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Review

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Promoting skin regeneration: research progress on hydrogel wound dressings related to scarless healing

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Abstract: This review summarizes progress made in research on hydrogel wound dressings in promoting scarless skin healing. Wound healing is a complex biological process that involves four stages: hemostasis, inflammation, proliferation, and remodeling. Scar formation is a common issue during this process, especially pathological scars such as hypertrophic scars and keloids, which severely affect aesthetics and function. In recent years, hydrogel dressings have become a research hotspot for promoting scarless healing due to their unique physicochemical and biological properties. Hydrogels promote wound healing and reduce scar formation through multiple mechanisms, including providing a moist environment, antimicrobial activity, anti-inflammatory effects, promoting tissue regeneration, and regulating the wound microenvironment. This article details the concept and mechanisms of scarless healing and explores the application of hydrogel dressings loaded with anti-scarring drugs, stem cells, and extracellular vesicles in scarless wound healing. Additionally, it summarizes progress in research on hydrogel dressings that regulate mechanical signals and innovative multifunctional hydrogel dressings, such as photo-responsive, organic biopolymer, and nanoparticle hydrogels. These hydrogel dressings show great potential for clinical application but still face challenges such as drug delivery efficiency, biocompatibility, and long-term safety. Future research needs to further optimize the composition and functionality of hydrogels and explore their potential applications in clinical settings.

Key words: Hydrogel; Wound dressings; Scarless healing; Tissue regeneration; Scars

1 Introduction

Skin wound healing is a complex and orderly biological process involving the interaction of various cells, molecules, and extracellular matrix components. This process is typically divided into four stages: hemostasis, inflammation, proliferation, and remodeling (Nowak et al., 2021; Yang et al., 2023b). When the skin is injured, the body's first response is to activate the coagulation mechanism to stop bleeding. Blood vessels constrict, platelets aggregate and release coagulation factors, forming a thrombus that seals the wound (Lei et al., 2022).

The inflammatory phase usually begins 48 to 96 h after wound formation and lasts for 3 to 5 days (Velnar et al., 2009; Younesi et al., 2024; Zhao et al., 2024). During this stage, white blood cells (such as neutrophils and macrophages) are attracted to the wound site to remove necrotic tissue and pathogens. Macrophages play a crucial role in this phase as they not only clear damaged tissue but also regulate the subsequent healing process by secreting cytokines and growth factors (Sorg et al., 2017). The proliferative phase is a key stage in wound healing, typically lasting from 2 to 24 days (Hassanshahi et al., 2022). In this stage, fibroblasts migrate to the center of the wound, begin to synthesize and remodel the extracellular matrix components (such as collagen), and gradually differentiate into myofibroblasts (Guo and Dipietro, 2010). Meanwhile, endothelial cells initiate angiogenesis under the stimulation of vascular endothelial growth factor (VEGF), providing nutrition to the wound. Additionally, keratinocytes proliferate and migrate to form a new epidermal layer

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that covers the wound (Peña and Martin, 2024).

The remodeling phase is the final stage of wound healing, usually lasting for several months or even years (Velnar, et al., 2009). During this stage, collagen and other extracellular matrix components are continuously remodeled, and the strength and function of the wound gradually recover (Talbott et al., 2022). However, this stage may also lead to scar formation, especially when the healing process is abnormal. After skin injury, pathological scars such as hypertrophic scars and keloids often form, which not only affect aesthetics but may also cause functional impairment and psychological burden (Talbott, et al., 2022; Yin et al., 2022). The formation of pathological scars is closely related to persistent inflammation, abnormal collagen deposition, and impaired remodeling of the extracellular matrix during the wound healing process (Ogawa et al., 2021; Yin, et al., 2022). Scars are a natural result of wound healing, but in some cases, they may over-proliferate to form pathological scars, such as hypertrophic scars and keloids (Zhang et al., 2020b). The formation of these pathological scars is associated with multiple factors, including genetic factors, wound infection, duration of inflammatory response, and abnormal remodeling of the extracellular matrix (Lee and Jang, 2018; Wang et al., 2020).

In recent years, hydrogel wound dressings have become a research hotspot for promoting scarless skin healing due to their unique physicochemical and biological properties (Zhang et al., 2021b; Hua et al., 2023; Anna-Lisa et al., 2024). Hydrogels are polymeric materials with a three-dimensional network structure that can promote wound healing by carrying various drugs, protein factors, or stem cells (Zhang et al., 2020a; Liang et al., 2021; Zhang et al., 2021a; Weng et al., 2024). The physicochemical properties of hydrogels, such as their ability to absorb large amounts of water and maintain a moist wound environment, make them effective in wound healing. Hydrogels can also carry antimicrobial agents, such as silver ions, antibiotics, or antimicrobial peptides, effectively inhibiting bacterial growth (Shan et al., 2023; Kavanagh et al., 2024; Song et al., 2024). Additionally, hydrogels can reduce inflammatory responses in wounds through antioxidant mechanisms (Li et al., 2024a; Weng, et al., 2024). By providing a moist environment, antimicrobial and anti-inflammatory effects, promoting tissue regeneration, and regulating the wound microenvironment, hydrogel dressings significantly promote the wound healing process (Rahimi et al., 2023; Han et al., 2025). Some hydrogels can also achieve multiple functions such as antimicrobial, anti-inflammatory, hemostatic, and drug delivery effects (Yuan et al., 2023). This multifunctionality gives hydrogel dressings a significant advantage in treating complex wounds, such as chronic diabetic wounds (Vagesjo et al., 2018; Qin et al., 2023). Hydrogel dressings also have good biocompatibility and biodegradability (Keykhaee et al., 2023; Govindharaj et al., 2024). These characteristics make hydrogel dressings promising for clinical applications.

Scarless (or scar-free) wound healing refers to an ideal state of wound healing without the formation of noticeable scars (Xiaojie et al., 2022). This concept was first proposed by Burrington in 1971, who observed that fetal skin could rapidly repair itself without scarring after injury. Scarless healing is an inherent property of embryonic skin but is rare in adults (Burrington, 1971). During scarless healing, the inflammatory response in the wound is mild, with fewer inflammatory cells. The extracellular matrix in the wound does not accumulate excessively, and collagen fibers are arranged in a mesh-like pattern rather than the parallel alignment commonly seen in scar tissue (Karppinen et al., 2019; Pratsinis et al., 2019). There are also fewer myofibroblasts in the wound, which play a key role in scar formation. Fetal skin heals faster than adult skin, and the healed skin is close to normal in function and appearance. However, this ability gradually weakens with increasing gestational age (Burrington, 1971). In recent years, scientists have explored strategies for scarless healing by studying its mechanisms. A research team at Stanford University, USA found that inhibiting the activation of the Engrailed-1 (En1) protein in fibroblasts could achieve scarless wound regeneration (Mascharak et al., 2021; Hao et al., 2025). Many researchers have also developed various biomaterials, such as photo-crosslinked hydrogels, which successfully achieved scarless healing by a pulsatile release of TGF-β inhibitors (Abedanzadeh et al., 2024). Additionally, regulating the lineage differentiation of fibroblasts to reduce key cell types

involved in scar formation has provided new ideas for scarless healing. Research on scarless healing is not only significant for skin trauma repair but also offers new directions for treating other fibrotic diseases (Bainbridge, 2013; Knoedler et al., 2023). This review systematically summarizes progress made in research on hydrogel wound dressings in promoting scarless skin healing, explores their potential and challenges in clinical applications, and provides references for future research and product development.

2 Skin Wound Healing and Scar Formation

2.1 Skin Wound Healing

Skin, the largest organ of the human body, serves as a vital barrier protecting the body from external environmental threats and performs multiple functions such as regulating body temperature and maintaining water balance (Nguyen and Soulika, 2019). However, when skin is injured, the repair process is often complex and can lead to functional impairment and aesthetic damage. Skin wound healing is a highly complex and dynamic biological process involving the interaction of various cell types, signaling molecules, and extracellular matrix (ECM) (Peña and Martin, 2024). The process of skin wound healing can be divided into four stages: hemostasis, inflammatory response, cell proliferation, and tissue remodeling. These stages are not strictly separated but overlap and dynamically change (**Fig. 1**) (Velnar, et al., 2009).

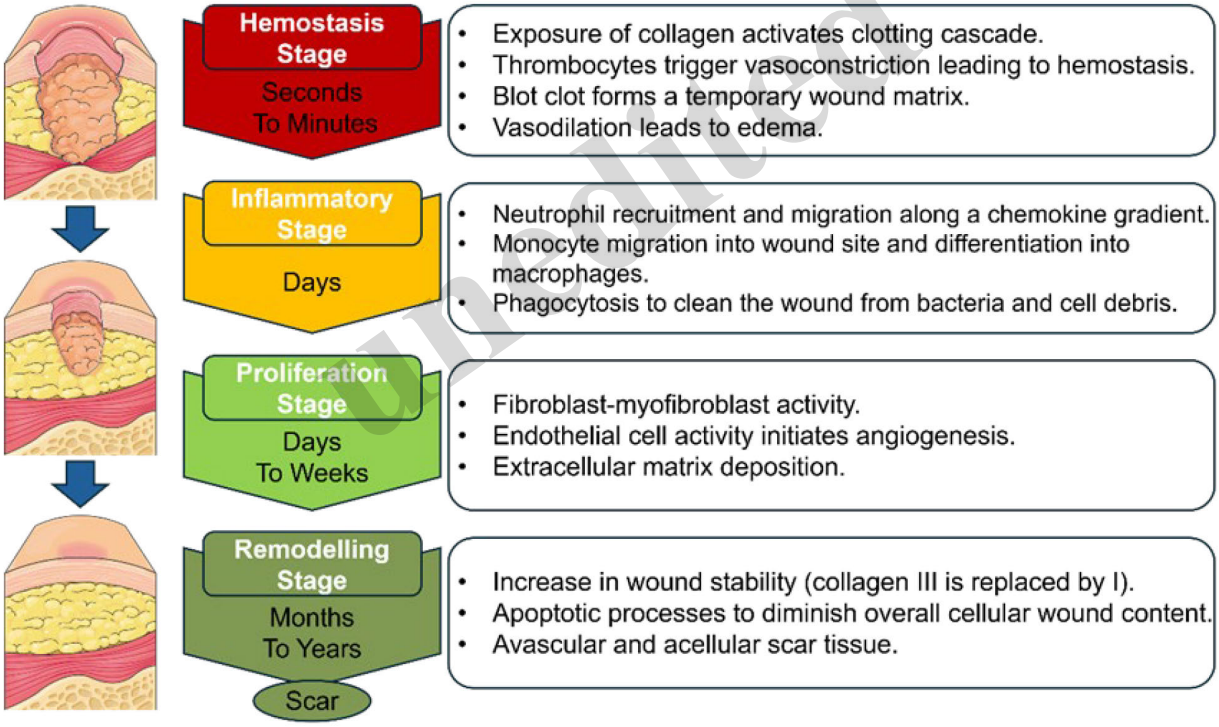

Fig. 1. Wound healing process.

