


Hydrogel Loaded with Components for Therapeutic Applications in Hypertrophic Scars and Keloids

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Abstract: Hypertrophic scars and keloids are common fibroproliferative diseases following injury. Patients with pathologic scars suffer from impaired quality of life and psychological health due to appearance disfiguration, itch, pain, and movement disorders. Recently, the advancement of hydrogels in biomedical fields has brought a variety of novel materials, methods and therapeutic targets for treating hypertrophic scars and keloids, which exhibit broad prospects. This review has summarized current research on hydrogels and loaded components used in preventing and treating hypertrophic scars and keloids. These hydrogels attenuate keloid and hypertrophic scar formation and progression by loading organic chemicals, drugs, or bioactive molecules (such as growth factors, genes, proteins/peptides, and stem cells/exosomes). Among them, smart hydrogels (a very promising method for loading many types of bioactive components) are currently favoured by researchers. In addition, combining hydrogels and current therapy (such as laser or radiation therapy, etc.) could improve the treatment of hypertrophic scars and keloids. Then, the difficulties and limitations of the current research and possible suggestions for improvement are listed. Moreover, we also propose novel strategies for facilitating the construction of target multifunctional hydrogels in the future.

Keywords: hydrogel, wound healing, hypertrophic scar, keloid

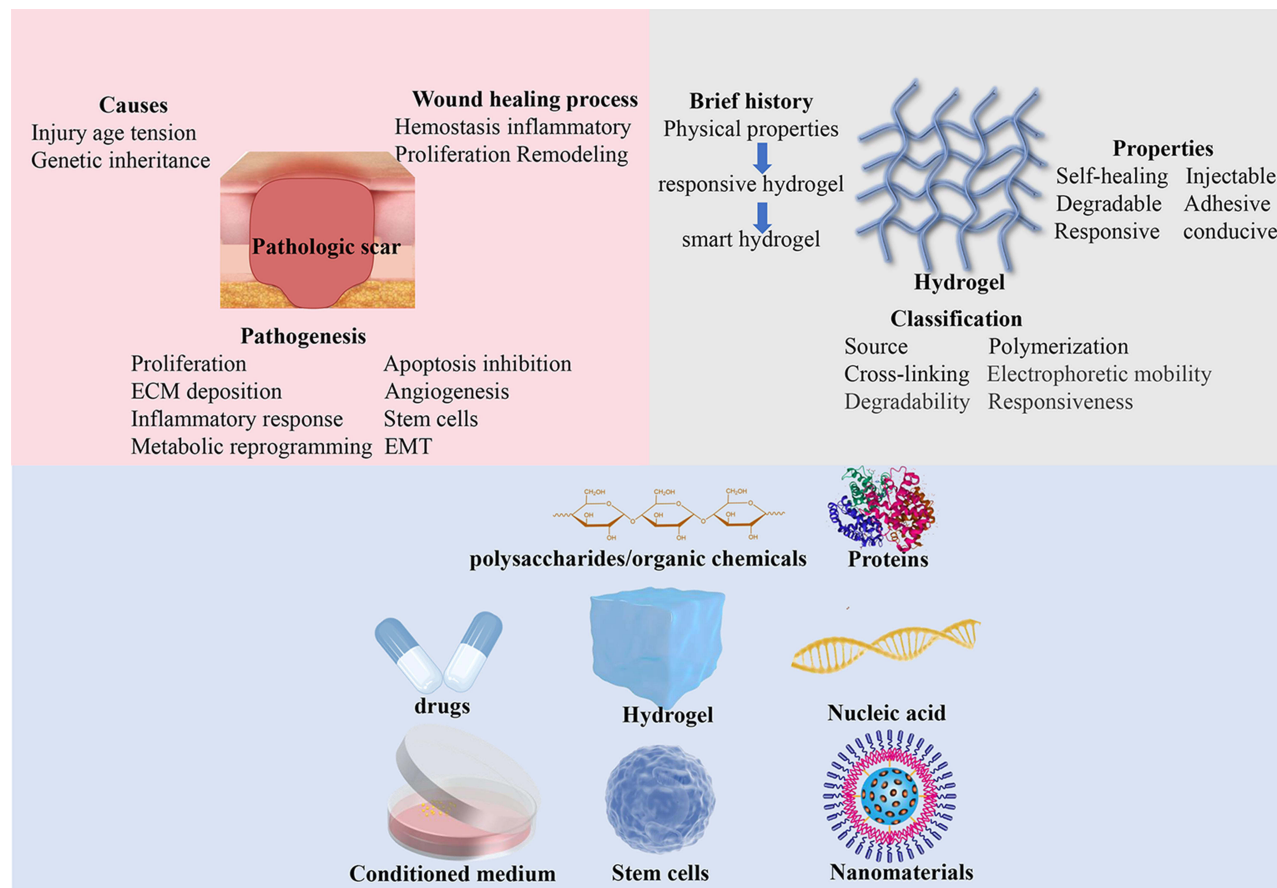
Introduction

Brief introduction of Keloid and Hypertrophic Scar

Hypertrophic scars and keloids are both benign fibrous growth diseases usually caused by skin injury. Hypertrophic scars are soft, with normal skin color, do not extend beyond the boundary of the injury, may regress over time, and histologically display well-organized type III collagen bundles. Keloids are clinically manifested as hard-raised and pigmented scars that grow beyond the original wound area, have high recurrence rates and histologically display disorganized, large thick, collagen type I and III bundles.¹ Giant hypertrophic scars and keloids can cause disfiguration and movement disorders, accompanied by functional symptoms of pruritus and pain, which severely damage their quality of life and psychological health.²

In addition to injury, ethnicity, age, skin tension, and genetic inheritance were also closely associated with the occurrence and progression of keloids.³ Hispanic and African populations are more prone to keloids, with an estimated incidence of 5–16%, than white populations.⁴ Keloids in young individuals tend to progress faster than those in old individuals.³ The most vulnerable sites are the shoulders, backs, chests, and earlobes with high tension.^{5–7} Current treatments for hypertrophic scars and keloids include surgical excision, glucocorticoid injection, radiation therapy, and mesenchymal stem cells.⁸ Meta-analysis revealed that surgery combined with radiotherapy had a lower recurrence rate than radiotherapy (22% vs 37%) in keloids.⁹ However, there is no optimal treatment that can completely prevent the

Graphical Abstract



formation, progression, and recurrence of pathologic scars; thus, more efforts need to be dedicated to developing novel therapeutic agents for hypertrophic scars and keloids.

