be the key focus for the development of smart controlled release materials.

4.3. *Biocompatible and low immunogenic biomaterials for endogenous skin regeneration*

Immune system may recognize the transplanted biomaterial as a

foreign object. Once the host immune system recognizes the foreign biomaterial, a series of immune cascade reactions will be initiated, leading to host's foreign-body response (FBR) [227]. FBR to implanted biomaterials will cause overreaction of immune cells and overproduction of hydrolytic enzymes, lead to biomaterial implant failure and fibrotic capsule formation [228]. Potential immunogenicity is also one of the major reasons why many biomaterials are difficult to be used clinically. There have been previous reports of biomaterial implants being discontinued due to immune rejection of the product in clinical trials [229]. Therefore, how to improve the biocompatibility of biomaterials and inhibit the occurrence of immune rejection is a challenge that needs to be faced in the clinical application of biomimetic biomaterials for skin wound healing.

Based on the new advances in the researches on the mechanisms of immune rejection reaction, a variety of strategies for designing and improving biomaterials to minimize immune rejection are now available. The first one is to choose biocompatible polymers as matrix materials. Some bioactive polymeric materials derived from natural organisms such as sodium alginate, hyaluronic acid, silk fibroin, gelatin, and chitosan have good biocompatibility and biodegradability, which are often used as matrix materials for wound dressings and artificial skin [230]. Synthetic polymers such as PEG, PVA and PLGA are somewhat less biocompatible and biodegradable than natural polymers, but they have better mechanical properties and customizability [231]. These polymer molecules often contain a large number of hydrophilic bioactive groups such as –OH, –COOH, $–NH_2$, etc., which can modulate macrophage attachment, polarization, and cytokine secretion through interactions with immune cells, thereby reducing the occurrence of immune rejection [232]. Inspired by the serine-rich sericin in silk, Zhang et al. reported a low foreign-body response Poly-β-homoserine monolayers material which can resist adsorption and adhesion of diverse proteins and cells. Three months after transplantation, the Poly--β-homoserine monolayers did not cause significant inflammatory response, macrophage aggregation, or tissue fibrosis compared to the PEG hydrogel used as a control [233]. In addition, cross-linking agents and *in vivo* degradation products of some polymers can induce FBR as well, that requires special attention [234].

The second key factor affecting the immune rejection to biomaterial is physical properties, such as surface structure, stiffness, and feature size. Just as reviewed in section 4.1, the physical properties of biomaterials can modulate the proliferation, migration, differentiation and polarization of immune cells as well [235]. The surface topography of biomaterials is closely related to protein adsorption and cell adhesion, further influence immune cell recruitment and macrophage phenotype [236]. Vassey et al. had researched the relationship between biomaterial surface topography and monocyte-derived macrophage attachment and phenotype used high throughput screening approach [237] The results show that the density of micron columns on the surface of biomaterials is key to controlling the immune response [238]. Another research revealed that silicone implants with an average roughness of 4 μm caused the least inflammation and foreign body response [239]. The relationship between mechanical properties of biomaterials and immune rejection response is still controversial. It has been reported in the literature that soft (11 kPa) and medium stiffness (88 kPa) polyacrylamide hydrogels tend to induce macrophages to an anti-inflammatory, highly phagocytic phenotype, thereby reducing the FBR [240]. However, there was report got the opposite result, harder collagen scaffolds could mediate M2 macrophage polarization and reduce the secretion of TNF-α, and prevent the formation of a fibrotic collagenous capsule [241]. Therefore, the relationship between the mechanical properties of biomaterials and immune rejection needs to be further investigated.

The third strategy to composite biomaterials with immunomodulatory agents. With the increasing research on the cellular and molecular mechanisms of immune rejection, a number of researches have begun to use immunomodulators to target and block the pathways associated with immune rejection, thereby inhibiting the occurrence of FBR. Incorporating bioactive molecules such as glucocorticoids, growth factors and cytokines into biomaterial scaffolds has been proved to be an effective way to prevent FBR [242]. TGF-β and IL-10 have the function of suppress the maturation of dendritic cells [243]; IFN-γ and IL-4 can mediate the transition of macrophages from M1 to M2 phenotype [244]; VEGF and PDGF are also reported to be able to prevent FBR [245], they are all commonly used rejection-inhibiting cytokines. Wang et al. developed a biodegradable nanoparticle loading CD40 siRNA, which can block the CD40/CD40L signaling pathway of mature dendritic cells and macrophages, thereby suppressing the immune response [246]. LAG-3 and PD-1 have also been identified as two potential therapeutic targets for immune rejection. In a recent report, MSC-derived FGL1/PD-L1 dual-target exosomes were prepared, which were able to significantly inhibit T cell activation, proliferation and cytokine secretion in an *in vitro* organ transplantation model [247]. Another research had used CRISPR/Cas9 system, encapsulated Cas9 mRNA and guide RNA targeting the costimulatory molecule CD40 into PEG-b-PLGA based cationic lipid-assisted nanoparticles, successfully silenced the expression of CD40, and inhibited T cell activation [248]. These provide ideas for the development of low immunogenicity biomaterials.

