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Functional Hydrogels for Wound Healing: Functional Design, Mechanisms of Action, and Research Progress

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Abstract. Wound healing is a complex pathological process covering four stages: hemostasis, inflammation, proliferation, and remodeling. Traditional dry dressings (such as gauze and bandages) have poor moisture retention, easily adhere to newly formed tissues, and lack sufficient antibacterial capacity, making it difficult to meet the repair needs of complex wounds. With their highly hydrophilic biomimetic three-dimensional network structure, hydrogels can highly mimic the Extracellular Matrix (ECM) and provide an ideal scaffold for cell proliferation. Their water content as high as 80%–95% can not only build a moist microenvironment conducive to healing and reduce damage during dressing changes, but also their excellent flexibility can adapt to high-mobility parts such as joints. In addition, hydrogels have excellent functional customizability and can serve as carriers for targeted delivery of drugs and bioactive substances, realizing the paradigm shift from "passive barrier protection" to "active regulatory therapy". This paper systematically sorts out the material design strategies of wound repair hydrogels, deeply discusses their core mechanisms of action in antibacterial, hemostatic, anti-inflammatory and pro-regenerative aspects, and summarizes their application progress in typical scenarios such as acute and chronic wounds as well as burns and scalds. Finally, this paper analyzes the current insufficient mechanical properties and barriers to clinical translation, and puts forward a prospective outlook on the future development trend of multifunctional integration and intelligence.

Keywords: Wound healing, medical hydrogels, antibacterial dressings, biocompatibility, smart responsive hydrogels

1. Introduction

1.1. Pathological mechanisms of wound healing and clinical requirements

Wound healing is a dynamic process of tissue repair through a series of highly coordinated biological cascade reactions after the body suffers trauma. This process is mainly divided into four overlapping stages in time and space: hemostasis, inflammation, proliferation, and remodeling, each with unique microenvironmental characteristics and cellular behaviors [1].

Wounds caused by different etiologies show distinctly different microenvironmental characteristics and treatment needs in clinical practice. For acute wounds (such as surgical incisions

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and sudden mechanical abrasions), the core demands are to quickly close the wound, reduce the risk of exogenous infection, and restore the tissue barrier function as soon as possible [2]. Chronic wounds (such as Diabetic Foot Ulcer (DFU) and pressure injuries) often fall into an uncontrollable vicious cycle of chronic inflammation due to long-term local exposure to abnormally high levels of Reactive Oxygen Species (ROS) and pro-inflammatory cytokines. There is an urgent need to effectively clear ROS and regulate the inflammatory state to reactivate the proliferation stage [3, 4]. Burn and scald wounds face the dual challenges of massive exudate in the early stage, which can easily cause fluid loss and severe deep infection, and the difficulty of standardized reconstruction of dermis and deep skin structures in the middle and late stages [5, 6].

Faced with these complex clinical pain points, traditional dry dressings (such as gauze and bandages) have extremely limited moisture retention capacity, which easily leads to dry scabbing of wounds and causes severe secondary mechanical tearing damage to newly formed granulation tissue during dressing changes. At the same time, they lack the function of actively regulating the pathological microenvironment, so they can no longer meet the needs of precise treatment for complex wounds [5, 7].

1.2. Unique advantages of hydrogels and purpose of this review

In response to the inherent defects of traditional dressings, hydrogels based on cross-linked networks of hydrophilic polymers have become one of the most promising materials in the field of wound repair due to their unique physicochemical and biological properties [7]. Their structural bionics is reflected in the fact that the highly swollen three-dimensional network of hydrogels highly mimics the natural extracellular matrix (ECM) in both macroscopic and microscopic structures, and can serve as an ideal spatial scaffold for cell adhesion, proliferation, and migration. In terms of physical properties, their high water content (80%–95%) perfectly fits the "moist wound healing theory". It can not only maintain the water balance of the wound microenvironment, but also prevent excessive evaporation of wound moisture, reduce dressing adhesion and wound scabbing, and significantly relieve trauma during dressing changes. In addition, their internal porous interconnected network provides excellent space as delivery carriers, which can accurately encapsulate antibiotics, antimicrobial peptides, growth factors, or stem cells, thus achieving a dual paradigm shift from traditional "passive physical barrier protection" to "active pathological remodeling and functional repair" [8, 9].

This review aims to systematically sort out the matrix selection, network cross-linking mechanisms, and advanced micro-nano preparation processes of wound repair hydrogels in recent years, deeply analyze their multimodal mechanisms of action (antibacterial, cascade hemostasis, anti-inflammatory regulation, and vascular remodeling), focus on summarizing their cutting-edge applications in acute and chronic wounds, burns and scalds, and nerve wounds, and discuss the design challenges and translation bottlenecks of future intelligent and multifunctional integrated dressings.