Pathological Scar Formation in the Wound Healing Process

Pathologic scarring is caused by abnormal wound healing (Figure 1). To improve the treatment of hypertrophic scars and keloids, we must understand the wound healing process. Wound healing is now considered a complicated process consisting of four interrelated stages: hemostasis. Inflammatory, proliferative, and remodelling, involving a variety of cells secreting different cytokines and other biomolecules.^{10,11}

Wound Healing Phases

Hemostasis usually lasts 2–3 hours, forming fibrin plugs and triggering the release of inflammatory mediators by platelets. Immune cells such as neutrophils and macrophages are recruited by cytokines, initiating the inflammatory phase.¹² The inflammatory stage initiates immediately after skin injury and typically lasts from hours to two or three days, forming platelet plugs and the extracellular matrix to prevent blood loss, close the wound, and guide cell migration.¹³ The proliferation stage may last several weeks and is marked by angiogenesis, new extracellular matrix (ECM) formation, and epithelization. Endothelial cell proliferation and migration promote angiogenesis and the construction of new vessels and capillaries to deliver oxygen and nutrients essential for other cells.¹³ Fibroblasts activated by transforming growth factor β facilitate the construction of new ECM and immune cells, such as macrophages, and the degradation of the old matrix by secreting proteases, such as matrix metalloproteinases (MMPs).¹⁴ In addition,

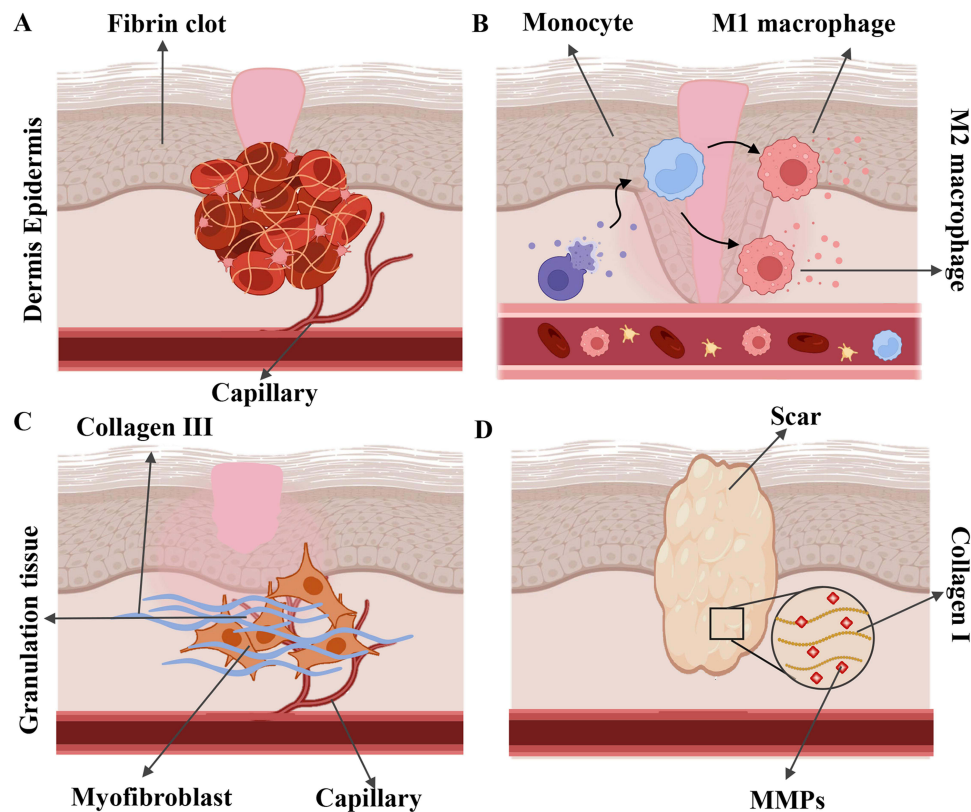


Figure 1 Four stages of wound healing.

Note: (A) Hemostasis stage, (B) inflammatory stage, (C) proliferation stage, (D) remodelling stage.

epithelialization is initiated by the migration of keratinocytes from the edge.¹⁵ The final phase, remodelling, can last for months to years and mainly leads to hypertrophic and keloid scar formation. A variety of proteases and their inhibitors participate in the remodelling phase. Type III collagen is converted to type I collagen to increase matrix density and stability.¹⁶ Excessive fibroblast proliferation and differentiation into myofibroblasts, as well as the imbalance between ECM disposition and degradation, is mainly responsible for pathologic scar formation.

Mechanical Forces Contributes to Abnormal Scar Formation

Notably, increasing evidence suggests that mechanical forces play a key role in abnormal scar formation. As stated above, keloids are prone to occur at sites with high skin tension. High skin tension can elongate or expand the ECM and cells, increasing ECM accumulation, the cell cytoskeleton, and membrane forces, leading to an increase in whole tissue stiffness.^{17,18} In the inflammatory phase, mechanical forces can promote macrophage proliferation and M1 macrophage polarization, aggravating the inflammatory response.^{19,20} In the proliferative phase, mechanical forces can facilitate the abnormal growth of fibroblasts and their transformation to myoblasts via mechanical transduction pathways, such as FAK/ERK and YAP/TAZ, which produce excessive ECM and contribute to the formation of hypertrophic scars and keloids.^{21,22} In the remodelling phase, excessive ECM accumulation leads to increased ECM stiffness, inhibiting the apoptosis of myoblasts, which continuously generate new ECM.^{19,23,24}

Keloid and Hypertrophic Scar Pathogenesis

Hypertrophic scars and keloids possess common pathological processes to varying degrees, involving proliferation, apoptosis inhibition, ECM deposition, angiogenesis, inflammatory response, metabolic reprogramming, epithelial-mesenchymal transition (EMT), and stem cells (Figure 2).