On the other hand, with the help of CRISPR/Cas9 gene editing technology, breakthroughs in xenobiotic tissue transplantation have been made in recent years. Removing endogenous retroviruses of animal cells and knocking out specific polysaccharide antigenic epitope genes through gene editing can greatly reduce body's rejection to xenogeneic tissues [249]. Through the combined use of biocompatible biomaterials and immunomodulators, it is promising to completely solve the problem of potential immune rejection of biomaterials.

5. Novel techniques for biomaterial-guided wound healing

Current clinical therapies for skin regeneration is far from being perfect. Some problems such as chronic wound, paresthesia, and abnormal pigmentation are still challenging. Recently, the development of computer science, microelectronic technology, reprogramming technique and next-generation sequencing technology have brought new concepts and ideas for developing new therapies of wound healing. In this section, we have summarized five new technologies that promise to be used in combination with biomaterials for high-quality endogenous regeneration of skin wounds (Fig. 10).

5.1. *Biomaterial delivered in situ cell reprogramming for endogenous skin regeneration*

The essence of endogenous skin regeneration is the process of activating or recruiting endogenous stem cells to achieve tissue regeneration [253]. However, patients with skin deep injuries or metabolic diseases such as diabetes always have difficulty in natural wound healing through differentiation and proliferation of stem cells. In this case, an ideal way is inducing skin regeneration by modulating the extracellular microenvironment or driving cellular reprogramming.

Reprogrammed autologous cells can avoid immune rejection compared to conventional skin grafting treatments. Specifically, bioactive molecules such as transcription factors, microRNA and chemical small molecule, can be used to direct endogenous cells to directly converted into a pluripotent state and differentiated into skin cells and skin appendages. Each of these reprogrammed tool molecules can be delivered with temporal and spatial precision through biomaterial vehicles. Therefore, biomaterials have great potential to promote wound healing by *in situ* cellular reprogramming in a simple and effective approach.

Now cellular reprogramming has four major approaches: (1) overexpressing the lineage-determining transcription factors; (2) regulating the expression of specific genes by small biomolecules, such as microRNA or small molecular inhibitors; (3) directly delivering mRNA into cells; (4) genetic reprogramming using CRISPR or CRISPR-Cas9. Unlike