Hemostasis Stage: The hemostasis phase is the initial stage of wound healing, initiated within minutes after injury to prevent excessive bleeding (Velnar, et al., 2009). Vasoconstriction, platelet aggregation, and the coagulation cascade work together to ensure the efficiency and reliability of hemostasis. The blood clot formed not only stops bleeding but also blocks external bacteria and contaminants from entering the wound, providing protection for the subsequent healing process (Matsuzaki and Upton, 2013; Childs and Murthy, 2017; Negut et al., 2018; Bian et al., 2022). Platelets are activated and secrete a variety of growth factors, such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF). These growth factors recruit inflammatory cells to the wound site

and trigger the inflammatory phase of wound healing (Yang et al., 2023a).

Inflammatory Response Stage: Triggered by the immune system, this is the initial phase of wound healing. Keratinocytes immediately release pro-inflammatory cytokines (such as interleukin-1, IL-1) after injury, attracting neutrophils and macrophages to the wound site (Verdolino et al., 2021). Neutrophils clear debris and microbes through phagocytosis, while macrophages, in addition to clearing neutrophils and other apoptotic cells, release various growth factors and cytokines to promote subsequent tissue repair (Childs and Murthy, 2017; Nguyen and Soulika, 2019). Although the inflammatory response is crucial for wound healing, excessive inflammation can lead to fibrosis and scar formation (Wang, et al., 2020). In addition, signaling molecules such as nuclear factor-κB (NF-κB) and Toll-like receptors (TLRs) are activated during this phase. They are involved in the transcription of cytokines and the recognition of pathogens, respectively, attracting macrophages and lymphocytes to the wound and activating them (Mussbacher et al., 2023). In the early stage of inflammation, macrophages are mainly of the classically activated M1 type, expressing various pro-inflammatory cytokines, such as interleukin-1β (IL-1β) (Kluwe et al., 2009; Mussbacher, et al., 2023). In the later stage of inflammation, macrophages shift to the M2 type, which has anti-inflammatory effects. They promote tissue regeneration by activating keratinocytes, fibroblasts, and endothelial cells, initiating the proliferative phase of wound healing (Huebener and Schwabe, 2013).

Cell Proliferation Stage: Based on the inflammatory response, fibroblasts, endothelial cells, and keratinocytes begin to proliferate, forming granulation tissue (Peña and Martin, 2024). Fibroblasts synthesize collagen to provide structural support to the wound, endothelial cells form new blood vessels to supply nutrients and oxygen, and keratinocytes promote epithelial regeneration to cover the wound surface (Li et al., 2007). The proliferation and migration of cells in this stage are key to wound healing. During the proliferative phase of wound healing, the Wnt/β-catenin, PI3K/AKT/mTOR, and VEGF signaling pathways all play important roles in regulating cell proliferation, migration, and differentiation, thereby promoting re-epithelialization, granulation tissue formation and angiogenesis (Hu et al., 2020; Gan et al., 2021; Zhao et al., 2025).

Tissue Remodeling Stage: The newly formed granulation tissue gradually matures, with collagen fibers being reorganized and the ECM undergoing degradation and reconstruction. The remodeling process in this stage determines the final function and appearance of the wound. Appropriate remodeling can restore normal skin function, while excessive remodeling can lead to scar formation (Pratsinis, et al., 2019). The TGF-β signaling pathway is activated in the second phase of wound healing and has potent pro-inflammatory and collagen deposition capabilities (Xiaojie, et al., 2022). TGF-β1 plays a dominant role in skin wound healing, mainly mediating pathological healing, such as chronic inflammation and excessive scar formation (Xiaojie, et al., 2022). The TGF-β signaling pathway can be activated by various stimuli, including cytokines, growth factors, and mechanical stress, and can interact with other pathways such as JAK-STAT, MAPK/ERK, PI3K/AKT/mTOR, and Wnt/β-catenin (Margadant and Sonnenberg, 2010; Jere et al., 2017; Kadota et al., 2021). In the later stages of wound healing, overactivation of the TGF-β signaling pathway may lead to scar formation and fibrosis, so it is necessary to regulate this pathway to balance collagen synthesis and degradation (Ou et al., 2022).

Inflammation, macrophages, angiogenesis and neovascularization, adipocytes, and mechanical forces are several major factors that influence wound healing (Sorg, et al., 2017). However, the absence of any one of these factors can lead to impaired wound healing. Studies have shown that inhibiting inflammation, regulating the polarization state of macrophages, promoting angiogenesis, and appropriate mechanical force application can improve wound healing outcomes (Zhao et al., 2016). Other research has indicated that adipocytes not only participate in the regeneration of skin and its appendages but also regulate wound healing through the secretion of growth factors and cytokines (Hassan et al., 2014). Therefore, the formation of adipocytes can help reduce scar formation (Zou et al., 2021).

Table 1 Signaling pathways involved in wound healing

Signaling Pathway	Wound Healing Stage	Functions	Ref
NF-κB signaling pathway	Inflammatory	Regulates inflammatory effects	(Mussbacher, et al., 2023)
Toll-like receptors (TLRs)			(Huebener and Schwabe, 2013)
Wnt signaling pathway	Cell Proliferation	Regulates cell proliferation, migration, and differentiation (promotes re-epithelialization, granulation tissue formation and angiogenesis)	(Hu, et al., 2020)
PI3K/AKT/mTOR signaling pathway			(Gan, et al., 2021)
VEGF signaling pathway			(Zhao, et al., 2025)
TGF-β signaling pathway	Tissue Remodeling	Balances collagen synthesis and degradation (scar formation)	(Ou, et al., 2022)
JAK-STAT signaling pathway			(Jere, et al., 2017)

1.1 Mechanisms of Scar and Pathological Scar Formation

Scars are a natural product of the healing process following skin injury and represent the body's repair response to tissue damage, which is the ultimate outcome of wound healing. Scar tissue is typically dominated by type I collagen, relatively hard, and lacks the elasticity and appendages (such as hair follicles and sebaceous glands) of normal skin. Scars not only affect appearance but can also cause functional impairment, such as restricted joint movement (Bharadia et al., 2023; Peña and Martin, 2024). However, in some cases, scars may over-proliferate, forming pathological scars, such as hypertrophic scars and keloids. These pathological scars not only affect appearance but can also lead to functional impairment and psychological stress (Li et al., 2024b).

The formation of pathological scars is due to abnormal regulation in certain aspects of the wound healing process, which mainly include the following:

Over-activation of the Inflammatory Response: Excessive inflammation leads to the release of large amounts of pro-inflammatory cytokines and chemokines, attracting more inflammatory cells to the wound site. These cytokines not only promote the proliferation of fibroblasts and collagen synthesis but can also lead to excessive deposition of the ECM, resulting in hypertrophic scars (Karppinen, et al., 2019). Studies have shown that inhibiting the inflammatory response can significantly reduce scar formation (Wang, et al., 2020).

Abnormal Deposition of Extracellular Matrix (ECM): The main components of ECM include collagen, elastin, and glycosaminoglycans (Younesi, et al., 2024). In normal healing, the synthesis and degradation of ECM are in a dynamic balance. However, in pathological scar formation, ECM synthesis is significantly increased while degradation is inhibited, leading to excessive accumulation of ECM (Kanchanawong and Calderwood, 2023). In particular, the over-deposition of type I collagen makes the scar tissue hard and inelastic (Schuster et al., 2023).

Dysregulation of Cellular Signaling Pathways: Multiple cellular signaling pathways play a key role in scar formation. For example, the TGF-β signaling pathway is crucial in regulating fibroblast proliferation and collagen synthesis (Zhang, et al., 2020b). Overexpression of TGF-β1 promotes the activation of fibroblasts and collagen synthesis, leading to scar formation (Xiaojie, et al., 2022). Signaling pathways such as PI3K/Akt and MAPK are also involved in the scar formation process (Wang et al., 2019).

Mechanical Forces: The impact of mechanical forces on scar formation has been widely studied. Appropriate mechanical forces can promote fibroblast differentiation and collagen synthesis, thereby improving wound healing (Zhang et al., 2022). However, excessive mechanical forces can exacerbate the inflammatory response and lead to excessive collagen deposition, resulting in fibrosis. Studies have shown that designing biomaterials capable of regulating mechanical forces can reduce

inflammation and fibrosis, achieving scarless healing (He et al., 2021).

Genetic Factors: Genetic factors also play an important role in scar formation. Certain individuals or ethnic groups are more prone to developing pathological scars, which may be related to genetic polymorphisms. For example, mutations in certain genes can increase the sensitivity of fibroblasts to TGF-β1, thereby promoting scar formation (Griffin et al., 2020).

Scarless healing is the goal of skin wound treatment. Recent research progress has provided new ideas and methods for achieving this goal. By designing biomaterials that can regulate inflammation, promote cell proliferation, and angiogenesis, significant improvements in wound healing outcomes can be achieved, and even pathological scars can be treated.

2 Hydrogels Loaded with Anti-Scarring Drugs

In clinical practice, treatments for scars include surgical and non-surgical approaches. Non-surgical treatments consist of pharmacological therapy, laser therapy, and pressure/physical therapy, among which pharmacological therapy is the commonly used method (Chen et al., 2022). Drugs for scar treatment mainly include silicones, corticosteroids, and certain plant extracts (Rabello et al., 2014). Among these, asiaticoside is a drug commonly used to reduce scar formation after wound healing. It can be applied topically or taken orally. Topical asiaticoside can improve early scar erythema, pigmentation, and inhibit fibroblast proliferation. Currently, topical asiaticoside is available mainly in the form of creams or ointments (Ju-Lin et al., 2009; Huang et al., 2021). To improve the drug delivery efficiency of existing products and enhance therapeutic efficacy, some scientists have begun to develop hydrogel materials as a new drug carrier to strengthen the anti-scarring effects of drugs.

Scar formation is a complex biological process involving the interaction of multiple signaling pathways, including the TGF-β/Smad pathway, Wnt/β-catenin pathway, NF-κB pathway, and FAK pathway. Among these, TGF-β1 is one of the most important fibrosis-promoting factors. After TGF-β1 binds to its receptor, it activates Smad proteins, which enter the nucleus to regulate the expression of related genes, promoting fibroblast proliferation and collagen synthesis. Excessive TGF-β1 can lead to pathological scar formation (Zhang, et al., 2020b). Therefore, drugs that can regulate these signaling pathways can be used for scar treatment research. As early as 2021, researchers developed a photo-induced imine crosslinking hydrogel-based pulsatile release platform loaded with TGF-β inhibitors for scarless wound healing (Zhang, et al., 2021b). They constructed a photo-responsive polymer PLGA-NB microcapsule to achieve pulsatile release of TGF-β inhibitor (SB-431542). In mouse and large animal models, this hydrogel significantly accelerated wound closure, effectively controlled the TGF-β signaling pathway, and reduced scar tissue formation (Zhang, et al., 2021b).