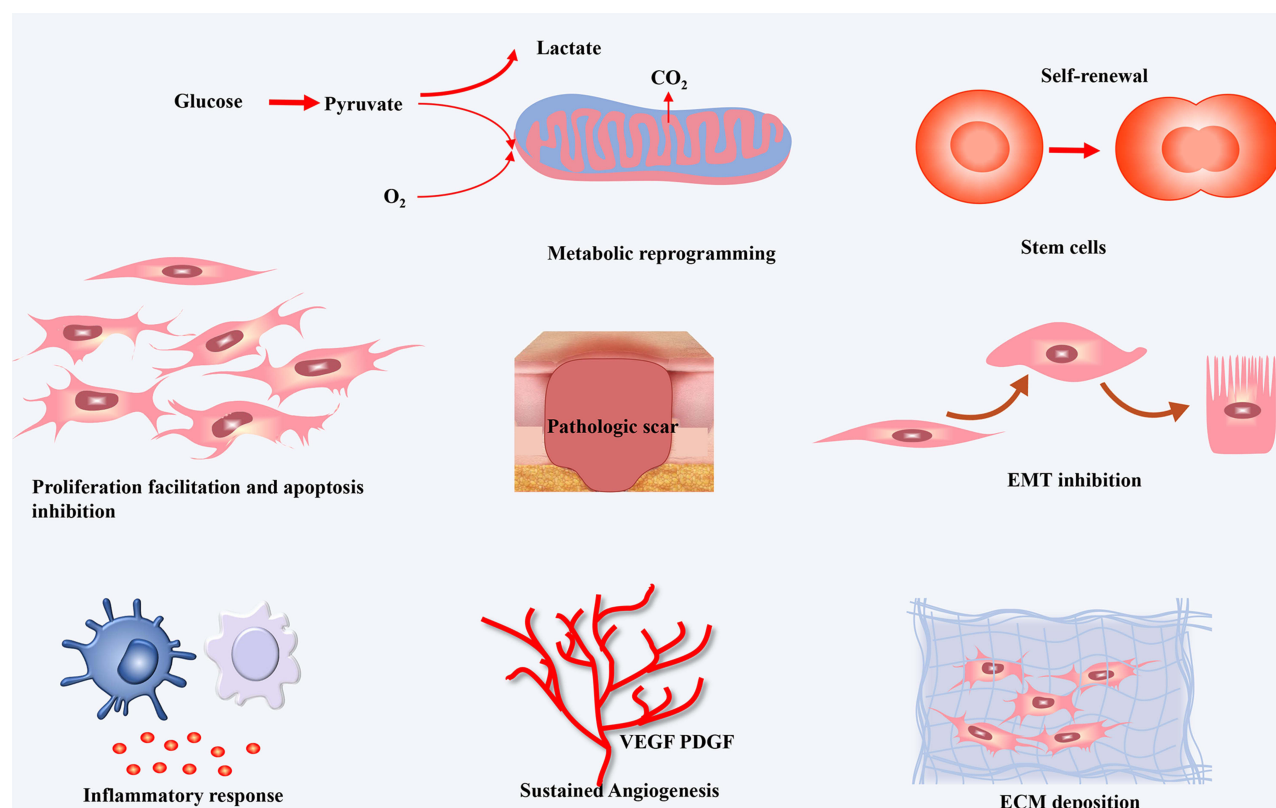


Figure 2 Pathogenesis of hypertrophic scars and keloids.

Proliferation and Apoptosis Inhibition

Excessive fibroblast proliferation and apoptosis inhibition are crucial to keloid and hypertrophic scar formation and progression. Continuous activation of the TGF β /SMAD pathway promotes fibroblast proliferation, which is necessary for collagen synthesis in hypertrophic scars and keloids. β -Catenin, Wnt5A, and Wnt10A might contribute to fibroblast growth by regulating the Wnt/ β -catenin signaling pathway.^{25–27} High levels of cMYC and Bcl-2 (anti-apoptotic proteins), transcription factors c-Jun and c-Fos, which facilitate continuous fibroblast growth signals, and decreased levels of TP53 (anti-apoptotic protein) were observed in keloids.^{28–30}

Deposition of ECM

Histologically, Hypertrophic scars exhibit well-organized type III collagen bundles, while Keloids manifest disorganized, large thick, collagen type I and III bundles. Excessive collagen deposition, or fibrosis, was observed in hypertrophic scars and keloids. Cytokines (TGF- β 1, IL-6, and IL-8) can facilitate the production of collagen, fibronectin, and fibrotic proteins (SPARC and tenascin) in hypertrophic scar fibroblasts.³¹ Meanwhile, it was reported that TGF- β 1 induces collagen type I, type III, and fibronectin accumulation in keloids.³² In addition, matrix metalloproteinases (MMPs) play a complex role in abnormal scar formation and progression. On the one hand, MMP was activated by IWR-1, an inhibitor of the Wnt/ β -catenin pathway, to attenuate the production of collagen in keloids and normal fibroblasts.³³ On the other hand, the level of MMP-2 was elevated in collagen bundle regions, which might collagen bundle remodelling and invasion of keloid fibroblasts by degrading ECM.³⁴

Angiogenesis

As stated above, in the proliferative phase, angiogenesis could deliver oxygen and nutrients essential for other cells. It was suggested that hypertrophic scar myoblasts contribute to the construction of microvessels, resulting in excessive vascularization of hypertrophic scars. Hypertrophic scar myoblasts can release microvesicles to facilitate endothelial cell proliferation, migration, and assembly, leading to excessive vascularization of hypertrophic scars.³⁵ Angiogenesis factors and their receptors vascular endothelial growth factor (VEGF) and VEGF/KDR complex, and platelet-derived growth factor (PDGF) and its receptor-PDGFR

α were all expressed in keloid-derived fibroblasts, phagocytes, endothelial cells, adventitial cells, epidermal cells, sustaining the vascularization for nutrient delivery and metabolism by enhancing the growth, migration and assembly of endothelial cells.³⁶

Metabolic Reprogramming

Sparse, occluded, and flattened microvessels suggested a hypoxic microenvironment in the keloid centers. The hypoxic zone exhibited an elevated level of hypoxia-inducible factor 1 α (HIF-1 α).³⁷ Similar to tumors, keloids display metabolic reprogramming, including enhanced anaerobic glycolysis and weakened oxidative phosphorylation under hypoxia. Compared with normal skin, lactic acid levels were higher in keloids. HIF-1 α may regulate glucose metabolic reprogramming via the PI3K/AKT pathway.³⁸ Enhanced anaerobic glycolysis facilitates tumor progression by providing energy and materials for macromolecule synthesis. Likewise, under hypoxia, the proliferation of keloid fibroblasts increases, while the apoptosis of cells decreases.^{38,39}

EMT

EMT is a biological process in which epithelial cells adjust to the mesenchymal phenotype with enhanced invasiveness.^{40,41} EMT plays a key role in the progression of hypertrophic scars and keloids. Mesenchymal markers such as vimentin and N-cadherin are significantly increased in hypertrophic scar tissue.⁴² Hypertrophic scar fibroblast-derived exosomes upregulated the EMT markers of keratinocytes.⁴³ Moreover, increased WNT5A promotes interleukin-6-dependent EMT in keloid keratinocytes by regulating the JAK/STAT pathway.⁴⁴ It was reported that pirfenidone, an antifibrotic drug, could reduce the EMT-like phenotype in keloid keratinocytes.⁴⁵ Hypoxia also contributes to EMT alteration in keratinocytes. Keloid keratinocytes acquire an EMT phenotype and exhibit elevated invasiveness under hypoxia.⁴⁶

Stem Cell

Keloid fibroblasts display high self-renewal capability and drug resistance and maintain themselves by asymmetric division, producing new cells to replace cells killed by medicines, laser or radiation therapy, resulting in expansion outwards from the boundary of keloids and recurrence.^{47,48} Haematopoietic and mesenchymal-like stem cells were identified in keloid lesions.^{47,48} Meanwhile, embryonic stem cell markers (OCT4, SOX2, pSTAT3, and NANOG) were positive in keloid-associated lymphoid tissue,⁴⁹ while Axin2 was overexpressed in patients with pathologic scars.⁵⁰ In addition, hypertrophic scar fibroblasts highly express mesenchymal stem cell markers (CD73, CD105, CD44, CD90, and OCT4), which might contribute to the multilineage differentiation potential of hypertrophic scars.⁵¹ These findings suggested the existence of stem cells in hypertrophic scars and keloids.