2. Material design and preparation of hydrogels for wound healing

2.1. Material selection and matrix design

In the selection of hydrogel matrix, natural polymers and synthetic macromolecules have their own characteristics. At present, most studies adopt composite hybridization strategies to achieve complementary properties. Natural polymer materials have excellent biological activity. Chitosan

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(CS), as the only basic aminopolysaccharide, has natural cationic properties due to its protonated amino groups, which can physically disrupt bacterial membranes for sterilization and has excellent hemostatic effects [10]. Hyaluronic acid (HA) is an important component of skin ECM. It regulates the inflammatory cascade by binding to CD44 receptors, and promotes vascular migration and granulation proliferation [11, 12]. Sodium alginate (SA) has excellent water absorption and swelling properties, and can undergo rapid and mild in-situ cross-linking with polyvalent cations (such as Ca^{2+}), making it suitable for filling irregular dead spaces [13]. Collagen and gelatin are easy to be modified by methacryloylation (GelMA), which perfectly preserves the binding ligand sites of dermal cells [12, 13]. Synthetic polymer materials (such as PEG, PAAm, PLGA) can provide highly accurate mechanical extension benchmarks and customizable in vivo degradation cycles for wounds in high-mobility areas [11].

2.2. Cross-linking methods and preparation technologies

The internal porous structure and service stability of hydrogels depend on the network cross-linking mechanism. Physical cross-linking constructs networks through ionic bonds, hydrogen bonds, and supramolecular interactions. The process is completely reversible without toxic reactions and has shear-thinning properties [10]. Chemical cross-linking forms permanent irreversible networks through covalent bonds (such as Schiff base and photoinitiated free radical polymerization), with extremely high mechanical elasticity and longer in vivo degradation half-life [11, 12]. Enzymatic cross-linking is catalyzed by horseradish peroxidase (HRP), with extremely mild gelation conditions and high specificity, which is suitable for encapsulating living cells and active proteins [12, 13], as shown in Table 1.

Table 1. Comparison of physicochemical properties and application standards of hydrogel cross-linking mechanisms and micro-nano manufacturing processes

Preparation and Cross-Linking Strategy	Principle of Molecular Network Construction and Key Groups	Core Advantages and Biomimetic Properties	Key Physicochemical/Biological Limitations	Typical Wound Repair Application Scenarios
Physical cross-linking [10, 13]	Ionic bonds (e.g., Ca^{2+}/carboxyl groups of sodium alginate), hydrogen bonds (hydroxyl groups on polysaccharide side chains), or supramolecular non-covalent bonds	The process is completely reversible, with no residual harmful chemical initiators or cross-linkers, and has excellent self-healing properties and injectable fluidity	Low mechanical strength; prone to structural depolymerization or excessively rapid hydrolysis under high tension/shear	Minimally invasive filling of irregular dead spaces, management of massive early wound exudate locking
Chemical cross-linking [11, 12]	Covalent bonding (e.g., photoinitiated GelMA polymerization, Schiff base reaction, click chemistry)	Dense and stable network, extremely strong mechanical tensile/elastic shear resistance, long in vivo degradation resistance	Initiators/light may cause local cellular DNA damage or induce inflammatory stimulation in the middle and late stages	Barrier dressings for high-tension and high-mobility areas such as joints, long-term drug delivery systems

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Table 1. (continued)

Enzymatic cross-linking [12, 13]	Highly specific catalysis by horseradish peroxidase (HRP) for in-situ condensation of phenolic hydroxyl groups and specific peptide bonds	Extremely mild reaction conditions (room temperature, neutral pH), fast gelation rate, no toxic by-products	High purification cost of engineered active enzymes; enzyme activity is limited by temperature/pH of the in vivo microenvironment	In-situ high-activity encapsulation and delivery of active factors (e.g., VEGF) and stem cells
3D bioprinting [14, 15]	Based on three-dimensional CAD spatial modeling, precise layer-by-layer extrusion and curing of drug-loaded/cell-laden bioinks	Achieves fully customized macroscopic morphology for irregular defects, guides spatial gradient distribution of multi-component active molecules	High shear force of nozzles and curing light intensity easily cause mechanical rupture and death of some living cells	Spatial personalized adaptation for large-area severe burns and full-thickness skin defects
Microfluidic microspheres [16]	Sheared by interfacial forces of immiscible two-phase fluids in chip channels, high-throughput curing of micron-sized microspheres	Highly uniform microsphere size, large specific surface area, can completely overcome the "burst release" bottleneck of high free water networks	Microchannels of preparation chips are prone to physical blockage; difficult for high-purity industrial continuous mass production	Cascade/multi-stage environment-targeted on-demand release controlled drug delivery systems for chronic ulcers