Bhattacharya, D. (2019) (Bhattacharya et al., 2019) prepared a polyacrylamide (PAGE)-based hydrogel loaded with curcumin and cerium oxide nanoparticles (CNP) for accelerated and scarless wound repair. The curcumin (ACC) and CNP in this hydrogel can activate multiple cells signaling pathways, such as TGF-β-Smad2/3 and MAPK/ERK, promoting rapid wound healing and tissue regeneration while reducing inflammatory responses and scar formation. The Wnt/β-catenin pathway is also closely related to wound repair and scar formation. Lee, S.H. from South Korea (2023) (Lee et al., 2023) screened two inhibitors of this pathway, PTD-DBM (a peptide that blocks the interaction between CXXC5 and Dvl in the Wnt/β-catenin pathway) and VPA (a GSK3β inhibitor). They loaded these two drugs into a novel regenerative-promoting material, a pyrrole phenol-functionalized hyaluronic acid (HA-PG) hydrogel patch. This patch promotes regenerative healing through a combined drug therapy and ultimately reduces scar formation. The above studies demonstrate that by specifically regulating signaling pathways related to scar formation, wound healing outcomes can be effectively improved and scar formation reduced. In addition to selecting appropriate drugs, the material comprising the hydrogel is also crucial, as its drug delivery efficiency can affect wound healing outcomes.

In addition to the above signaling pathways, inflammation is a key factor affecting scar formation. The stronger the initial inflammatory response, the larger the scar that typically forms after healing.

Many researchers are currently using drugs with anti-inflammatory effects to study scarless wound repair. Asiaticoside (AC) is a triterpenoid saponin compound extracted from *Centella asiatica*, with multiple biological activities, including anti-inflammatory, antioxidant, collagen synthesis-promoting, and angiogenic effects (Huang, et al., 2021). These properties make it widely used in clinical practice for treating scars, promoting wound healing, and improving skin health. Some researchers are also combining asiaticoside with novel biomaterials to enhance its therapeutic efficacy. Liu et al. (2021) chemically dispersed asiaticoside uniformly in silk fibroin nanofiber hydrogel to prepare an AC-SNF hydrogel. This hydrogel exhibited good bioactivity in vitro, regulating inflammatory responses and angiogenesis. In a full-thickness skin defect model, the AC-SNF hydrogel achieved scarless wound repair by reducing excessive collagen deposition and scar formation (Liu et al., 2021). Loading asiaticoside into silk fibroin nanofiber hydrogel effectively enhanced its application in skin regeneration and reduced scar formation. Although asiaticoside alone has shown good anti-inflammatory and angiogenic effects, some researchers attempted to enhance these effects by introducing magnesium ions to achieve faster and better wound healing. They loaded asiaticoside and magnesium ions separately into silk fibroin nanofiber hydrogels and then mixed the two hydrogels to prepare an SNF-AC-Mg hydrogel (Yang et al., 2024a). In a rat full-thickness skin defect model, wounds treated with SNF-AC-Mg hydrogel healed faster, with significantly reduced scar formation. Compared with hydrogels containing asiaticoside or magnesium ions alone, the SNF-AC-Mg hydrogel showed better effects in promoting M2 macrophage polarization and angiogenesis (Yang, et al., 2024a).

Deng, J. (2024) developed a multifunctional hydrogel by dynamically crosslinking oxidized dextran and quaternized chitosan, and incorporated asiaticoside-loaded nanoparticles with reduced graphene oxide (rGO) and polydopamine (PDA). They chemically prepared oxidized dextran (ODex) and quaternized chitosan (QCS) and combined them with rGO@PDA and AC@PDA nanoparticles to produce an OQG hydrogel (Deng et al., 2024). This hydrogel has injectability, self-healing properties, tissue adhesiveness, antibacterial properties, and antioxidant effects. The introduction of rGO also allowed the hydrogel to better simulate the electrophysiological characteristics of normal skin and conduct electrical signals to promote cell migration and tissue regeneration (Deng, et al., 2024). Animal experiments also showed that asiaticoside-loaded nanoparticles with polydopamine (PDA) effectively reduced skin scar formation and promoted scarless healing (Deng, et al., 2024).

In addition to asiaticoside, many plant extracts are used in the development of anti-scarring hydrogels, such as quercetin, aloin, and ginsenosides. Xing et al. (2024) combined oxidized alginate (OAlg) with chitosan (CS) through Schiff base and electrostatic interactions, and incorporated quercetin via hydrogen bonds to produce an injectable polysaccharide hydrogel (PECE) (Xing et al., 2024a). Using this hydrogel they showed that PECE effectively promoted burn wound healing, demonstrated excellent infection prevention capabilities, reduced inflammation, promoted angiogenesis and collagen deposition, ultimately reduced scar formation, and even induced new hair follicle formation (Xing, et al., 2024a). Chinese researcher Ying, X. (2024) integrated aloin, arginine, and sodium alginate to prepare a multifunctional 3A hydrogel. The preparation of the 3A bio-patch involved mixing different concentrations of aloin (0, 0.25, 0.5, and 1.0 mg/mL) with sodium alginate, followed by crosslinking reactions with EDC and NHS, and the addition of arginine to form a porous hydrogel (Ying et al., 2024). Antibacterial experiments showed that the 3A hydrogel had significant antibacterial activity against *Staphylococcus aureus*, with enhanced effects as aloin concentration increased. This hydrogel also exhibited significant anti-inflammatory properties, promoting skin regeneration and angiogenesis to achieve scarless healing (Ying, et al., 2024). Ginsenosides, extracted from ginseng, are a group of active compounds with multiple pharmacological effects, including anti-inflammatory, antioxidant, immunomodulatory, and tissue repair-promoting properties (Li et al., 2024c). In recent years, the potential application of ginsenosides in scar treatment has attracted widespread attention. Previously, researchers used photocoagulation techniques to load

ginsenoside Rg3 (GS-Rg3) onto poly-γ-glutamic acid (γ-PGA) electrospun fiber scaffolds and anchored cell-adhesive peptides (RGDC) on the fiber surface via click chemistry to enhance cell adhesion (Xu et al., 2019). The results showed that wound dressings made from these fibers could effectively prevent the formation of hypertrophic scars (Xu, et al., 2019). Honey, a food with multiple medicinal values widely used in traditional Chinese medicine, has also attracted the attention of researchers. A dual-crosslinked infiltration gel casting method was used to embed an optimized mixture of honey and ghee into sodium alginate hydrogel to produce a novel hydrogel (HGSAG) (Gope et al., 2022). HGSAG exhibited significant antibacterial effects against *S. aureus* and *Escherichia coli* and enhanced the viability and proliferation of 3T3 fibroblasts. In a rat full-thickness skin wound model, wounds treated with HGSAG healed the fastest, with a wound closure rate of 99.67%, and virtually no scar formation during the healing process (Gope, et al., 2022). This confirmed that honey has antibacterial and tissue-regenerating properties and can be used to treat burns and trauma, aiding wound healing.

Table 2 Recent hydrogels loaded with anti-scarring drugs

Hydrogel	Drug	Target (Mechanism)	Ref
HA gel+PLGA-NB	SB-431542(TGF-β inhibitor)	TGF-β Signaling	(Zhang, et al., 2021b)
Poly (acrylamide) hydrogel (PAGE)	Cerium oxide nanoparticle (CNP) and curcumin (ACC)	HER2/ErbB2, TGF-β-Smad2/3, MAPK/ERK, AKT, and VEGF	(Bhattacharya, et al., 2019)
Phenol-functionalized hyaluronic acid (HA-PG) hydrogel	PTD-DBM (a peptide) and VPA (a GSK3β inhibitor)	CXXC5, Dvl and GSK3β in the Wnt/β-catenin pathway	(Lee, et al., 2023)
AC-SNF hydrogel	Asiaticoside	Reducing excessive collagen deposition	(Liu, et al., 2021)
SNF-AC-Mg hydrogel	Asiaticoside and Mg^{2+}	M2 macrophage polarization and angiogenesis	(Yang, et al., 2024a)
OQG hydrogel	Asiaticoside、reduced graphene oxide (rGO), polydopamine (PDA), oxidized dextran (ODex) and quaternized chitosan (QCS)	Conduct these electrical signals to promote cell migration and tissue regeneration	(Deng, et al., 2024)
Polysaccharide hydrogel (PECE)	Quercetin	Excellent infection prevention capabilities, reduced inflammation, promoted angiogenesis and collagen deposition	(Xing, et al., 2024a)
3A hydrogel	Aloin	Antibacterial and anti-inflammatory	(Ying, et al., 2024)
HGSAG hydrogel	Honey	Antibacterial and enhanced the viability and proliferation of fibroblasts	(Gope, et al., 2022)

The above examples all involve loading drugs with anti-inflammatory or antioxidant effects into hydrogels (Table 2). The related multifunctional hydrogels serve as novel drug delivery carriers, providing a stable platform for drug loading, and have shown great potential in anti-scarring treatment and perfect skin regeneration.

3 Hydrogel Dressings for Modulating Mechanical Signals

After skin injury, changes in the local tissue tension can stimulate the activation and proliferation of fibroblasts, promoting the synthesis and deposition of ECM, which in turn leads to scar hyperplasia. Skin mechanical signals can regulate the upstream proteins

of YAP in the Hippo signaling pathway, such as Large Tumor Suppressor Kinase 1 (LATS1), affecting the phosphorylation and expression of YAP. Therefore, YAP can sense mechanical forces and other physical properties (Mascharak, et al., 2021). Additionally, Neuropilin-1 (NRP1) is a co-receptor for mechanical stimuli, and its expression is increased in the endothelial cells of hypertrophic scars, with interactions with YAP. When the balance of their interactions is disrupted, pathological scar formation occurs (Li et al., 2023). Therefore, in clinical practice, reducing wound tension is often used to decrease scar formation during the later stages of skin healing. Currently, there are also many developments in methods that can control the mechanical morphology of wounds, reduce wound tension, or inhibit mechanical signal transduction to reduce scar formation after wound healing.