Hydrogel

Brief History

Hydrogels are hydrophilic polymers that chemically or physically crosslink together to form a three-dimensional (3D) network. It can absorb water without dissolving and swell while maintaining a 3D structure. The concept of hydrogels was first proposed in 1894,⁵² and the properties of biocompatibility and high water affinity were defined in 1960.⁵³ Near-exponential growth of hydrogel research started in the 1990s due to the versatility of hydrogels. It was suggested that hydrogels develop through three stages: the first stage, a simple polymer with physical properties; the second stage, a more complicated material responsive to stimuli such as temperature and pH; and the third stage, a smart hydrogel with a variety of variable properties and applications such as small interfering RNA (siRNA) delivery.⁵⁴

Classification

Hydrogels can be classified according to their source, polymerization method, crosslinking method, electrophoretic mobility, degradability, and responsiveness (Figure 3).⁵⁵ According to the source, hydrogels are classified into natural hydrogels, generally consisting of polysaccharide chains, such as hyaluronic acid, sodium alginate, and collagen; synthetic hydrogels composed of polymers, such as polyethylene glycol (PEG), poly-acrylamide (PAM) and polyvinyl pyrrolidone (PVP); and hybrid hydrogels, consisting of both natural and synthetic polymers.^{56–59} As for the polymerization method, hydrogels can be made up of homopolymers, copolymers, semi-interpenetrating networks (semi-IPNs), or IPNs (Figure 4).⁶⁰ When it comes to the crosslinking method, hydrogels are divided into physical hydrogels and chemical hydrogels. Physical hydrogels are transient, and polymers interact with hydrogen bonds and van der Waals forces, while chemical hydrogels are permanent, and polymers crosslink with

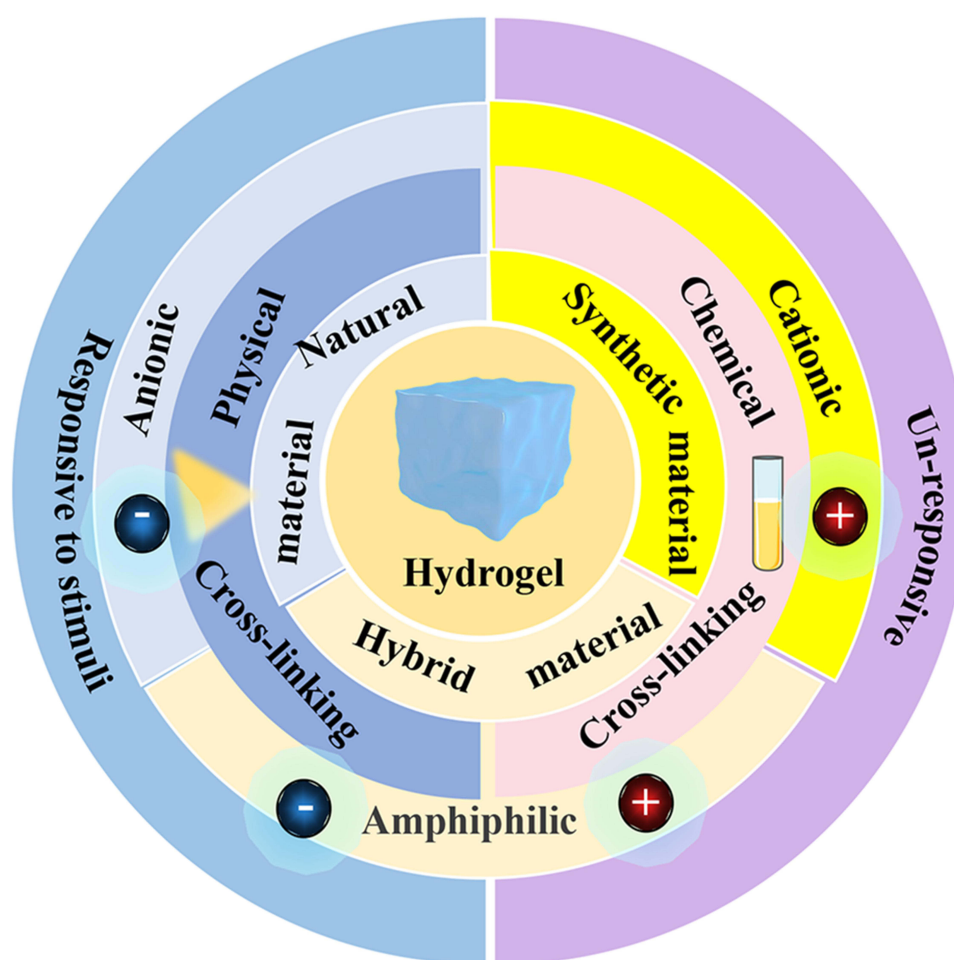


Figure 3 Classification of hydrogels based on different methods.

chemical bonds. Four categories of hydrogels exist based on electrophoretic mobility: nonionic hydrogels and ionic hydrogels, including cationic, anionic, and amphiphilic hydrogels. Degradable and nondegradable hydrogels were classified according to degradability: unresponsive hydrogels and responsive hydrogels, such as thermosensitive and pressure-sensitive hydrogels, in regard to responsiveness to stimuli.⁶¹ This review mainly focuses on the classification of hydrogels based on their source (Table 1).

Natural Hydrogels

As natural components of the ECM, natural hydrogels display the best biocompatibility. Matrigel™ is a basement membrane derived from Engelbrecht–Holm–Swarm mouse sarcoma cells, which are composed of hyaluronic acid, laminin, fibrin and collagen and are rich in growth factors and MMPs.⁶² Alginate is a polysaccharide extracted from brown algae or bacteria that is widely used in food, medicine, and engineering fields due to its stability, safety, adhesiveness, and liquid-absorbing quality.⁶³ Chitosan is the only canonic polysaccharide;⁶⁴ hyaluronic acid is also a natural polysaccharide. Hyaluronic acid-based hydrogels are widely applied in wound healing and tumor inhibition through their ability to be adjusted by chemical modification, physical blending, and nanocomposites.⁶⁵ Besides, gelatin is extracted from the hydrolysis of animal-origin collagen and gelatin-based hydrogels were also extensively used in biomedical fields.⁶⁶ However, natural hydrogels have relatively poor mechanical properties and a high degree of swelling, limiting their use in different areas. Meanwhile, it is difficult to control the differences between batches when extracting these natural products. In addition, the tumour-derived natural restricts the clinical application of natural hydrogels.⁷⁵ For instance, Matrigel TM could facilitate tumor progression by promoting cell migration and invasion.⁷⁶

Synthetic Hydrogels

Synthetic hydrogels are composed of engineered polymers, which are polymerized by a monomer, such as PEG, polyethylene oxide (PEO), and PAM.^{67–69} Synthetic hydrogels are reproducible, possess tunable chemical or mechanical