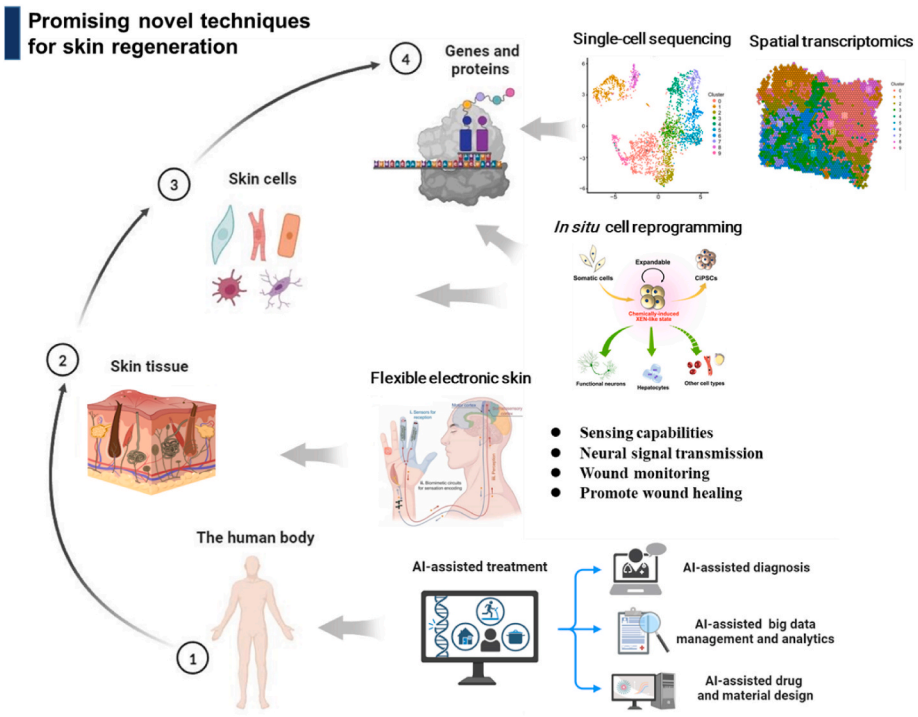

Fig. 10. Schematic diagram of five promising novel techniques that have potential to be used in skin regeneration applications: *in situ* cell reprogramming, novel flexible electronic skin, artificial intelligence, single-cell sequencing, and spatial transcriptomics technology. Reprinted from Refs. [250–252], created with BioRender.com.

the internal organs, skin is located on the surface of the body, so *in situ* reprogramming of skin cells does not require specific methods for targeted delivery. In the year of 2018, researchers transduced four transcription factors (DNP63A, GRHL2, TFAP2A and MYC) into wound-resident mesenchymal cells and reprogramed them into expandable epithelial tissues which could promote efficient and rapid epithelialization of skin wounds in mice [254]. *In situ* cellular reprogramming provides a new therapeutic method for treating skin wounds.

Biomaterials used for cells reprogramming requires high biocompatibility and biodegradability, high loading and releasing efficiency, and good stability. Macromolecular hydrogels, nanoparticles, microspheres and electrospun scaffolds have been used for *in situ* cellular reprogramming [255]. Recently, Ji et al. in our group developed artificial hair follicles seeding (AHFS) hydrogel microspheres. By combining the liposome nanoparticles, photo-responsive hydrogel shell, microfluidic and photo-crosslinking techniques, the AHFS hydrogel/microspheres drug delivery system delivered sever small molecule drugs to fibroblasts and successfully *in situ* reprogramed them to dermal papilla cells (DPCs). The results of following experiments indicated that the AHFS system could activate the PI3K/AKT pathway, promoting wound healing and endogenous hair follicles regeneration, also could inhibit the transformation of fibroblasts to myofibroblasts and inhibit scar formation [256]. Biswas et al. successfully delivered myoblast determination protein 1 (MYOD1) transcription factor in the cell nucleus of myoblast cells by PEG nanoparticle, and then reprogramed myoblast differentiation into skeletal, cardiac or smooth-muscle cells [257]. However, there are still few reports about using biomaterial vehicles to reprogram cells for the promotion of wound healing. Kurita et al. used collagen hydrogel loading Rock inhibitor and FGF-2, greatly increased the efficiency of reprogramming system and enhanced wound healing [258]. Gan et al. developed konjac glucomannan modified SiO_2 nanoparticles that could induce mannose receptor clustering on the cell surface and reprogram the macrophages to differentiate from M1 to M2-type, and further decrease inflammation and increase angiogenesis in the wound tissues [259]. These researches provided effective strategies for endogenous skin regeneration by *in situ* cell reprogramming.

Compared with traditional wound healing methods, *in situ* reprogramming can solve the immune rejection problem of allogeneic cell transplantation and the seed cell source problem of endogenous regeneration. Now with the aid of big data technology, single-cell sequencing and omics technology, the optimal combination to achieve effective reprogramming can be found through exhaustive screening of transcription factors by CRISPR activation (CRISPRa) technology, and improve reprogramming efficiency [260]. Although *in situ* cell reprogramming has great potential for application in skin wound repair, but the off-target effects limit its clinical application. The use of targeted delivery biomaterials or non-insertional delivery vectors (e.g., Sendai virus, sgRNA, etc.) is expected to reduce the potential risks of traditional lentiviral vectors [261]. Methods to promote reprogramming efficiency and the long-term fate of reprogrammed cells also need to be overcome to translate this technology into the clinic. With the research, *in situ* reprogramming techniques offer new possibilities to address the clinical problems of skin, skin appendages, even limbs regeneration and reversing aging.