1.2 YAP Inhibitor Hydrogel Dressings

Verteporfin (VP) is a photosensitizer approved by the FDA for the treatment of age-related macular degeneration. Recent studies have found that it has the potential to inhibit fibrosis in multiple organs, including the skin (Mascharak, et al., 2021). VP is also a well-known inhibitor of the Hippo/YAP signaling pathway. Researchers have developed an injectable composite hydrogel (VP-CMCS-OSA) composed of carboxymethyl chitosan (CMCS) and oxidized sodium alginate (OSA), loaded with VP (Yang et al., 2024b). They successfully synthesized the VP-CMCS-OSA hydrogel, which has good tissue adhesion, self-healing ability, and stretchability. Cell migration experiments showed that the VP-CMCS-OSA hydrogel inhibited cell migration, possibly due to the reduced expression of YAP1 by VP, thereby inhibiting mechanical signal transduction. Relevant animal experiments also proved that the VP-CMCS-OSA composite hydrogel effectively inhibited the expression of YAP1 through the slow release of VP, reducing scar formation and promoting scarless full-thickness skin regeneration (Yang, et al., 2024b). In addition, Chen, X. et al. (2024) have studied a temperature-sensitive Pluronic® F-127 hydrogel that can release pectolinarin to promote scarless wound healing (Chen et al., 2024c). Their experiments showed that pectolinarin can inhibit the expression of the YAP gene, thereby reducing skin scar formation and promoting scarless wound healing (Chen, et al., 2024c).

Arsenic trioxide (ATO), once a well-known poison, has been found to have certain clinical therapeutic effects. ATO has been proven to modulate the Hippo/YAP signaling pathway. Therefore, at appropriate doses, it can be used as a therapeutic agent with potential anti-fibrotic and anti-angiogenic properties (Xu et al., 2024). Xu, X. et al. (2024) developed a hydrogel dressing that effectively inhibits scar formation by combining ATO with chitosan (CS) and sodium alginate (SA) (Xu, et al., 2024). Through live/dead cell staining experiments, they found that the ATO@CS/SA hydrogel was non-toxic to cells and promoted cell proliferation. Hemolysis experiments also showed that the hemolysis rate of the ATO@CS/SA hydrogel was significantly reduced, showing good blood compatibility (Xu, et al., 2024). Thus, the ATO-loaded hydrogel has good biocompatibility, ensuring its potential for future clinical therapeutic research. Their research also proved that the ATO@CS/SA hydrogel effectively inhibited scar formation and promoted scarless wound healing by modulating the YAP/TAZ signaling pathway (**Fig. 2)** (Xu, et al., 2024).

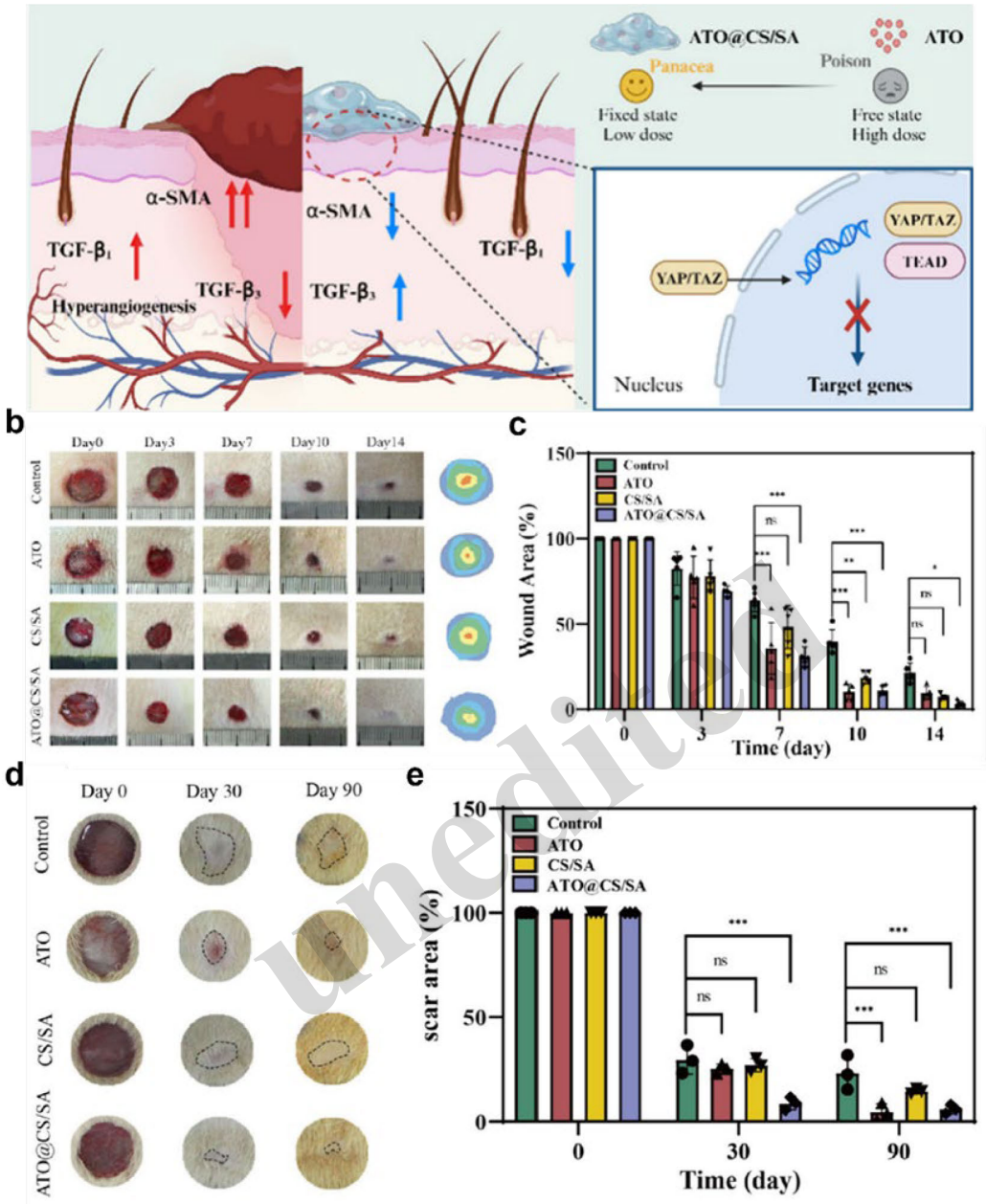

Fig. 2. The mechanism of ATO@CS/SA hydrogel promoting scarless wound healing. (a) Design strategy of the ATO@CS/SA hydrogel for scarless wound repair. (b) Photographs and schematic representation of the wound healing site on days 0, 3, 7, 10, and 14. (c) Statistical data of wound closure ratio (n = 5). Reproduced with the permission of Xu, X. (2024) (Xu, et al., 2024).

The development of these hydrogels targeting the Hippo/YAP signaling pathway to regulate scar formation provides a new strategy for scarless wound healing, with potential clinical application value. In addition to using drugs to modulate mechanical signaling pathways to inhibit scar formation, some scholars have also begun to adjust the mechanical environment of wound tissues. They have developed hydrogels that change shape to resist tension, thereby directly altering the mechanical signaling pathways of wound tissues and ultimately reducing scar formation during wound healing.

1.3 Hydrogel Dressings for Reducing Skin Tension

During the wound healing process of the skin,

mechanical tension is one of the key factors leading to scar formation (He, et al., 2021). Reducing wound tension can promote scarless healing. Chen et al. (2024) developed a hydrogel wound dressing based on body temperature-responsive contraction. This dressing can contract at body temperature, reshape the mechanical microenvironment of the wound, and reduce skin scar formation. The hydrogel is composed of modified hydroxypropyl methylcellulose (M-HPMC) and a polyacrylic acid network, and also has temperature-responsive contraction, skin tissue adhesion, and antibacterial properties (Chen et al., 2024b). In a rat full-thickness skin defect model, this hydrogel significantly reduced the scar area, mainly by decreasing the expression of Transforming Growth Factor-β1 (TGF-β1) and Collagen I, as well as inhibiting the Integrin-Focal Adhesion Kinase (FAK/p-FAK) signaling pathway (Chen, et al., 2024b). By reducing wound tension and affecting the interaction between collagen fibers and fibroblasts in the newly formed tissue, the dressing achieved the goal of scar reduction (**Fig. 3a-b**) (Chen, et al., 2024b). Cheng, X. (2024) prepared an elastic hydrogel dressing using hydroxyethyl cellulose (HEC), silk fibroin nanofiber-magnesium ion complex (Mg^{2+}-SNF), and glycerol to optimize the mechanical microenvironment, reduce inflammation, and promote angiogenesis (Cheng et al., 2024). By adjusting the ratio of HEC and glycerol, the hydrogel dressing exhibited elasticity and modulus similar to that of skin. Studies have shown that the Mg^{2+}-SNF complex has an effective therapeutic effect on diabetic chronic wounds and reduces scar formation during wound healing (**Fig. 3c**) (Cheng, et al., 2024).