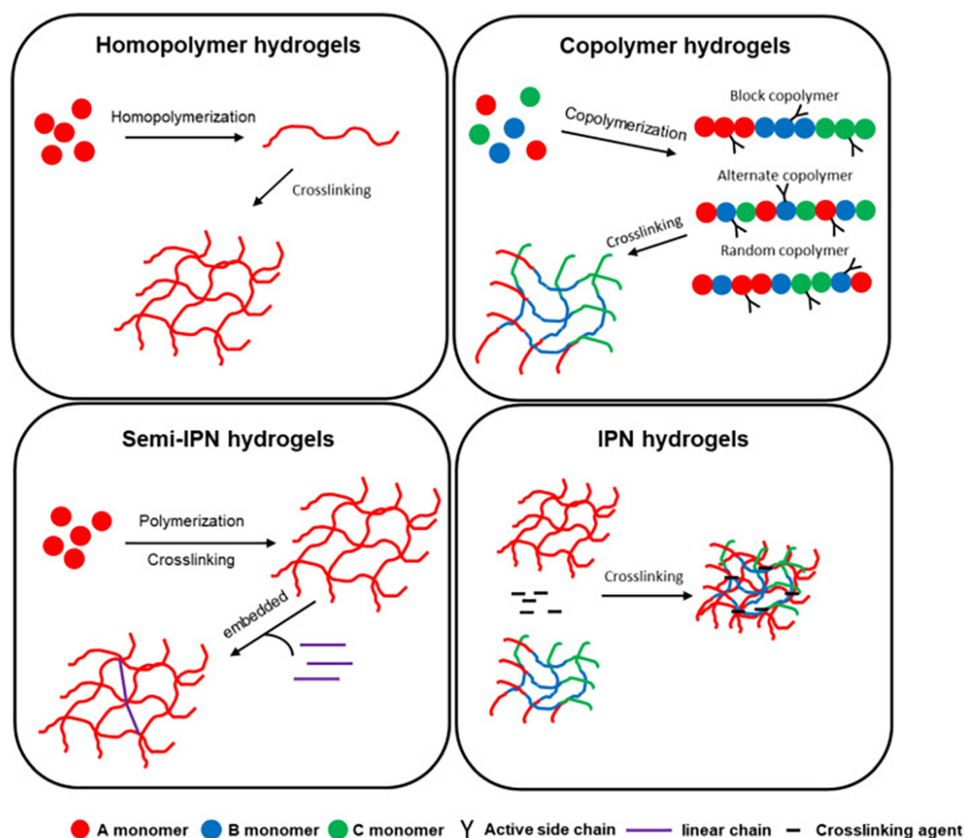


Figure 4 Simple diagram of homopolymer hydrogels, copolymer hydrogels, semi-IPNs, and IPNs.

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properties and can be standard controlled between different batches.⁷⁷ For instance, PEG hydrogels are stable, highly stretchable, self-healing and injectable, exhibiting anti-infection properties.⁶⁷ Besides, synthetic PVP hydrogels were widely used in drug delivery of cancer.⁷⁰ Polyvinyl alcohol (PVA) hydrogels display excellent mechanical properties, dictating its applications in medical fields, and can be blended with PVP to improve their properties.^{71,78} Synthetic hydrogels are not as biocompatible as natural hydrogels due to their sources, but their biodegradability and biocompatibility can be improved by modifying functional group or incorporating with natural polymers.⁶⁰

Table I Classification of Hydrogels According to Source

Source	Example	Advantage	Disadvantage
Natural	Matrigel ⁶² Alginate ⁶³ Chitosan ⁶⁴ Hyaluronic acid ⁶⁵ Gelatin ⁶⁶	Most biocompatible Most bioactive	Poor mechanical properties High degree of swelling Batch difference Tumor-related risk (tumor-origin hydrogel)
Synthetic	PEG ⁶⁷ PEO ⁶⁸ PAM ⁶⁹ PVP ⁷⁰ PVA ⁷¹	Tuneable Reproducible	Least biocompatible
Hybrid	GelMA ⁷² PEG-fibrin ⁷³ PEG-collagen ⁷⁴	Multi-tuneable Biocompatible Bioactive	Complicated Expensive

Hybrid Hydrogels

Hybrid hydrogels are chemically modified natural polymers or a combination of natural and synthetic materials to gain the advantages of these two types.⁷⁹ A widely used hybrid hydrogel is methacryloyl-modified gelatin (GelMA), which is a chemically modified natural material,⁷² while PEG crosslinked fibrinogen, or collagen, is a combination of natural and synthetic matrices.^{73,74} Hybrid hydrogels can not only possess the multi-tuneable mechanical properties of synthetic hydrogels by adjusting chemical parameters but also preserve the biocompatibility and bioactivity of natural hydrogels.⁸⁰

Properties

Hydrogel is extensively applied in biomedical files, such as tissue engineering scaffolds, bone generation, wound dressing, and drug delivery, due to its multifunctional properties. The properties of hydrogels mainly include swelling, self-healing, injectable and degradable capability, adhesiveness and responsiveness.⁸¹ In this review, we mainly focus on the injectability, self-healing, adhesiveness, and responsiveness of hydrogels (Figure 5).

Injection and Self-Healing Capability

Injectable hydrogels could flow through a medical needle and aggregate into a whole bulk hydrogel at the targeted site. Injectable hydrogels are composed of precursor and self-healable hydrogels. Precursor hydrogels are referred to as hydrogels, which gelatinize under physical or chemical conditions such as light, temperature or pH.^{82,83} Self-healing hydrogels could automatically reconnect their network via chemical or physical bonds after being broken.⁸⁴ Notably, injectable hydrogels are characterized by high flowability, given the dynamic variation of cross-linking bonds and motion of polymer chains.⁸⁵ Therefore, hydrogels can be easily injected and then recover to their original structure or mechanical properties at the targeted area.

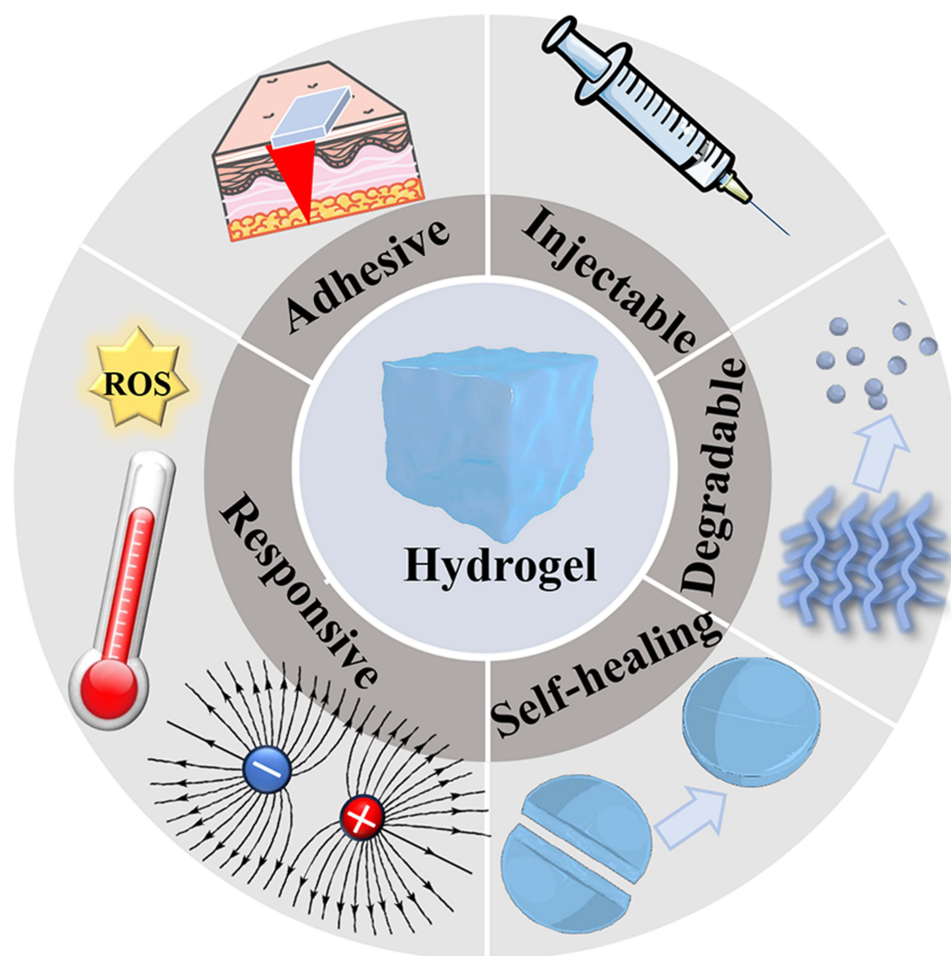


Figure 5 Properties of hydrogels: injectable, self-healing, adhesiveness and responsiveness.