3. Core functions and mechanisms of action

3.1. Broad-spectrum antibacterial and smart response strategies

Bacterial infection is one of the most critical environmental factors hindering normal wound healing, and antibacterial strategies for hydrogels are gradually becoming multimodal and intelligent. Physical antibacterial strategies rely on protonated cations of chitosan to bind to negatively charged bacterial membranes through Coulomb force, physically tearing the outer membrane to kill bacteria without inducing bacterial resistance [17]. Chemical antibacterial strategies load silver nanoparticles (AgNPs) or MOFs through porous multi-dimensional skeletons, but the pharmacokinetic release needs to be precisely controlled to prevent systemic biological toxicity [18]. Biological antibacterial strategies encapsulate highly selective antimicrobial peptides (such as LL-37) or specific bacteriophages, which can accurately kill MRSA and are highly safe for human dermis [19]. Smart responsive antibacterial mainly utilizes local pathological pH changes caused by acidic metabolites produced by bacterial growth and inflammation. It triggers swelling and targeted drug release only when pH deviates abnormally, achieving on-demand sterilization [20].

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3.2. Cascade hemostasis and inflammatory microenvironment remodeling

Efficient hemostasis and rapid recovery from chronic inflammation are the cornerstones of ensuring later tissue regeneration. Porous, water-absorbent, and highly swollen sodium alginate can quickly absorb excess plasma and concentrate coagulation factors [21]. Collagen can specifically activate platelets, and combined with the electrical neutralization of red blood cells by positively charged chitosan, forms a rapid coagulation bridge [22]. The high porosity of the hyaluronic acid network can not only neutralize and clear excess local pro-inflammatory factors (such as TNF-α and IL-6) [23], but also use polarization factors to induce pro-inflammatory M1 macrophages to switch to the pro-angiogenic and collagen-synthesizing M2 phenotype, breaking the inflammatory vicious cycle of wounds and initiating tissue repair [24].

3.3. Promotion of tissue regeneration and vascular remodeling network

The introduction of sulfated modification similar to heparin structure can stably chelate and protect unstable pro-angiogenic growth factors (VEGF) for a long time, and achieve gentle and precise release in wounds for several weeks. It activates downstream receptors and efficiently drives the migration and sprouting of neovascular endothelial cells to reconstruct local microcirculation [25, 26]. The composite dermal RGD peptide ligand collagen network can act as a "cell highway" to guide the orderly extension of epidermal cells. The degradable half-life of hydrogels needs to be strictly matched with the time sequence of new tissue generation to avoid disordered hyperplasia and mechanical scars caused by tension imbalance [27].

3.4. Smart responsive drug release driven by complex microenvironments

In response to the multi-stage characteristics of wounds, various environmental sensor bonds have been integrated into the network. Responsive imine bonds or boronate ester bonds are cleaved under abnormal ROS or slightly acidic conditions to achieve micro-targeted drug release [28]. The thermosensitive hydrogel Pluronic is fluid at room temperature and undergoes instantaneous in-situ gelation after contacting skin temperature, perfectly self-filling dead spaces [29]. For matrix metalloproteinases (MMPs) that are abnormally highly expressed in diabetic ulcers, specific peptide chain recognition is introduced to trigger enzymatic degradation and proportional drug release, achieving an automatically monitored feedback closed-loop drug delivery [30], as shown in Figure 1.

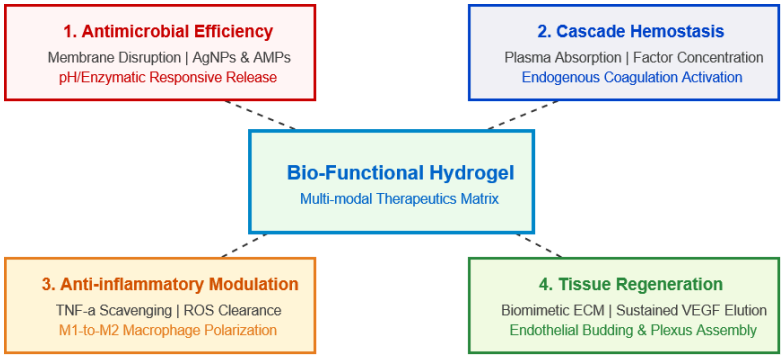

Figure 1. Model of multimodal active regulatory mechanisms of functional hydrogels during wound healing stages

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4. Applications in typical wound repair

According to the physiological and pathological characteristics of different types of wounds, the material matrix matching and regulation strategies of hydrogels in practical applications are highly customized.