5.2. *Biomaterial derived flexible electronic skin for skin functional reconstruction*

Natural skin is constructed by a 3D network structure of collagen fiber bundles. These 3D network structure endow skins with excellent mechanical properties, proper electrical conductivity, and multifunctional stimulus-responsive ability. Current clinically used wound dressings for covering wounds and accelerating healing can only provide a scaffold for cells migration and proliferation, cannot mimic the sensory functions of the skin. In order to achieve sensory healing and wound status monitoring of large, difficult-to-heal wounds, researchers have combined new material technologies, microelectronics and tissue engineering techniques to invent a series of novel electronic skins (e-skins).

In order to fully mimic human skin, the basic characteristic of e-skins

is mechanical similarity with human skin. Furthermore, it should be able to sense and respond to external stimuli like heat, cold, desiccation and mechanical force. From the perspective of applications, e-skins should not only have high biocompatibility, but also high conductivity, mechanical strength, stretchability, and toughness to withstand cyclic stresses generated from movement of human body [262]. At first, in the past twenty years, conductive polymer films have attracted great interest in developing electronic skins due to their excellent physical properties in density, flexibility, stretchability and customizable shapes [263]. In the field of electronic skin films, poly(3, 4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) is the most widely studied polymeric conductive materials [264]. Besides, some other conductive film materials like the polyurethane (PU)/polydimethylsiloxane (PDMS) nanofilms and ultrathin graphene films are also reported to be used in monitoring of human physiological signals [265,266]. However, as the film materials cannot mimic the complex three-dimensional structure of human skin, they have been found to be more suitable for use as extra-skin electronic patches rather than transplantable electronic skins. Taking the above requirements into account, conductive hydrogels are the most suitable substrate material for electronic skins. But conductive hydrogels generally limited by their poor mechanical properties (fracture strength less than 1.0 MPa). Lots of strategies have been used to improve the mechanical properties of conductive hydrogels such as incorporation of nanofibers, construction of interaction networks, design of microstructure, salting out, etc. Recent report developed a hydrogel e-skin with outstanding tensile strength (7.33 MPa), puncture resistance, moisture retention, self-healing and antibacterial properties through the integration of betaine, silver nanoparticles, and sodium chloride in a glycerol/water binary solvent [267]. Similarly, Duan et al. presented a water-modulated biomimetic hyper-attribute-gel hydrogel, the mutual effect between water, silk fibroin, Ca^{2+}, H^{+}, and MXene endowed the hydrogel skin-like physical-chemical properties and sensory properties, make it had great potential in application as an on-robot e-skin [268].

The e-skins are regarded as ideal electronic devices for noninvasive human-machine interaction and wearable devices. Jiang et al. integrated wirelessly powered electronic sensors, stimulators and hydrogel electrodes into a wearable hydrogel patch, which could continuously sense wound impedance and temperature. This smart bandage not only enables active monitoring and closed-loop treatment of wounds, but also deliver the electrical stimulation to the wound and accelerate wound healing by promoting stem cell recruitment. It is an example of the combination of biomaterial wound dressings and microelectronics [269]. Recently a great breakthrough has been achieved in soft e-skin. Wang et al. developed a prosthetic e-skin that incorporates organic semiconductor transistors and it has no rigid components. With a trilayer, high-permittivity elastomeric dielectric, this e-skin could mimic the biological sensorimotor loop of animal, and further sensed these external stimuli and encode them into electrical pulses. More importantly, this research firstly showed that the e-skin could evoke neuronal firings at the motor cortex in a rat *in vivo*, which triggered toe twitching [252]. This research contributes to the development of intelligent artificial skin, human-robot interaction and neuro-robotic technology.

Besides, some other type stretchable conductive polymers, such as ionic gel skin are also potential candidate for fabricating e-skins [270]. The molecular basis of human tactile receptors ion channel protein is molecular basis of human tactile receptors, by mimicking the movement of ions within the skin, the ionic skin is already well equipped to perform feedback to pressure, shear, and friction [271]. By the help of development and combination of delicate materials and circuits structure design, novel e-skins with abilities of intelligent responsiveness and continuous health care management are desired to be developed and promising to revolutionize traditional wound dressings.