Adhesiveness to Tissue

Recently, increasing research has focused on developing different types of adhesive mechanisms of hydrogels, such as mussel-inspired hydrogels, Schiff base-bond hydrogels and bioactive proteins.⁸⁶ The adhesiveness of mussel-inspired hydrogels lies in the pyrocatechol of mussel foot proteins, which form chemical interactions with and cross links with different matrices.⁸⁷ The amino group of surfaces of tissue could bind with the aldehyde group of hydrogels, which is called the Schiff-base bond, contributing to the tissue adhesiveness of hydrogels.⁸⁸ Bioactive proteins such as silk fibroin and elastin can form hydrogen bonds or electrostatic interactions, leading to adhesion to cells and tissues.^{89,90} Moreover, adhesive hydrogels applied in wound healing could reduce the boundary tension.⁹¹ These studies revealed that adhesive hydrogels show great potential in wound closure following different types of injury.

Responsiveness

Responsive hydrogels, also referred to as smart hydrogels, can respond to physical stimuli, such as light, electricity, temperature, and pressure, or chemical stimuli, such as pH and reactive oxygen species (ROS). Responsive hydrogels could undergo changes in phase, volume, or other physicochemical characteristics under different stimuli. Compared with traditional hydrogels, smart hydrogels display multifunctional variables and tunable characteristics and are thus more widely used in biomedical fields, especially in wound healing.⁸¹ It was reported that a pH/ROS dual-responsive injectable hydrogel displayed antibacterial and antioxidant effects in the wound healing process.⁹² Li et al designed a pressure-sensitive antibacterial hydrogel to monitor wound pressure and facilitate skin healing in bedridden patients.⁹³ More importantly, skin tension is closely associated with the formation, progression, and recurrence of pathologic scars;¹⁷ thus, smart hydrogels, which also display promising potential in reducing skin tension in wound healing,⁹⁴ might be novel therapies for preventing hypertrophic scar and keloid occurrence and recurrence.

Loaded Components of Hydrogels

Given their three-dimensional and porous structure, hydrogels can carry drugs, biomolecules such as exosomes, cytokines, and proteins, or nanomaterials. More importantly, sustained and prolonged release of drugs and biomolecules can be achieved by slow diffusion and degradation of hydrogels or by their responses to stimuli, such as temperature or pressure. This review focuses on five categories of loaded components in composite hydrogel dressings for therapeutic use in hypertrophic scars and keloids: organic chemicals, mesenchymal stem cells and their conditioned medium, drugs, nucleic acids, and proteins (Table 2). More importantly, this review also proposes a variety of components that have not been explored but possess promising therapeutic potential to be delivered by hydrogels.

Table 2 Loaded Components of Hydrogels in Hypertrophic Scars and Keloids

Classification	Components	Hydrogel Source	Disease
Polysaccharides/Organic chemicals	Genipin Dextran Polysaccharides Collagen-glycosaminoglycan	Polyurethane Carboxymethyl chitosan Gelatin PAM PVA	Hypertrophic scar ⁹⁵ Hypertrophic scar ⁹⁶ Keloid ⁹⁷ Hypertrophic scar ⁹⁸ Hypertrophic scar ⁹⁹
Drug	5-fluorouracil, dexamethasone Gallic acid, quercetin Betamethasone Imiquimod Caffeine Salicylic acid Triptolide/liposome Menthol and methyl salicylate Hydrophobic/hydrophilic drug	Thermosensitive hydroxybutyl chitosan Gelatin GelMA/PEGDA (2-(2-methoxyethoxy) ethyl Methacrylate) Hyaluronic acid/PEG Avogel Thermosensitive RGD-modified PEG Guar-gum Silk fibre	Keloid ¹⁰⁰ Keloid ¹⁰¹ Hypertrophic scar ¹⁰² Keloid ¹⁰³ Hypertrophic scar ¹⁰⁴ Hypertrophic scar ¹⁰⁵ Keloid ¹⁰⁶ Hypertrophic scar ¹⁰⁷ Hypertrophic scar ¹⁰⁸
Stem cell	BMSC ADSC ADSC-conditioned medium Xeno-fibroblasts	RGD-modified hydroxybutyl chitosan Hyaluronic acid Polysaccharide Collagen-glycosaminoglycan	Keloid ¹⁰⁹ Hypertrophic scar ¹¹⁰ Hypertrophic scar ¹¹¹ Hypertrophic scar ⁹⁹
Nucleic acid Protein	SiRNA-TGFβ1-337 Papain Silk fibroin	PVP/PVA Glutamic acid/chitosan PEG	Hypertrophic scar ¹¹² Hypertrophic scar ¹¹³ Hypertrophic scar ¹¹⁴
Nanomaterials	Silver Silver	Alginate Silicone	Hypertrophic scar ¹¹⁵ Hypertrophic scar ¹¹⁶

Polysaccharides/Organic Chemicals

Hydrogels are 3D hydrophilic polymer networks. The polymer, which directly composes the hydrogel, exhibits therapeutic effects through its inherent properties. Below, we discuss polymers alone that inhibit hypertrophic scar and keloid formation, progression, and recurrence. It was reported that biocompatible polyurethane-based hydrogels could ease pain and prevent skin maceration and hypertrophic scar formation. However, this study did not establish a control group, and the selection criteria are confusing and should be improved to further confirm the efficacy of hydrogels in burn patients.⁹⁵ In addition to hypertrophic scar formation, Zhang et al utilized carboxymethyl chitosan hydrogels chemically crosslinked with genipin to attenuate hypertrophic scar progression by inhibiting α -SMA and facilitating MMP-1 generation, showing the potential use of chitosan-based wound dressings in hypertrophic scar treatment.⁹⁶ A polyvinyl alcohol-collagen-glycosaminoglycan-based semisynthetic hydrogel decreased the thickness, ECM deposition, and vessel-like structure of hypertrophic scars in a rabbit ear model.⁹⁹ Keloids have a higher recurrence rate than hypertrophic scars. Berman et al found that injecting gelatin-dextran hydrogels could effectively reduce the symptoms and recurrence of keloid scar postsurgical excision. Dextran could modulate the immune response, prevent infection, and facilitate wound healing, which might contribute to the anti-keloid recurrence effect.⁹⁷ Additionally, pregnancy might be associated with the progression of hypertrophic or keloidal scarring. A clinical trial was conducted to evaluate the erythema fading of hypertrophic scars that progressed in 45 Caucasian pregnant women. Polysaccharides and polyacrylamide hydrogel combined with laser therapy decreased the redness of the scar by cooling the skin. However, this study lacks a corresponding control and has a limited number of samples, which needs further investigation.⁹⁸