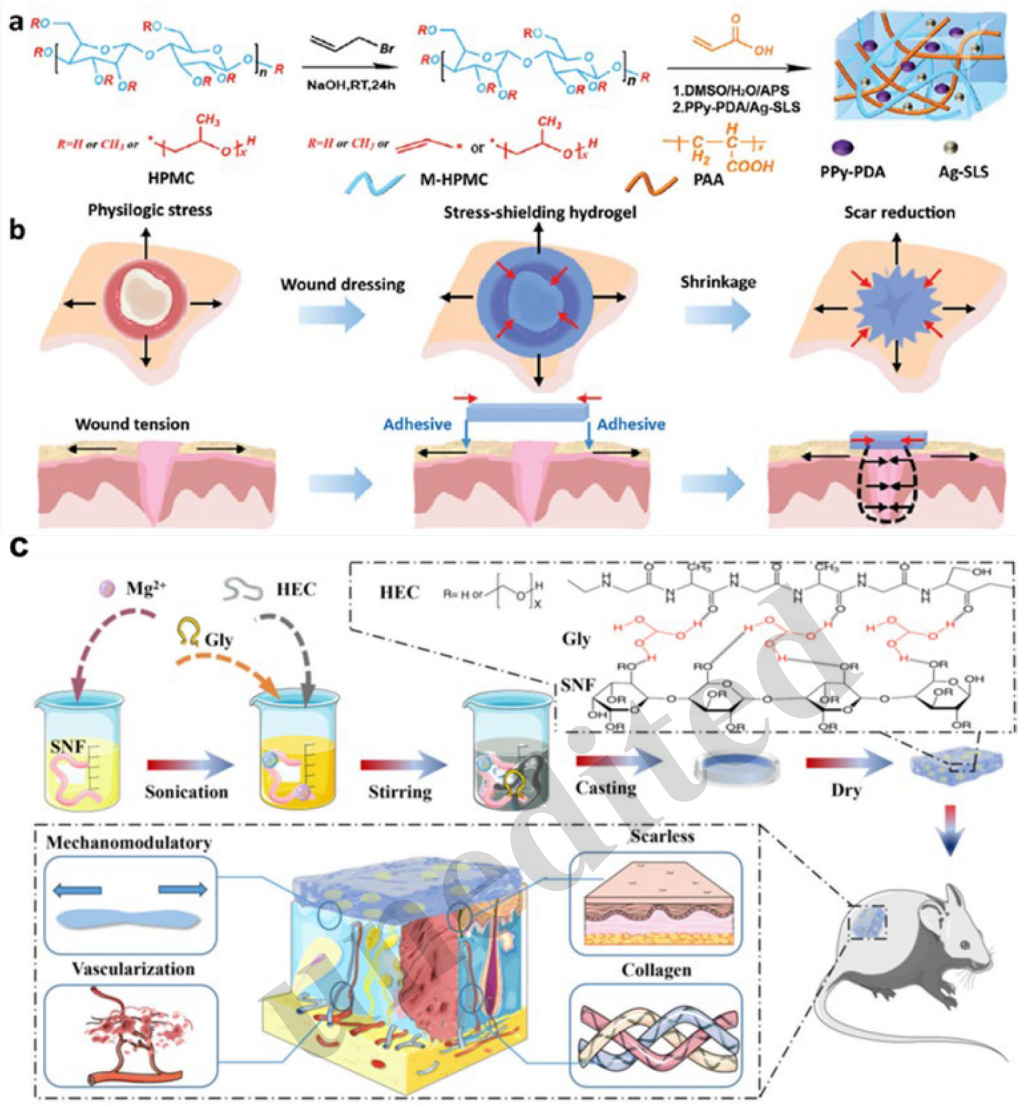

Fig. 3. Mechanical hydrogels promote scarless wound healing. (a-b) Schematic of the skin stress-shielding hydrogel dressing's synthesis and application. a) M-HPMC and PAA/M-HPMC hydrogel synthesis. b) Stress-shielding hydrogel enables active wound shrinkage, remolding the wound mechanical environment to reduce scarring. (c) Schematic of the Mg^{2+}-SNF/HEC/Gly hydrogel dressing's fabrication and its wound healing mechanism. Reproduced with the permission of Chen, Q. (2024) and Cheng, X. (2024) (Chen, et al., 2024b; Cheng, et al., 2024).

In addition, tension wounds (such as those in joint areas) are prone to hypertrophic scar formation (HTS), and there is currently a lack of effective clinical treatments. Fu, D. from China (2024) designed a tension-shielding hydrogel system (HTA system) grafted with catechol and composed of hyaluronic acid and silver nanoparticles of tannic acid for photopolymerization, to reduce scar formation in tension wounds (Fu et al., 2024). The HTA hydrogel has tension-shielding capabilities and reduces wound tension through shape fixation. Results also showed that the HTA hydrogel reduced fibrotic responses by inhibiting the activation of Engrailed-1 through the suppression of mechanical signaling pathways (Fu, et al., 2024). This also provides new ideas for the clinical treatment of pathological scars.

Hydrogel dressings for modulating mechanical signals provide a new strategy for scarless wound

healing. YAP inhibitor hydrogel dressings significantly reduce scar formation by inhibiting the Hippo/YAP signaling pathway, showing good application prospects. At the same time, hydrogel dressings that reduce skin tension reshape the mechanical environment of wounds through physical means, also providing new ideas for scar prevention. Future research can combine these two approaches by applying YAP inhibitors and anti-tension hydrogels for skin wound repair. However, these hydrogel dressings still face challenges in clinical applications, such as drug delivery efficiency, biocompatibility, and long-term safety. Future research needs to further optimize the composition and function of hydrogels, explore the integration of mechanisms of mechanical and biological signals, and conduct clinical trials to advance the development of this field.

4 Bioactive Hydrogel Dressings

With the continuous development of stem cell technology, its prospects for application to wound healing and scar treatment will become even broader. Stem cells have the ability for self-renewal and multilineage differentiation, enabling them to differentiate into various functional cells required for wound repair, such as keratinocytes, fibroblasts, and vascular endothelial cells, which can directly participate in the regeneration of skin tissue (Shi et al., 2022). Moreover, stem cells can secrete a variety of growth factors, including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and transforming growth factor (TGF-β). These factors can promote angiogenesis, regulate cell proliferation and migration, and accelerate wound healing (Hassan, et al., 2014). Stem cells can also reduce the deposition of abnormal collagen by regulating the production of fibroblasts and collagen. For example, adipose-derived stem cells (ASCs) can alter the structure of scar tissue and reduce scar formation by inhibiting the synthesis of the ECM and promoting the degradation of its components (Hassan, et al., 2014). Future research directions in stem cell therapy for the treatment of skin wounds and prevention of scar formation include establishing efficient stem cell banks, optimizing the performance of biomaterials, exploring the mechanisms of directed stem cell differentiation, and improving the application of stem cell-derived extracellular vesicles.

1.4 Stem Cell-Loaded Hydrogel Dressings

To better incorporate stem cells into biomaterials and create a bioactive wound dressing, in 2020, Zheng, X developed a silk fibroin nanofiber-based hydrogel loaded with mesenchymal stem cells (MSCs). This hydrogel mimics the microstructure of skin by loading MSCs into microgels with aligned structures to regulate the paracrine function of MSCs (Zheng et al., 2020). The microgels are dispersed in an injectable silk fibroin nanofiber hydrogel to form a composite biomaterial. In vitro experiments showed that MSC-loaded microgels can regulate cell behavior, promote angiogenesis, and induce the M1-M2 phenotypic shift in macrophages, providing a suitable microenvironment for wound healing (**Fig. 4a**) (Zheng, et al., 2020). In animal experiments, compared to hydrogels without MSCs, the MSC-loaded composite hydrogel healed wounds more rapidly and formed scarless tissue with hair follicles (Zheng, et al., 2020). This is the first report of scarless skin regeneration with hair follicles based on silk fibroin materials, offering a new direction for future clinical skin regeneration therapies. Subsequently, other research teams embedded silver-doped bioactive glass-ceramic (Ag/GC) nanoparticles into electrospun nanofibers of chitosan and gelatin, loaded with mouse embryonic fibroblasts (MEFs), to accelerate wound healing (Sharifi et al., 2022). With the addition of Ag^{+}, those wound dressings also showed antibacterial and anti-biofilm activity, effectively inhibiting both Gram-negative and Gram-positive bacteria. In a BALB/c mouse full-thickness excisional wound model, the MEF-loaded Ag/GC-Ch/PEO/Gel nanofiber scaffold significantly enhanced angiogenesis, collagen synthesis, and the regeneration of sebaceous glands and hair follicles (Sharifi, et al., 2022). This represents an innovative application of bioactive glass-ceramic materials in wound dressings.

The treatment of burn wounds remains challenging, as significant scar tissue often forms after burns, leading to impaired skin function and appearance. Scar contracture may limit joint mobility and affect limb function. Severe burns can result in the loss of skin appendages (such as hair follicles and sweat glands), impacting the normal physiological functions of the skin (Shpichka et al., 2019). Existing biomaterials and dressings struggle to fully simulate the physiological environment of the skin and achieve

scarless healing. Stem cell therapy offers a new treatment option for burns, but direct injection of stem cells faces issues such as low retention and survival rates at the wound site (Yu et al., 2023). To address this problem, Yu et al. (2023) developed an injectablee, self-healing zwitterionic polysaccharide hydrogel (DSC), prepared from sulfobetaine-derived polysaccharides and carboxymethyl chitosan through a Schiff base reaction. This hydrogel has high anti-fouling properties, resisting bacterial and non-specific protein adsorption while providing a biomimetic microenvironment for adipose-derived stem cells (ADSCs) to maintain their stem cell characteristics (Yu, et al., 2023). ADSCs loaded in the DSC hydrogel can avoid immune system recognition and activation, reduce inflammatory responses, promote collagen deposition and angiogenesis, and enhance M2 polarization of macrophages. In a burn mouse model, ADSC-loaded DSC hydrogel significantly accelerated wound healing rates, reduced scar formation, and promoted scarless skin tissue regeneration (**Fig. 4b**) (Yu, et al., 2023). Recently, Abedanzadeh, M. (2024) optimized the physical, chemical, and mechanical properties of photocrosslinked methacrylated hyaluronic acid (MAHA) hydrogel by adjusting the degree of methacrylation of hyaluronic acid (HA), polymer concentration, photoinitiator concentration, and UV irradiation time (Abedanzadeh, et al., 2024). Subsequently, they loaded tannic acid (TA) and Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) into the MAHA hydrogel to promote perfect skin regeneration. The MSCs maintained good bioactivity, and the MAHA-TA-MSC composite hydrogel significantly accelerated wound healing and reduced scar formation (Abedanzadeh, et al., 2024).

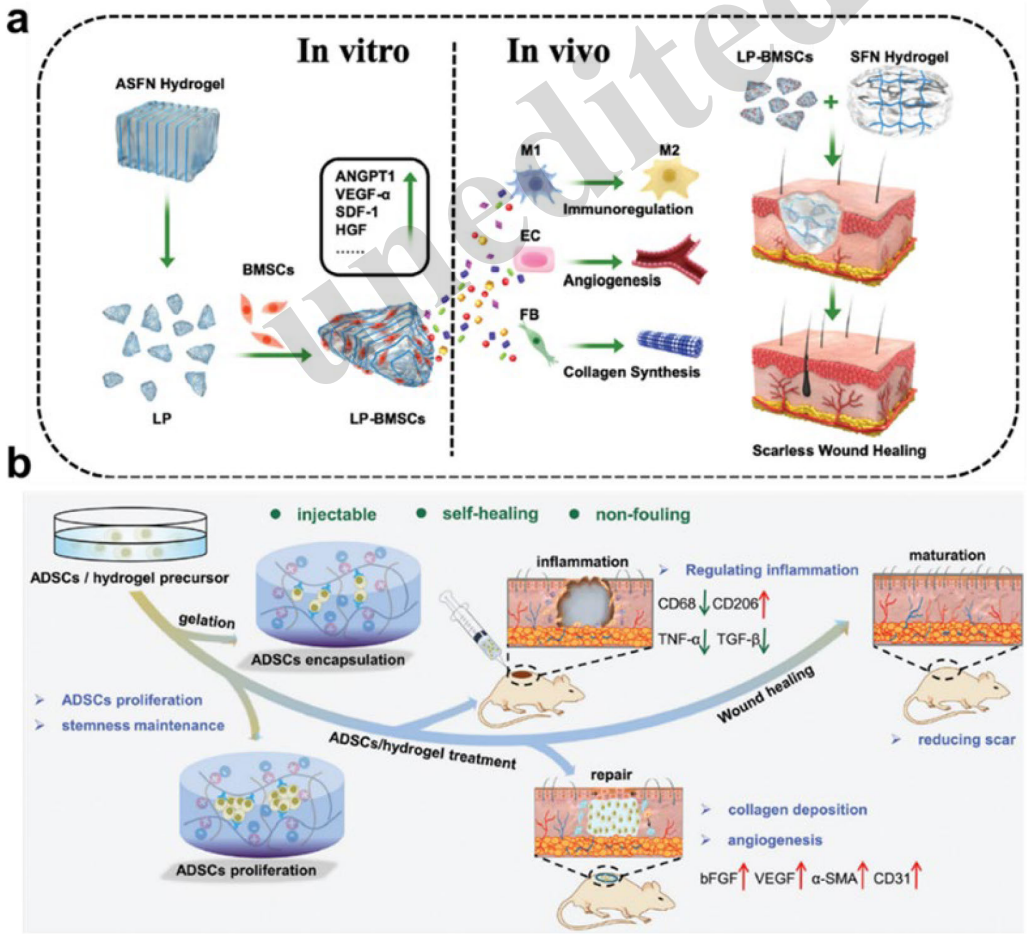

Fig. 4. Stem cell-loaded hydrogel dressings. (a) Schematic diagram of the fabrication process of the MSC-laden SFN composite hydrogels. Injecting MSC-laden hydrogels into wounds achieves scarless skin regeneration with hair follicles. (ASFN hydrogel: aligned