There have been a number of flexible electronic skins reported in the last decade. Currently, flexible electronic skin has well realized the bionic functions of human skin, such as using biomaterials to mimic the skin's mechanical properties, pressure sensing, temperature sensing, and self-repairing ability [272]. But the current challenges facing flexible electronic skin are also evident: (1) The space inside the flexible electronic skin is very small, thus requiring a high level of precision and integration of the microelectronic devices inside; (2) Flexible electronic skin needs to be subjected to frequent changes in stress signals, so its hydrogel matrix not only needs to be strong enough and biologically stable to support the electronics inside, but also flexible and self-healing to ensure long-term durability; (3) Because of the need for long-term contact with open skin tissue, Because of the need for prolonged contact with open skin tissue, permeability, conformability and immune rejection must also be considered; (4) How to reduce the cost is also a challenge that must be faced for the commercial production and clinical application of flexible e-skin. Currently, flexible electronic skin is still in the animal experiment and preclinical stage [269]. However, it has the potential to be truly clinically applied in the near future, bringing benefits to patients with extensive skin injuries and skin sensory deficits.

5.3. Application of artificial intelligence for dermatological treatment and wound management

In recent years, artificial intelligence (AI) technology has brought about a revolution in dermatology and wound treatment, including AI-assisted diagnosis, personalized treatment planning, and AI-based algorithms for optimizing biomaterial design for wound healing [273].

AI-assisted diagnosis is the most widely used application of artificial intelligence in medicine field. Currently, AI-assisted diagnosis is revolutionizing the medical imaging examination like X-ray, computerized tomography (CT), ultrasonic testing and magnetic resonance imaging (MRI), etc [274]. Skin injuries and skin diseases always do not require complex invasive examinations, and obtaining patient imaging data is relatively easy, making it more suitable for AI training and big data analysis using AI. With the help of deep convolutional neural network (DCNN), the diagnosis to the skin disease like inflammatory dermatoses, autoimmune dermatoses, and melanomas has achieved the encouraging diagnostic accuracies better than 90 %, comparable or even better than the diagnosis from dermatologists [275]. The database of wound massive data (wound images, wound-specific electronic health records, etc.) can be a powerful date resources for wound healing researches [276]. In a quasi-experiment of Australian health service, speed of wound healing of patients intervened by AI application improved more significantly than control group (24 % vs 70 %, $P < 0.001$), revealed the usability and effectiveness of AI in wound assessment and management [277]. Raelina et al. reported a wound assessment tools based on AI, which can precisely assess the wound area and percentage of granulation tissue of wounds [278]. The remote diagnosis and treatment based on AI applications can facilitate patient monitoring and reduced patient travel time to receive optimal wound care.

AI technology has shown great potential for polymer biomaterial design and drug development as well. With the underlying AI logic algorithms continue to be developed, more advances in novel materials and drugs for wound treatment are expected. Recently AI aided drug design have made much progress in developing potential drugs for treating cancer, diabetes and neurodegenerative disease [279,280]. In the field of wound healing materials, Chen et al. combined AI-assisted image-analysis algorithm with 3D printing technology, proposed an AI-assisted high-throughput printing-condition-screening system (AI-HTPCSS), which could obtain the optimal hydrogel architectures of hydrogel scaffolds in a high-throughput manner. The AI screened 3D-printed hydrogel scaffolds demonstrated satisfying mechanical properties and efficacy in accelerating the diabetic wound healing [281]. Based on high throughput sequencing of diabetic patients' skins and AI-assisted bioinformatics, Xue et al. excavate a potential therapeutic agent Trichostatin A (TSA) and a potential target histone deacetylase 4 (HDAC4) for diabetic wound healing. The results of animal experiments revealed that the microneedle patch loading TSA could

reduce inflammation, promote tissue regeneration, and inhibit HDAC4, which had positive contribution to diabetic wound healing [282]. AI systems can also be combined with flexible e-skins. Next-generation e-skins will be able to use artificial intelligence (AI) to optimize their design and collect and analyze wound microenvironmental data in real time, allowing for a balance of wound monitoring and health management [283]. AI assisted e-skins has also contribute to personalized therapy. AI-assisted e-skins will be able to assess the pharmacokinetics and pharmacodynamics of personalized doses using feedback data of the wound microenvironment, pave the way for the development of personalized therapy [284]. In addition, AI technology provides new ideas to solve the problem of lack of specialized doctors in backward areas.