Medicine/Drug

Research suggests that hydrogels are a promising and ideal vehicle to deliver drugs in hypertrophic scars and keloids due to their biocompatibility and prolonged release of drugs. Ma et al utilized caffeine embedded in hydrogel to treat hypertrophic scar tissue on rabbit ears, and the results showed that caffeine hydrogel significantly downregulated the expression of Type 1 collagen by inhibiting TGF β .¹⁰⁴ Chen et al developed a GelMA/polyethylene glycol diacrylate (PEGDA) hydrogel containing betamethasone as a microneedle patch, which significantly reduced the scar elevation index, collagen I/III, and TGF- β 1 expression.¹⁰² Imiquimod was proven to be useful in keloids but had few effects, including erythema, pain, pruritus, and slight hyperpigmentation. To better control the release of imiquimod, Lin et al developed a hydrogel delivering imiquimod for the treatment of keloids, which significantly decreased the growth of keloid fibroblasts.¹⁰³ In addition to imiquimod, triptolide was extracted from *Tripterygium*, displaying anti-inflammatory and antifibrotic effects. As a triptolide derivative, LA67 possesses the original activity of triptolide and improved antitumour effects, with less toxicity compared to triptolide. Wan et al used a thermosensitive hydrogel to deliver liposome-encapsulated LA67, which significantly prevents keloid progression by downregulating collagen and α SMA expression.¹⁰⁶

In addition to a single drug, a dual-drug delivery hydrogel might be more effective in the treatment of hypertrophic scars and keloids. Bao et al loaded 5-fluorouracil and dexamethasone in a thermosensitive hydroxybutyl chitosan hydrogel, which prevents keloid fibroblast growth and VEGF expression in keloid tissues. It was revealed that the codelivery of 5-fluorouracil and dexamethasone in hydrogels exhibited promising potential in keloid therapy.¹⁰⁰ In addition, Chen et al fabricated a dual drug-gelatin hydrogel carrying gallic acid and quercetin, which inhibited the growth and mRNA level of type I and III collagen in keloid fibroblasts and the production of reactive oxygen species and might be effective in keloid formation and progression.¹⁰¹ Patients with pathologic scars often suffer from itch and pain, which might be associated with the inflammatory response. A case study showed that a 2% salicylic acid-based hydrogel could significantly reduce redness, itch, and burning pain in hypertrophic scar patients, which might be due to the anti-inflammatory effects of salicylic acid, such as preventing prostaglandin production and NF- κ B generation.¹⁰⁵ Wu et al developed a guar gum-based hydrogel to deliver menthol and methyl salicylate, which was proven to effectively alleviate the pruritus of burn-induced hypertrophic scars in a multicenter, controlled trial.¹⁰⁷ More importantly, combined therapy could increase the transdermal delivery of drugs in hypertrophic scars. CO₂ fractional laser therapy combined with a silk nanofiber hydrogel could enhance the skin penetration of hydrophilic and hydrophobic substances into rabbit ear hypertrophic scar tissue.¹⁰⁸

Stem Cells and Conditioned Medium

Hydrogels are considered ideal scaffolds for stem cells and their secretome due to their 3D dimensional properties and superior biocompatibility (Figure 6). Qu et al first used a thermosensitive Arg-Gly-Asp (RGD)-modified hydroxybutyl chitosan hydrogel to deliver bone marrow-derived mesenchymal stem cells (BMSCs) in treating keloids, and HE staining showed that ex vivo keloid tissue in the BMSC/Hydrogel group histologically displayed thin, loose nodule collagen fibres and small collagen bundles.¹⁰⁹ Adipose-derived stem cells encapsulated in hyaluronic acid hydrogel inhibited hypertrophic scar formation by decreasing the collagen type I/collagen type I ratio and α -SMA expression in fibroblasts. It was reported that hyaluronic acid gel containing mesenchymal stem cells could effectively limit excessive fibroblasts and collagen together with chronic inflammation and correct the imbalance of ECM transformation by reducing fibronectin and tenascin-C expression.¹¹⁰ More importantly, clinical studies are crucial to confirm the therapeutic use of transdermal MSC hydrogels in hypertrophic scars. A random, controlled clinical trial was registered to test the effectiveness of transdermal MSC hydrogels in treating cesarean section skin scars, but the results have not been published thus far.¹¹⁷ Conditioned medium is referred to as the medium of MSCs and contains a variety of growth factors, cytokines, chemokines, and extracellular vesicles, such as ectosomes and exosomes.¹¹⁸ A polysaccharide hydrogel containing lyophilized adipose-derived stem cell conditioned medium was fabricated to inhibit hypertrophic scarring of rabbit ears by decreasing fibroblast proliferation and collagen disposition.¹¹¹ It was reported that hybrid hydrogels containing xenofibroblasts reduced ECM accumulation and vessel-like structures in hypertrophic scars.⁹⁹ In addition to stem cells and conditioned medium, exosomes perform therapeutic roles in hypertrophic scars and keloids.^{119–121} Thus, the role of exosome-based hydrogels in pathologic scars is worth exploring in the future.