4.1. Applications in acute wounds

For surgical incisions and sudden deep scratches: absorbable oxidized regenerated cellulose hydrogel dressings can physically aggregate platelets and fibrinogen instantly upon filling contact. After hemostasis, they can be endogenously degraded, completely eliminating the tearing pain caused by repeated mechanical debridement and dressing removal [31]. At the same time, the application of high-molecular-weight HA-collagen system can specifically stimulate the directional migration of keratinocytes at the wound edge to the wound center in a short period of time, greatly shortening the inflammatory exposure period, and blocking the uncontrolled division of unoriented fibers caused by uneven tension, thereby inhibiting postoperative hypertrophic scar hyperplasia [32].

4.2. Applications in chronic wounds

For diabetic foot and severe pressure ulcers: such wounds have microvascular occlusion and overlapping necrotic biofilms. The chitosan-AgNPs antibacterial network can efficiently pierce and kill stubborn biofilms wrapped in the deep layer. Copolymerization and grafting of VEGF growth factor on the hydrogel substrate can provide neurotrophic targets and induce vascular sprouting, achieving repair and proliferation from the inside out [9, 33]. In addition, multi-arm pH/ROS dual-driven polymer nanogels can intelligently scavenge free toxic oxygen free radicals in chronic wounds, down-regulate necrosis factors, and reshape the slightly acidic microenvironment [28].

4.3. Applications in severe burns and scalds

For ultra-large area thermal injury with massive fluid leakage: high water-retention sodium alginate-gelatin hydrogels are used to build a highly elastic moist sealing barrier on the wound surface, which can flexibly adapt to irregularly curved limbs and maintain the internal balance of electrolytes and water molecules [34]. In the tissue proliferation stage, HA hydrogels loaded with living adipose-derived stem cells (ADSCs) can provide a safe niche for living cells, promote their long-term paracrine secretion of trophic factors, and guide the parallel arrangement of dermal collagen, completely avoiding joint movement limitation caused by tendon contraction and scar adhesion [35].

4.4. Applications in nerve and special wounds

For war wounds and compound trauma with damaged and broken peripheral nerves: the introduction of a new conductive polymer polyaniline (PANI)-chitosan conductive hydrogel can re-connect the microelectrical conduction pathways across the damaged section [36]. The dressing uses its high electrical conductivity to transmit exogenous electrical signals, which can trigger neuronal action potentials and activate membrane calcium channels, thereby promoting the directional transport of growth factors, and ultimately achieving simultaneous and integrated regeneration of directional nerve bundle extension and vascularized dermal microcirculation [37], as shown in Table 2.

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Table 2. In-depth analysis of design strategies, material systems, and multimodal regulatory mechanisms of hydrogels applied to different types of wounds

Typical Clinical Wound Scenarios and Research Basis	Core Pathological Microenvironmental Characteristics and Treatment Pain Points	Targeted Core Material Matrix and Components of Hydrogels	Multimodal Active Regulatory Mechanisms / Repair Cascade Reactions
Acute wounds [31, 32]	Wounds urgently need antibacterial sealing; heavy bleeding; in the middle and late stages, uneven local tension easily induces disordered entanglement of fibroblasts, forming mechanical scars.	Absorbable oxidized regenerated cellulose hydrogel; high-molecular-weight hyaluronic acid (HA)-collagen biomimetic network	1. Rapid cascade hemostasis: the swollen network physically blocks and enriches coagulation factors, activating zymogens. 2. Inhibition of excessive hyperplasia: promotes directional migration of keratinocytes and blocks runaway fibroblast collagen.
Chronic wounds [9, 10, 33]	Continuously uncontrolled high reactive oxygen species (ROS), abnormal pH changes, inflammatory vicious cycle, and degeneration and necrosis of deep capillary microcirculation.	Cationic chitosan (CS)-polyethylene glycol (PEG) blended synthetic network; loaded with silver nanoparticles (AgNPs) and vascular endothelial growth factor (VEGF)	1. Physical piercing antibacterial: CS/AgNPs synergistically destroy biofilms of charged drug-resistant bacteria. 2. Inflammatory polarization regulation: drives inflammatory M1 macrophages to transform into repair M2 macrophages, regulates ROS, and remodels blood vessels.
Severe burns and scalds [34, 35]	Massive wound exudate, rapid depletion of body fluids with risk of systemic collapse shock and infection; difficult standardized reconstruction of deep dermis in the middle and late stages.	Sodium alginate (SA)-gelatin hydrogel dressing; encapsulated highly migratory adipose-derived mesenchymal stem cells (ADSCs)	1. Precise water locking and moisturizing: rapidly absorbs and locks massive exudate, isolates bacteria. 2. Cell nutrition support: ADSCs secrete pro-angiogenic factors paracrinally, and dermal collagen arranges in parallel to prevent scar contraction.
Peripheral nerve war trauma [36, 37]	Interruption of endogenous bioelectromagnetic signal conduction at tissue stumps, lack of neurotrophic feedback pathways, and interruption of neurotrophy and capillary growth.	Conductive polyaniline (PANI)/polypyrrole (PPy) modified hybrid chitosan/oxidized dextran multi-dimensional in-situ hydrogel system	1. Electrical signal connection: reshapes physiological electrical balance channels in micro-damaged areas. 2. Neuron guidance: activates voltage channels to promote the release of neurotrophic factors, guiding directional axon extension and microvascular development.