silk fibroin nanofiber hydrogel; SFN hydrogel: silk fibroin nanofiber hydrogel; LP: large microparticle; BMSCs: bone marrow mesenchymal stem cells; LP-BMSCs: BMSC-laden LP; M1: type 1 macrophage; M2: type 2 macrophage; EC: endothelial cell; FB: fibroblast.). (b) Schematic illustration of the polysaccharide-based zwitterionic hydrogel as a versatile platform for stem cell delivery to accelerate burn wound healing. Reproduced with the Zheng, X. (2020) and Yu, Q. (2023) (Zheng, et al., 2020; Yu, et al., 2023)

1.5 Extracellular Vesicle-Loaded Hydrogel Dressings

In addition to research on stem cell therapy, the study of extracellular vesicles (EVs) has attracted increasing attention from scholars. EVs can carry a variety of bioactive molecules, including proteins, lipids, mRNA, miRNA, growth factors, and cytokines, which can promote tissue repair and regeneration (Ding et al., 2023). They are widely involved in processes such as intercellular communication, immune regulation, tissue repair, and disease progression. As research progresses, the prospects for the application of EVs in disease diagnosis, treatment, and regenerative medicine will become even broader.

Studies have shown that exosomes secreted by MSCs can promote wound healing, reduce scar formation, and promote tissue regeneration (Ding, et al., 2023). Yang et al. (2022) investigated a hyaluronic acid hydrogel loaded with small extracellular vesicles (sEVs) derived from MSCs for scarless healing in a rat skin wound model (Yang et al., 2022). They found that MSC-sEVs can inhibit fibroblast activation by inducing an anti-inflammatory and anti-fibrotic (M2c) phenotypic shift in macrophages, thereby reducing scar formation (Yang, et al., 2022). In vitro experiments showed that sEVs significantly promoted the proliferation and migration of skin fibroblasts. In vivo experiments showed that MSC-sEVs significantly improved wound healing, reduced scar area and contraction, and promoted the regeneration of blood vessels, epidermis, hair follicles, and sweat glands (Yang, et al., 2022). Additionally, sEVs promoted skin tissue regeneration by reducing the production of reactive oxygen species (ROS) and regulating inflammatory responses (Yang, et al., 2022). Yang, Y. (2024) developed a hydrogel wound dressing loaded with human MSC-derived exosomes (HucMSC-Exos) combined with the antimicrobial peptide DP7 (Yang et al., 2024d). The study found that HucMSC-Exos regulated the functions of macrophages, endothelial cells, and fibroblasts by targeting PDCD4, PTEN, and TGFBR2 genes via miR-21-5p, thereby inhibiting inflammation, promoting angiogenesis, cell proliferation and migration, and reducing collagen deposition (**Fig. 5**)(Yang, et al., 2024d). In a mouse deep second-degree burn infection model, this hydrogel significantly accelerated wound healing, reduced scar formation, and proved convenient for long-term storage and transportation through lyophilization (Yang, et al., 2024d). The results indicated that this hydrogel dressing has the potential to serve as an alternative to MSC therapy for scarless healing of burn wounds (Yang, et al., 2024d). Shen et al. (2021) designed a bilayered thiolated sodium alginate/polyethylene glycol diacrylate (BSSPD) hydrogel for the sequential release of sEVs (Shen et al., 2021). In their study, sEVs released from the lower layer of the hydrogel promoted angiogenesis and collagen deposition during the early inflammatory and proliferative phases, while sEVs rich in miR-29b-3p released from the upper layer inhibited excessive capillary proliferation and collagen deposition during the late proliferative and maturation phases (Shen, et al., 2021). In a rabbit ear wound model, the hydrogel with sequential sEV release (SR-sEVs@BSSPD) promoted more uniform vascular structure distribution, more regular collagen alignment, and a lower hypertrophic scar volume, showing great potential for scarless wound healing as an extracellular therapy (Shen, et al., 2021).

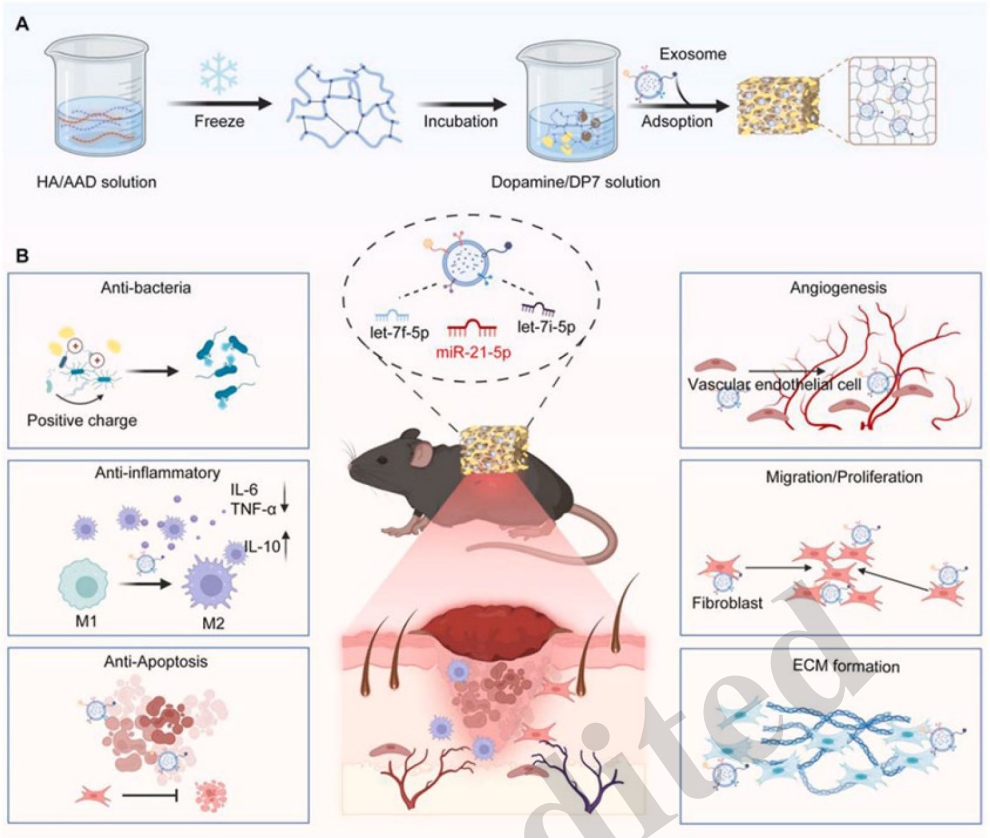

Fig. 5. Scheme of the preparation of macroporous hydrogel HD-DP7/Exo (A) and its functions for promoting wound healing. Reproduced with permission of Yang, Y (2024) (Yang, et al., 2024d).

In addition to exosomes, liposomes are commonly used in clinical treatment research for some diseases. With a structure like exosomes, liposomes can carry bioactive molecules or drugs, offering better drug delivery precision and efficiency (Xing et al., 2024b). Xing et al. (2024) introduced a multifunctional nanocomposite hydrogel based on dual-loaded liposomes for scarless wound healing. They encapsulated tetrahydrocurcumin (THC) and hepatocyte growth factors (HGF) in the hydrophobic and hydrophilic layers of liposomes, respectively, and embedded them in a gelatin methacrylamide (GelMA) hydrogel (Xing, et al., 2024b). This composite hydrogel, through the sustained release of THC and HGF, demonstrated good mechanical properties and biocompatibility, as well as antioxidant and anti-inflammatory capabilities (Xing, et al., 2024b). The hydrogel significantly accelerated wound healing, reduced scar formation, and exhibited good therapeutic effects and biosafety (Xing, et al., 2024b).

In recent years, significant progress has been made in the research of skin wound healing, especially in the application of hydrogel dressings based on stem cells and sEVs for scarless healing. The core of these studies lies in the innovative design of biomaterials to precisely regulate the wound microenvironment, thereby promoting tissue regeneration and reducing scar formation. Researchers have significantly improved the performance of wound dressings by designing hydrogels with specific functions, such as mimicking skin microstructures, regulating cell behavior, and promoting tissue regeneration. These innovative designs not only increase the retention and survival rates of stem cells and sEVs but also optimize the wound healing microenvironment by regulating inflammatory responses and promoting angiogenesis. EVs and liposomes, as efficient drug delivery systems, combined with hydrogels, have provided new solutions for wound healing. These studies have offered new directions for skin regeneration therapy, especially in the treatment of burns and chronic

wounds.

5 Innovative Multifunctional Dressings

With the rapid development of materials science and biomedical research, the field of wound healing has witnessed many innovative breakthroughs. Among them, multifunctional hydrogel dressings, as an emerging type of biomaterial, have gradually become a research hotspot due to their unique physical and chemical properties and biocompatibility. An increasing number of innovative ideas have been applied to material design and synthesis, laying a foundation for better solutions to related clinical problems.