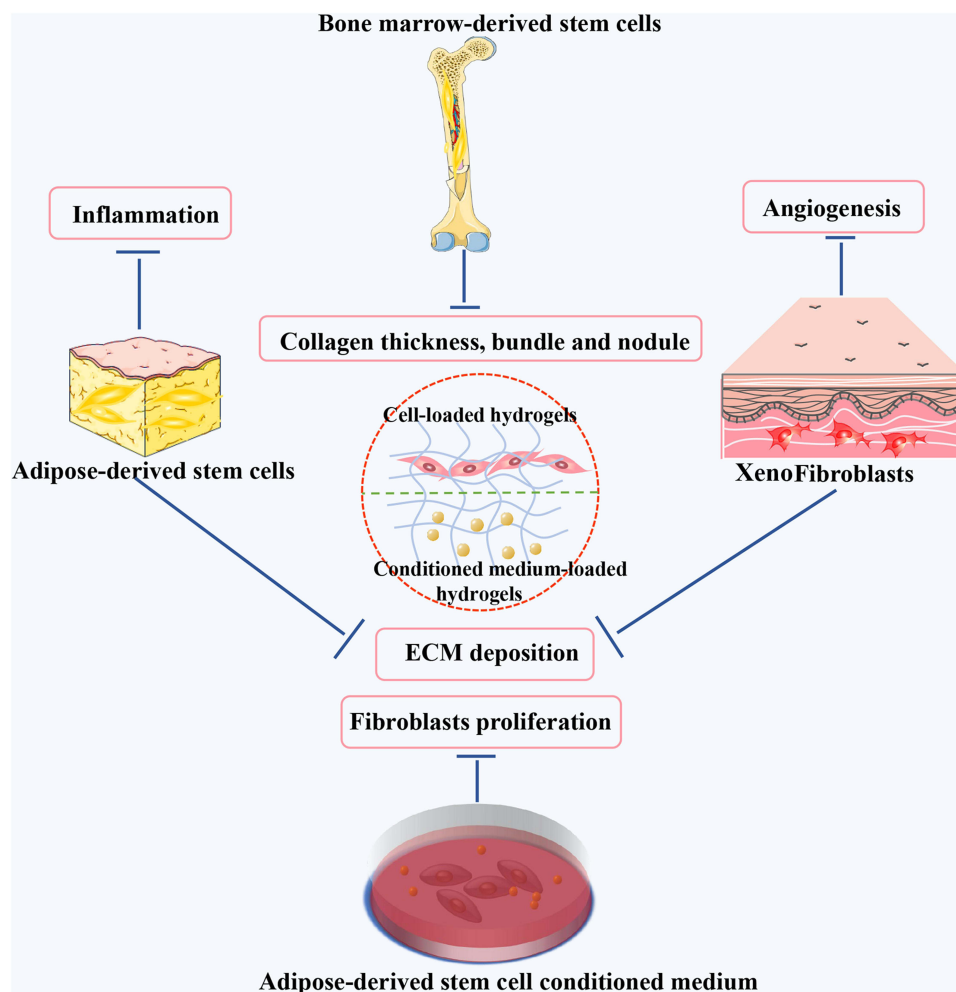


Figure 6 Stem cell and conditioned medium-loaded hydrogels.

Nucleic Acids and Proteins

Given the increasing understanding of the molecular mechanisms underlying hypertrophic scars and keloids, researchers found that siRNA, which directly targets genes, and several protein products were effective in attenuating pathologic scars. It was reported that siRNA-TGF β 1-337 embedded in a pressure-sensitive adhesive hydrogel was developed for hypertrophic scar treatment, which resulted in TGF β 1 and collagen type I inhibition and regularly arranged fibroblasts in a hypertrophic scar nude mouse model.¹¹² The poly (γ -glutamic acid)/chitosan/papain hydrogel promoted cell migration and significantly attenuated abnormal growth of fibroblasts, collagen deposition, and hyperplastic scar formation. Papain might inhibit fibroblast proliferation and degrade ECM, contributing to the prevention of the development of hypertrophic scars.¹¹³ As an elastic and firm protein, silk fibroin has attracted attention due to its wound healing-facilitating effects, but its antihypertrophic scar effects remain elusive. Thus, Li et al designed silk fibroin-based PEG hydrogels, which exhibited excellent biocompatibility and decreased the density of hypertrophic scar tissue and collagen expression.¹¹⁴ These results suggest that silk fibroin or silk fibre-based hydrogels are promising treatments for hypertrophic scars. Further studies are needed to compare the therapeutic efficacy and loading efficiency to keloid and hypertrophic scar tissues, fostering the application of silk-based hydrogels in pathologic scars.

Nanomaterials (Metal Ions/Carbon Materials)

Nanomaterials are referred to as materials with diameters of 1–100 nm that possess unique physical-chemical properties due to their structure. To further improve therapeutic efficacy, nanomaterials combined with hydrogels could form a hybrid biomaterial system for their controlled and prolonged release.¹²² Nanomaterials applied in hypertrophic scars and keloids mainly include nanoparticles, liposomes, carbon nanomaterials, and metallic nanoparticles. Liposomes and exosomes were described above;^{106,121} thus, in this section, we mainly discuss metal ions and carbon nanomaterials in pathologic scars. Silver ions are widely used in skin dressings and facilitate wound healing, given their antimicrobial effects. It was revealed that silver ion dressing could prevent pathologic scar formation in postburn patients.¹¹⁶ Jia et al found that silicone-derived silver hydrogel significantly decreased the scar elevation index.¹¹⁵ In addition, cuprous oxide nanoparticles in glucose solution were also proven effective in treating hypertrophic scars by inhibiting fibroblast growth and promoting cell apoptosis.¹²³ In addition to metal ions, carbon nanomaterials were also effective in inhibiting hypertrophic scars. Weng et al demonstrated that carbon nanotubes directed hypertrophic scar fibroblast growth and decreased excessive proliferation and collagen expression in fibroblasts by suppressing TGF β .¹²⁴ Carbonate apatite nanoparticle-loaded siTIMP1 significantly suppressed hypertrophic scar formation and collagen expression and density and attenuated the thickness and disorganization of collagen bundles.¹²⁵

Current Limitations and Future Prospects

To date, researchers are facing some challenges that restrict the fabrication and applications of hydrogels in hypertrophic scars and keloids. We herein propose the main challenges and potential possibilities as follows to shed light on the future direction of hydrogel-based studies in keloids and hypertrophic scars.

1. The mechanism underlying these hydrogel components remains unclear, while high-throughput sequencing, such as transcriptome, spatial and single-cell transcriptome analysis, as well as proteomics, has been carried out to elucidate the molecular mechanism.^{126–128} Therefore, when designing hydrogels, researchers should look deeper into the mechanism and develop more specific therapies targeting abnormal cells, genes, and proteins.
2. The clinical application of hydrogels in hypertrophic scars and keloids is mainly confronted with three pitfalls: lack of animal model of keloid; lack of standard random clinical trials; and high manufacturing cost. It is believed that developing animal models of keloids, carrying out clinical trials and optimizing materials will accelerate the clinical use of hydrogels in hypertrophic scars and keloids.
3. Current research in hypertrophic scars and keloids only explores a limited number of drugs, stem cells, nucleic acids, and proteins. Nanomaterials such as metal ions and carbon nanomaterials exhibit multifunctional roles in medical fields;^{129,130} thus, these nanomaterials are worth investigating in keloid treatment.
4. Furthermore, traditional therapy, such as surgery, X-ray, laser and cryotherapy, could be combined with hydrogels to enhance therapeutic efficacy and even exert synergistic effects for the treatment of keloids and hypertrophic scars.

5. Although various types of hydrogels have been designed, their function is mainly restricted to one effect, such as anti-inflammatory, antiangiogenic or antifibrotic effects. Therefore, developing multifunctional hydrogels by loading different materials or tuning the physical and chemical properties of hydrogels will definitely promote their therapeutic efficacy in the future.

Conclusion

Hydrogels have been gaining increasing attention in hypertrophic scars and keloids due to its biocompatibility and effectiveness. In this review, the pathogenesis of pathologic scars and the classification and properties of hydrogels, as well as their loaded components, are discussed and highlighted, followed by the advances in nanomaterials in the area of hydrogels for biomedical applications. And smart hydrogel, which could respond to different stimuli is a future trend of hydrogels in biomedical fields. However, challenges still exist, such as tumor-related risks of tumor-derived natural hydrogels and elusive mechanism of pathologic scars. Associating hypertrophic scar and keloid pathogenesis with hydrogels as well as loaded components will shed light on further exploration and clinical applications. Thus, it is crucial to elucidate pathologic scar pathogenesis and improve efficacy and biocompatibility of hydrogels, in order to guide the therapeutic use of hydrogels in hypertrophic scars and keloids.

Data Sharing Statement

Data sharing is not applicable to this article, as no datasets were generated or analysed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare they have no conflicts of interest.

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