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5. Challenges and future development trends

5.1. Main technical challenges and engineering bottlenecks currently faced

Although hydrogels have made rapid progress in laboratories and animal models, they still face multiple bottlenecks in large-scale industrial and commercial translation:

1) The inherent contradiction between bulk mechanical strength and high water content: the high swelling property of hydrogels leads to sparse cross-linking of polymer molecules, making the structure prone to deformation and collapse. Their mechanical tensile, shear-resistant, and tear-resistant properties are extremely low, making it difficult to maintain long-term integrity in high-stress areas such as high-mobility joints. At present, scholars mostly improve fracture toughness by introducing double network (DN) structures with energy dissipation characteristics or multi-dimensional rigid-flexible crystals.

2) Severe initial "burst release" effect of encapsulated hydrophilic active drugs: the multi-dimensional free water network with large voids will cause the loaded active small molecule factors to undergo spontaneous and rapid penetration with the medium in the early stage, making it difficult to ensure a long-lasting and uniform pharmacokinetic trajectory in vivo. The latest research has begun to introduce microfluidic high-throughput microcapsule encapsulation technology to pre-load drugs, or design mild, stimulus-responsive covalent chemical bonds that specifically cleave in response to the microenvironment, to permanently anchor active small molecules to the chain network and achieve proportional, uniform, and self-leveling sustained release.

3) Difficulty in batch continuous standardization of precision technologies and lack of evaluation scales: due to high processing precision, 3D micron-level precise extrusion and microfluidic integrated devices are difficult to maintain low-cost mass production of dressings. Moreover, there is still a lack of unified and standardized gold standards for preclinical evaluation of the in vivo tensile elasticity, degradation kinetics, and long-term sterilization efficiency of smart hydrogels in the global academic community.

4) Lack of long-term immunological safety assessment data for highly composite materials: it is urgent to prove through long-term multi-phase clinical follow-up data whether composites introduced with various inorganic nano-components (Ag, metal quantum dots, carbonized polymers) will accumulate in the body with metabolism during long-term service and whether there is potential multi-organ transport system toxicity.

5.2. Future development trends and prospects

The ultimate form of hydrogel dressings will tend to be highly integrated, micro-sensing, and personalized. First, build a "diagnosis-treatment-monitoring" closed sensing loop for the microenvironment. In the future, it will further combine highly flexible microelectronic monitoring patches to automatically monitor and release drugs when sensors detect abnormal wound indicators. Second, achieve complete synchronization between degradation rate and endogenous regeneration to avoid secondary dressing peeling damage. Third, deeply integrate AI and 3D printing digital twins to customize absolutely personalized biomimetic bioinks and perform instant 3D printing at the clinical bedside. Fourth, transform to low-carbon and natural green materials, shifting from expensive and complex petrochemical polymers to natural non-toxic polysaccharides extracted from agricultural or marine wastes.

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6. Conclusion

The rapid iteration of hydrogel dressings has successfully driven the fundamental paradigm shift of modern wound management from "passive physical coverage" to "active targeted remodeling of the microenvironment". Through the in-depth interdisciplinary integration of polymer materials science, biomedicine, and micro-nano manufacturing engineering, hydrogels are gradually overcoming the traditional bottlenecks of low physical and mechanical properties and rapid in vivo drug release. The next generation of diagnosis-treatment closed-loop hydrogels with high bionic mechanical strength, dynamic pathological cascade stimulus response, and real-time intelligent monitoring capabilities will surely release irreplaceable core value in future precise wound care and clinical regenerative medicine applications.

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