However, AI technology currently used in healthcare faces some skepticism. For example, AI-assisted diagnosis may not be able to accurately diagnose difficult cases and rare diseases with similar symptoms; and the worries about the risk of leakage of medical data, which is personal privacy, may also lead to many patients refusing to cooperate; and the legal responsibility for AI diagnostic results is also a blank [285]. Furthermore, as an emerging technology, the safety and efficacy of AI-designed drugs need further validation, and AI-designed drugs and materials have many restrictions when applied to clinical treatments until now [286]. But there is no denying that AI technology will play more and more important role in developing new treatments, improve the medical level in economically underdeveloped areas, and improving the efficient use of healthcare resources for patients suffer from skin wounds in the future. We believe that with the continued development of all the above novel technologies, wound repair biomaterials will realize their full potential. In the future, high-performance, integrated, and intelligent wound repair biomaterials will revolutionize traditional clinical practices of wound healing.

5.4. Application of single-cell sequencing and spatial transcriptomics in analyzing cellular subtypes, distributions and interactions of wound healing process

Wound healing is a complex process that requires the collaboration of multiple cells. With the development of biotechnology, single-cell sequencing and spatial transcriptomics technologies have enabled us to explore the interactions between cells and their location in tissues with unprecedented precision. These technologies have provided us with a wealth of data revealing the molecular state of cells and their distribution in physical space, offering the potential for a deeper understanding of disease mechanisms and tissue regeneration.

Based on high-throughput sequencing technologies, single-cell sequencing has shown unprecedented capabilities in identifying cellular heterogeneity, cellular differentiation trajectories, and cellular communication [287]. Single-cell RNA sequencing (scRNA-seq) is the most widely used single-cell sequencing method to analyzes the key cell subpopulations during wound healing. As the key cell that determines normal wound healing and scar healing, analyzing the heterogeneity of fibroblasts by single-cell RNA sequencing is a current research hotspot. A recent research explored the fibroblast heterogeneity in keloid by scRNA-seq, and found that keloid fibroblasts were divided into 4 subpopulations: secretory-papillary, secretory-reticular, mesenchymal and pro-inflammatory. Compared to normal scar, the percentage of mesenchymal fibroblast subpopulation is significantly increased in keloid. Mesenchymal fibroblast could be a potential target for skin fibrotic disease treatment [288]. Guerrero-Juarez et al., analyzed fibroblast diversity of 21,819 cells from the wound dermis of mice using single-cell RNA-sequencing. The results confirmed that some wound myofibroblasts and regenerated adipocytes were originated from hematopoietic lineage cells, and the wound fibroblasts had a high degree of heterogeneity [289]. Using scRNA-seq, Siriwach et al. identified a lysophosphatidic acid induced keratinocyte subpopulation which expressing the extracellular matrix protein, thrombospondin-1 (THBS1). The THBS1+ keratinocyte is a migratory keratinocyte subpopulation after injury that could promote epidermal wound healing [290]. ScRNA-seq can identify multiple cell subpopulations within a tissue, but cannot capture their spatial distribution, which happens to be the specialty of spatial transcriptomics technology.

Combining single-cell sequencing and spatial transcriptomics can spatially map specific cell subpopulations in disease and tissue regeneration. This will not only reveal cellular heterogeneity, but also obtain information of cell location of cells in tissue space and elucidate the mechanisms by which these cellular subpopulations interact [291]. Through integrated analysis of single-cell sequencing and spatial transcriptomics, Foster et al. precisely tracked fibroblast fate during the physiologic response to skin injury across both time and space. They identify and characterize four fibroblast subpopulations with divergent transcriptional and epigenomic programs: Mechanofibrotic, Activated responder, Proliferator, and Remodeling. Based on the location and timeline of these cell subtypes, it was demonstrated that the active migration, proliferation, and differentiation of fibroblasts were responses to the disruption of tissue microenvironment [292]. Similarly, Chen et al. systematically analyzed the characteristics of Wharton's jelly mesenchymal stem cells (WJ-MSCs) by single cell and spatial transcriptome sequencing. It has been found that the S100A9+CD29^{+}CD142+ biofunctional-type WJ-MSCs subpopulation exhibited best wound repair properties *in vitro* and *in vivo*, provided a reference for future development of WJ-MSC-based cell therapy for skin endogenous regeneration [293]. A recent research depicted the development of hair follicles during embryonic life and the integrated spatiotemporal transcriptomic atlas of hair follicle development in pigs through these two technologies [294]. It is worth mentioning that the data of single-cell RNA sequencing and spatial transcriptomics can be efficiently processed by artificial intelligence algorithms. A recent study developed an environmental variational inference (ENVI) algorithm, which could simultaneously incorporate scRNA-seq and spatial data into a single embedding. The ENVI algorithm could not only accurately output the expression of genes in diverse developmental contexts, but also project valuable spatial information onto dissociated scRNA-seq data [295]. The integration and analysis of these complex datasets through intelligent algorithms provides a powerful tool for future exploration of cell behavior and function, disease mechanisms, and the development of new therapies.