5.1 Photoreactive Hydrogel Dressings

How can we rapidly form a hydrogel dressing in situ on large-area wounds that closely contacts the tissue, adapts to various wound shapes, achieves effective drug release and utilization, and ultimately forms a protective layer on the wound surface? Photoreactive or photocrosslinkable hydrogels are a promising solution. Methacrylated gelatin (GelMA) and methacrylated hyaluronic acid (HAMA) are currently widely used photocrosslinkable hydrogels, especially in the fields of bio-3D printing and tissue engineering repair (Yue et al., 2015). For scarless skin healing, researchers have developed a novel composite hydrogel composed of dual-crosslinked photocured hyaluronic acid methacrylate (HAMA) and laprolite (Lap), loaded with bioactive bone morphogenetic protein 4 (BMP4) (Chang et al., 2023). They mixed HAMA with Lap and added the photoinitiator I2959 to form the hydrogel under UV light. The properties of the hydrogel were optimized by adjusting the ratio of HAMA to Lap and the UV irradiation time (Chang, et al., 2023). Studies have shown that the HAMA/Lap composite hydrogel has excellent swelling properties (swelling rate exceeding 700%) and a high compressive modulus (over 100 kPa), which can maintain a moist wound environment and resist bacterial invasion (Chang, et al., 2023). Additionally, the porous structure of the hydrogel facilitates cell migration and nutrient exchange. In a New Zealand rabbit ear scar model, the HAMA/Lap/BMP4 hydrogel significantly reduced scar formation, decreased the expression of α-smooth muscle actin (α-SMA), and reduced the collagen I/III ratio, promoting the regeneration of skin appendages (such as hair follicles) and achieving scarless healing (Chang, et al., 2023).

Another example is from Yang, Y from Hong Kong (2024) who developed a sprayable, biomimetic bilayer wound dressing (BDM) based on GelMA and poly(lactic-co-glycolic-co-lactic) dimethacrylate (PLD) that can rapidly self-phase and protect wounds in layers (Yang et al., 2024c). The BDM consists of two layers: the top layer is hydrophobic poly(lactic-co-glycolic-co-lactic) dimethacrylate (PLD) and the bottom layer is hydrophilic gelatin methacrylamide (GelMA) hydrogel. Through photocrosslinking, the BDM can rapidly solidify to form a bilayer structure with strong interfacial bonding, good tissue adhesion, and adaptability to joints (Yang, et al., 2024c). The bottom GelMA layer can quickly release calcium ions to achieve rapid hemostasis, while the top PLD layer maintains a moist, breathable, and sterile environment (**Fig. 6**). Moreover, the BDM promotes angiogenesis and achieves scarless healing by inhibiting inflammatory pathways (such as tumor necrosis factor-α) and coordinating the cGMP/PKG-Wnt/Ca^{2+} signaling pathways (Yang, et al., 2024c).

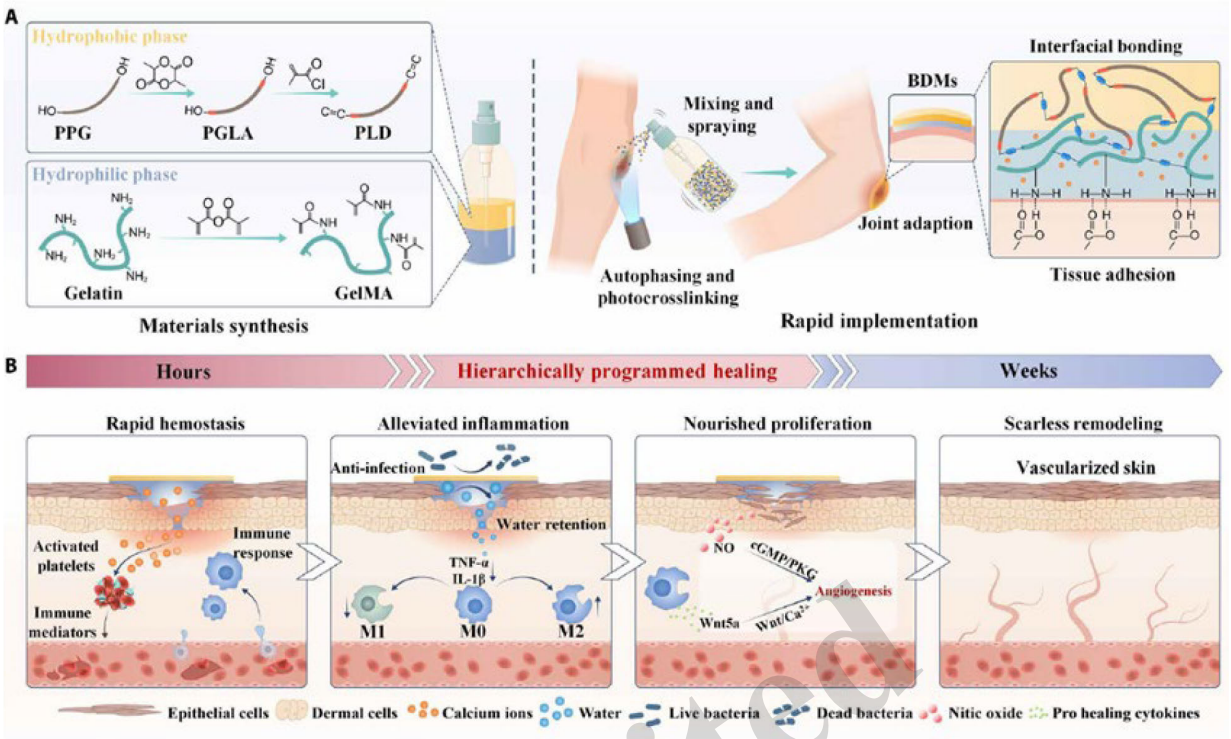

Fig. 6. Schematics showing sprayable BDMs with rapid auto-phasing and hierarchical programming for scarless wound healing. Reproduced with the permission of Yang, Y.(Yang, et al., 2024c)

In addition to the innovative development of photocrosslinkable hydrogels for wound dressings mentioned above, researchers have modified silk fibroin to obtain silk fibroin (SF) hydrogels that can polymerize in response to light (Indrakumar et al., 2023). SF hydrogels have been explored as burn dressings due to their regenerative capabilities, but unfavorable gelation conditions have limited their clinical application (Indrakumar, et al., 2023). *Indrakumar, S.* (2024) achieved rapid gelation of SF hydrogels using white light-responsive photopolymerization technology and developed an SF gel dressing (SFD) suitable for irregular burn surfaces. They extracted SF from bivoltine silkworm cocoons and achieved photo-oxidative crosslinking of SF under white light by adding a photo initiator (riboflavin and ammonium persulfate), ultimately forming an SF hydrogel (Indrakumar, et al., 2023). They also combined SF hydrogel with nonwoven cotton gauze to create an SF gel dressing with flexibility and ease of use. Studies have shown that the SF hydrogel has good swelling ability (swelling rate of 106%) and moisture retention capability (moisture retention time of about 10 h) and exhibits good stability in PBS and collagenase I solution, with excellent biocompatibility (Indrakumar, et al., 2023). The SFD can load tetracycline and achieve sustained drug release over 48 h, controlled mainly by diffusion. In a rat second-degree burn model, the SFD significantly accelerated wound healing, reduced inflammatory cell infiltration, promoted the formation of a continuous epidermal layer, and increased the regeneration of skin appendages. Compared with commercial collagen dressings, wounds treated with SFD showed less scar formation and higher elastin deposition (Indrakumar, et al., 2023).

1.6 Organic Biomacromolecule Hydrogel Dressings

Polymer hydrogels have wide applications in the fields of wound sealants, adhesives, hemostats, and dressings. However, their development is limited by issues such as multi-component gelation, tissue damage, poor hemostatic effects, and scar formation during wound healing. Therefore, there is an urgent need to develop single-component multifunctional

polymer hydrogels with benign tissue separation, high-performance hemostasis, and scarless wound healing properties.

Bai, Q. et. al. (2022) constructed a polyglutamic acid hydrogel modified with dopamine, with gelation achieved through oxidative catechol crosslinking and subsequent catechol-carboxyl hydrogen bonding interactions (Bai et al., 2022). This hydrogel has an ultra-low critical gelation concentration (0.1 wt%) and exhibits thermal stability, salt resistance, urea resistance, self-healing properties, injectability, adhesiveness with separability, and excellent biocompatibility with a hemolysis rate of less than 0.5% and a negligible inflammatory response (Bai, et al., 2022). Compared with commercial cyanoacrylate-based sealants and fibrin glue, the hydrogel and its graphene oxide (GO) composite hydrogel showed a faster hemostasis time (only 12 s) and lower blood loss (1.4%) in hemostasis (Bai, et al., 2022). The hydrogel achieved 100% wound healing within 14 days and regenerated a thick dermis with embedded hair follicles, demonstrating superior full-thickness wound healing and scar prevention capabilities (Bai, et al., 2022). Additionally, researchers designed a new collagen-binding mussel adhesive protein (MAP) by mimicking the structure of mussel adhesive proteins and combining it with specific glycosaminoglycans to create an innovative collagen-targeted surgical protein glue. This protein glue accelerates wound regeneration and is characterized by effective re-epithelialization, neovascularization, and rapid collagen synthesis (Jeon et al., 2017). It also improves the dermal collagen structure, with collagen fibers of uniform size and regular arrangement, restoring healthy tissue components.

Recently, researchers developed a novel regeneration-directed artificial skin (RDAS) based on a DNA supramolecular hydrogel, which simulates the structure and mechanical properties of natural skin matrix through a multilayer structural design (Xiong et al., 2024). This hydrogel can precisely regulate the regeneration process of wound fibroblasts without the need for exogenous cell transplantation. They first designed specific DNA sequences based on the desired functions, which may contain base-pairing regions that can self-assemble into a network structure. By chemically crosslinking DNA molecules with crosslinking agents (such as crosslinkers or crosslinking enzymes), a three-dimensional network structure is formed, resulting in a DNA supramolecular hydrogel. Their research results showed that RDAS significantly inhibited inflammatory cell infiltration and reduced inflammatory cytokine levels while promoting the migration and regenerative capacity of fibroblasts (Xiong, et al., 2024). In a mouse dorsal incision model, wounds treated with RDAS healed faster with less scar formation and successfully induced the regeneration of skin appendages such as hair follicles and sebaceous glands. Additionally, RDAS regulated the immune microenvironment at the wound site, promoting the polarization of M2 macrophages and inhibiting the activity of M1 macrophages (Xiong, et al., 2024). As a cell-free anti-scarring therapeutic strategy, RDAS shows great potential in regenerative wound healing, promoting rapid scarless healing and successfully achieving in situ regeneration of multiple skin appendages, offering a new solution for burn rehabilitation and skin regenerative medicine (Xiong, et al., 2024).