Moreover, the scRNA-seq and spatial transcriptomics can guide the development of novel drugs and biomaterials for promoting wound healing. Hu et al. fabricated three electrospun membranes with different types of surface topography (random, aligned, and latticed) and evaluated their effects on wound healing and immune cells heterogeneity through scRNA-seq [296]. Liu et al. revealed the transcriptomic heterogeneity of neutrophils and macrophages of skin wound repair after hucMSC-exosomes interventions [297]. With the help of scRNA-seq, researchers also revealed the role of quercetin in promoting hair regeneration [298]. However, there are still some challenges in these novel genetic tools. For example, errors due to the cell extraction process, abundance, size and total mRNA of the cells were difficult to avoid and could not be verified by setting up orthogonal experiments. Besides, lacking of standardization of cell type annotation and marker selection strategies also make it difficult to achieve efficient data processing [299]. But as emerging technologies in recent years, it is believed that single-cell sequencing and spatial transcriptomics technologies will become representative of histologic technologies in the future to facilitate skin endogenous regeneration.

6. Summary and prospect

The rapid, scar-free, perfect healing containing intact skin appendages is the ultimate goal of skin regenerative medicine. Endogenous skin regeneration is a more promising approach avoiding foreign cell implantation and taking advantage of skin's own repair potential. Novel

therapies, drugs and biomimetic biomaterial based on molecular biology, materials science and medicine are shedding new light on achieving perfect wound healing. In this review, we have summarized the recent advancements in biomimetic materials with different physical and biological properties which can promote the rebuilding of injured tissue structure and microenvironment, and achieve skin high quality endogenous regeneration.

Biomimetic biomaterials induced endogenous skin regeneration extends the therapies available for skin regeneration. There is a rapid increase in researches of biomimetic biomaterials for endogenous wound regeneration in recent years. But biomimetic biomaterials currently used to promote skin regeneration still face a number of challenges. For example, while biomimetic biomaterials generally use biocompatible polymers as matrix materials, long-term wound covering or subcutaneous implantation may also carry risks of inflammation and immune rejection. The mechanism of interaction between many biomaterials and the human being has not been fully clarified, and small differences in material design may lead to a big difference in the effects of biomaterials on people. Therefore, new biomimetic biomaterials need to undergo rigorous animal experiments and clinical trials to avoid implant failure, long-term toxicity, and immune rejection before they are marketed, and this process cannot be replaced by the results of similar biomaterials. In addition, the risk of tumorigenesis associated with the induction of endogenous cell proliferation and differentiation also requires special attention. Finally, high costs have limited the commercial production and clinical application of many biomimetic biomaterials as well. The reported biomaterials should be further improved according to market and patient needs before application.

In conclusion, the need for rapid, high-quality endogenous healing of wounds in modern society has driven the development of biomaterials for wound healing, and the novel biomimetic biomaterials provide a promising avenue to revolutionize the traditional wound management of skin injuries and disorders. Although biomimetic biomaterials have been reported from various aspects, such as structural design, functional modification, and multifunctional composites, the vast majority of the current reports still remain at the stage of animal experiments and preclinical experiments, still far from commercialization and clinical application. New technologies such as 3D printing, microfluidics, AI-assisted design, *in situ* reprogramming and advanced genetic tools have opened up new possibilities to achieve high-quality endogenous skin regeneration by biomimetic biomaterials. It is believed that in the future, with the help of novel smart biomimetic biomaterials, the ultimate goal of rapid and perfect skin regeneration will be realized.

Ethics approval and consent to participate

This review is not concerned with ethical issues.

Ethics approval and consent to participate

This review is not concerned with ethical issues.

CRediT authorship contribution statement

Mengyang Wang: Writing – original draft, Investigation, Conceptualization. **Yiyue Hong:** Writing – review & editing. **Xiaobing Fu:** Validation, Methodology, Funding acquisition. **Xiaoyan Sun:** Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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