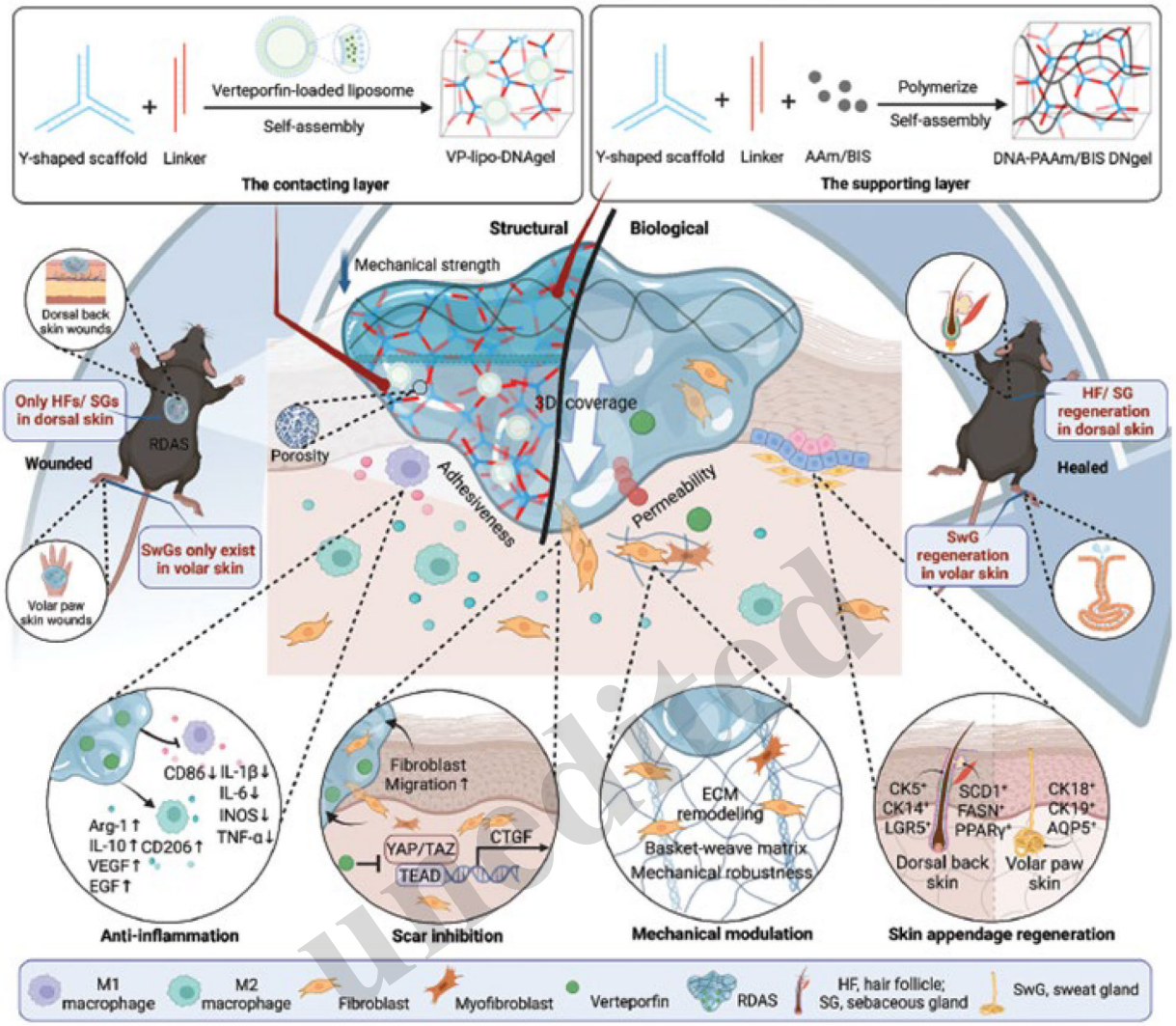

Fig. 7. Schematic illustration of the preparation of the regeneration-directing artificial skin system RDAS and in vivo beneficial application using a mice model. Reproduced with the permission of Xiong, M. (2024) (Xiong, et al., 2024).

1.7 Nanoparticle-Loaded Hydrogel Dressings

Nanomaterials have a wide range of applications and significant roles in wound repair. Their unique physicochemical properties enable them to meet various needs during the wound healing process. Nanomaterials can serve as drug carriers to achieve targeted drug delivery, sustained release, and modulation of the immune microenvironment at the wound site. For example, nanoparticles loaded with growth factors (such as bFGF, VEGF) can continuously release drugs to promote cell proliferation and angiogenesis. Some nanomaterials (such as MXenes and gold nanoparticles) have photothermal conversion capabilities and can generate local heat under near-infrared light irradiation for photothermal therapy (Xing, et al., 2024b).

Bacterial infections, complex wound microenvironments, and persistent inflammatory responses can delay wound healing and lead to scar formation, affecting the normal function and appearance of the skin. Although silver nanoparticles (Ag NPs) have strong antibacterial effects and have been widely studied, they are prone to oxidation and aggregation in aqueous solutions, reducing their antibacterial efficacy and increasing toxicity (Zhang et al., 2023). To address this issue, researchers developed a novel silver nanoparticle composite

hydrogel (Ag NCH) to modulate the wound microenvironment and promote scarless healing. They embedded Ag NPs into a matrix formed by catechol-modified hyaluronic acid (HA-CA) and 4-arm PEG-SH crosslinking (Zhang, et al., 2023). In this hydrogel, Ag NPs act not only as an antibacterial agent but also as a crosslinking agent. They also loaded basic fibroblast growth factor (b-FGF) to ensure its sustained release (Zhang, et al., 2023). Their studies showed that Ag NCH, as a novel silver nanoparticle composite hydrogel, significantly promoted scarless healing of infected wounds by modulating the immune and regenerative microenvironment (Zhang, et al., 2023). Jin et al. (2022) also developed a novel NIR (near-infrared) photothermal-responsive hydrogel (MNFs@V–H@DA) that can control drug release through NIR irradiation. They prepared a core-shell structured hydrogel using electrospinning and surface coating techniques (Jin et al., 2022). The core consisted of MXene nanofibers (MNFs) and mesoporous silica nanoparticles (SiO2 NPs) loaded with VEGF. The shell was composed of dopamine-hyaluronic acid (HA) hydrogel, which encapsulated the nanofibers and loaded an H2S donor (diallyl trisulfide, DATS) (Jin, et al., 2022). MNFs@V–H@DA exhibited excellent photothermal conversion performance under NIR light, converting light energy into heat to promote the release of VEGF. As a novel NIR photothermal-responsive hydrogel, MNFs@V–H@DA significantly promoted scarless wound healing by regulating angiogenesis and the immune microenvironment (Jin, et al., 2022).

In summary, the innovative development of multifunctional hydrogel dressings in the field of wound healing is providing new ideas and methods for solving clinical problems. Photoreactive hydrogels, organic biomacromolecule hydrogels, and nanoparticle-loaded hydrogel dressings each have unique characteristics that meet various needs during the wound healing process, from antibacterial effects and drug delivery to immune modulation and tissue regeneration. The above studies suggest their materials are non-toxic and harmless to cells or animals, but further in-depth research is needed for confirmation. This is particularly the case for nanomaterials, which can easily enter the systemic circulation through wounds. These innovative dressings not only improve the speed and quality of wound healing but also reduce scar formation and enhance patients' quality of life. In the future, with further advancements in materials science and biomedical research, multifunctional hydrogel dressings are expected to play a greater role in clinical applications, offering more effective solutions for wound healing.

6 Conclusions and Perspectives

Hydrogel wound dressings have shown significant potential for promoting scarless skin healing due to their unique physicochemical properties and biological functions. In recent years, with the rapid development of materials science, biomedical research, and tissue engineering, the study of hydrogel dressings has made remarkable progress. Through the incorporation of anti-scarring drugs, stem cells, EVs, and other bioactive components, as well as modulating mechanical signals and designing innovative multifunctional dressings, hydrogel dressings have achieved important breakthroughs in reducing scar formation, promoting skin regeneration, and improving the quality of wound healing.

However, despite these achievements, hydrogel dressings still face several challenges in clinical applications, especially for different types of wounds like burn, diabetic foot, surgical, and chronic wounds. Future research needs to further optimize treatment methods, improve treatment outcomes, reduce complications, and enhance patients' quality of life. For burns, which are prone to scar contracture and infection, skin mechanical tension-reducing hydrogels may help. Also, combining them with anti-infective drugs can be beneficial. For surgical wounds, preventing infection is the focus. As for chronic wounds, the key is to regulate inflammation, clear exudate, and prevent infection. Meanwhile, the efficiency of drug delivery needs to be further improved to ensure precise release and effective maintenance of the concentration of drugs at the wound site. In particular, for novel nanomaterial and composite-based hydrogel dressings, the metabolism of these substances within the body and their potential toxicity requires more in-depth research and relevant clinical trials. Researchers should incorporate long-term observation indicators for animal experiments, such as monitoring adverse effects on the animals' overall health, including weight changes,

blood routine indicators, and other physiological parameters, as well as assessing the treated wound area by observing scar formation, skin texture, elasticity, and other characteristics, and evaluating potential impacts on surrounding tissues and organs (Naasani et al., 2022; Lou et al., 2025). Moreover, clinical trial designs should focus on long-term patient follow-up to collect data on wound healing outcomes, recurrence rates, and the occurrence of adverse reactions. Imaging techniques and other diagnostic methods could also be used to monitor potential impacts on deep tissues and organs (Lou, et al., 2025). By adopting these approaches, researchers can comprehensively evaluate the long-term safety of hydrogel dressings, providing a more solid foundation for their clinical application.

Future research directions should focus on the following aspects: first, further optimization of the composition and structure of hydrogels to develop new types of hydrogel materials with higher biocompatibility and functional diversity. Second, in depth exploration of the integration of mechanisms of mechanical and biological signals to develop intelligent hydrogel dressings that can simultaneously regulate multiple signaling pathways. Third, strengthening preclinical and clinical studies to verify the efficacy and safety of hydrogel dressings in different types of wounds, such as burns and chronic wounds. Fourth, promotion of interdisciplinary collaboration to leverage the strengths of materials science, biomedical research, and clinical medicine, accelerating the clinical translation of hydrogel dressings. For instance, with the advancement of artificial intelligence, it should be possible to develop a smart diagnosis and treatment system for wounds (Chen et al., 2024a). This system could conduct real-time monitoring of the wound healing process and provide early timely warning for the treatment of wound infections.

In summary, hydrogel wound dressings hold broad prospects for promoting scarless skin healing. Through continuous innovation and optimization, they have the potential to provide more effective solutions for skin trauma repair and improve the quality of life for patients.

Data availability statement

Not available.

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Author contributions

Conceptualization, Xian Hu and Qing-Qing Fang; Investigation and Writing – Original Draft, Xian Hu; Writing – Review & Editing, all authors, Funding Acquisition and Supervision, Wei-Qiang Tan and Qing-Qing Fang.

Compliance with ethics guidelines

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.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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