Materials and Interfaces

Review

Interfacial Engineering of Biofunctional Materials for Soft Tissue Repair

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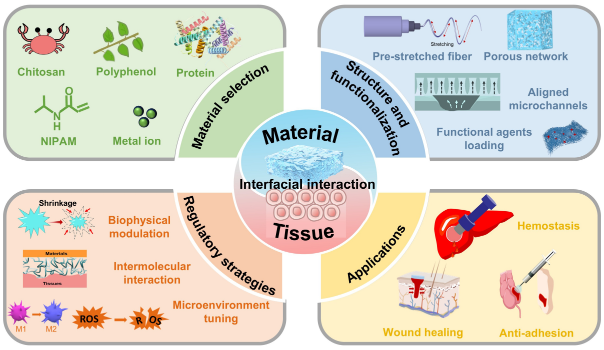
Abstract: Interfacial materials provide an emerging platform for regulating biomaterial-tissue interactions to improve the therapeutic efficacy. Herein, this review systematically examines the lasted progress in interfacial engineered biomaterials, emphasizing the design principles and the benefits for soft tissue repair. This review begins with a discussion on material selection, structural design, and functionalization aimed to steer the biophysical, chemical, and biological interactions at the interfaces. Then, the basic regulatory strategies are highlighted, including mechanical modulation, intermolecular interaction regulation, and microenvironment tuning. Additionally, the applications of the functional interfacial materials in diverse soft tissues are discussed. Finally, this review offers the current challenges for interface design, and proposes future directions for improving therapeutic outcomes and translation.



Keywords: biofunctional materials; interfacial engineering; intermolecular interaction regulation; microenvironment tuning; soft tissue repair

1. Introduction

Soft tissues refer to the non-mineralized structures within the body that connect, support, or surround other organs and skeletal frameworks [1]. The repair of damaged or lost soft tissues, such as skin, muscle, tendon, nerve, etc., remains a significant clinical challenge. Biomaterials show great potential for repair and regeneration of the damaged soft tissues [2–4]. However, poor biomaterial-soft tissue interfaces often trigger adverse events, such as abnormal adhesion, chronic inflammation, and impaired tissue integration. Such interfacial dysfunction compromises the therapeutic efficacy and may even lead to repair failure. Whereas biomaterials with feasible interfacial properties are capable of promoting material-tissue integration and eventual outcomes [5,6]. Therefore, the interfacial engineering of functional biomaterials is urgently needed to improve the therapeutic efficacy.

Currently, the common limitations of biomaterials for soft tissue repair include poor adhesion in wet wound environments, mechanical mismatch-induced tissue stress or isolation, and inability to modulate the pathological conditions, such as persistent inflammation or excessive oxidative stress, resulting in treatment failure. Thus, an ideal interfacial biomaterial should provide adaptive and dynamic physical, chemical, and biological regulation rather than passive coverage or filling. The emergence of interfacial engineered materials provides promising platforms for soft tissue repair by enhancing the interactions at the material-tissue interfaces. By leveraging the interaction mechanisms between materials and tissues, the engineered biomaterials can transmit beneficial mechanical signals [7], establish strong molecular linkages [8], and regulate local microenvironments [9], thereby actively promoting soft tissue repair. For example, polymers with thermal-responsive shrinkage behaviors have been designed into wound dressings to deliver mechanical cues for inducing wound contraction [10]. Similarly, self-expanding sponges have been engineered to provide continuous compression on surrounding tissues via volume expansion, enabling non-compressible hemostasis [11–13]. Another strategy is to regulate the adhesion state between materials and soft tissues by modulating intermolecular forces [14–16]. For example, strong adhesion is required for dressings to ensure excellent fitting with the wounds, while low adhesion is desired during dressing changing to avoid secondary damage. Furthermore, biomaterials functionalized with therapeutic agents, such as polyphenols, peptides, drugs, and growth factors, can actively regulate the interfacial microenvironment to promote tissue regeneration [17–19].

This article provides a comprehensive review of engineered interfacial biomaterials, covering design principles, regulatory strategies, and applications in soft tissue repair. First, the principles of raw material selection, structural design and functionalization of interfacial biomaterials are reviewed. Next, we explore the regulatory strategies including biophysical modulation, intermolecular interaction regulation and microenvironment tuning. Afterward, the applications in diverse soft tissue repair are discussed. In the end, current challenges and future directions for rational design of next-generation materials are highlighted.

2. Design Principles of Interface-Engineered Biomaterials

The composition of biomaterials builds the foundation for regulating the mechanical property, degradation behavior, cell response and tissue integration. Meanwhile, the structural design of the materials plays a crucial role in engineering interfacial interactions. Furthermore, the biofunctionalization endows the interfacial materials with desired bioactivities to improve soft tissue regeneration.

2.1. Material Selection

The chemical composition determines the basic properties of the materials, including physical, chemical, and biological behaviors, which directly dictate the efficacy of material-tissue interactions [20,21]. The material hydrophilicity and compliance directly govern cell adhesion and mechanical matching with the host tissue. Furthermore, the chemical groups provide active sites for additional functionalities, such as microenvironmental responsiveness, antibacterial activity, and antioxidant property. The biomaterials are typically classified into natural and synthetic materials. Natural materials possess superior biocompatibility and biological properties. In contrast, synthetic polymers provide versatile platforms for programmable engineering of mechanical property, drug release degradation behavior, and surface modification.

Derived from biological sources, natural materials exhibit super biocompatibility and inherent bioactivity, making them ideal candidates for soft tissue repair. Additionally, natural biomolecules are crucial to build active interfaces with host tissues [22]. Polysaccharides, including sodium alginate [23], hyaluronic acid (HA) [24], chitosan (CS) [25], and cellulose acetate [26], possess abundant hydroxyl, carboxyl, and amino groups that can form physical or chemical crosslinking networks, serving as hydrophilic backbones of the substrates. Additionally, the abundance of active groups facilitates the formation of hydrogen bonds and other chemical interactions with tissue surfaces, which is essential for stable wet adhesion [27,28]. Cationic polymers, such as CS, which enables electrostatic interactions with negatively charged cell membranes, have been widely used as anti-bacterial wound dressings [29]. Oxidized natural polymers are able to achieve strong interfacial adhesion through dynamic Schiff base bonds, which formed by amino groups on tissue proteins and their aldehyde groups [30]. Proteins such as collagen, gelatin, and silk fibroin play a vital role in mediating specific cellular interactions. Their cell-adhesive motifs directly engage integrin receptors on cell surfaces to promote focal adhesion, spreading, and migration. As a typical example, gelatin, a denatured collagen that retains biologically active sites and exhibits temperature-dependent sol-gel transition properties, has been widely utilized for injectable delivery and in-situ gelling strategies [31]. Furthermore, methacrylation of proteins such as gelatin methacryloyl (GelMA) enables the construction of photo-crosslinkable systems, combining the inherent bioactivity with tunable *in situ* formability [32,33]. However, the practical applications of natural materials are limited by batch-to-batch variability and mechanical instability.

Synthetic materials offer distinct advantages, including tunable degradation, tailorable mechanical properties, and versatile functionalization. The degradation behavior is of decisive significance for the success of intervention [34]. It has been well known that tissue repair scaffolds require suitable degradation behavior that provide structural support yet does not hinder tissue regeneration and growth [35]. In addition, degradation products interact with the surrounding environment and cells, leading to local pH change and inflammatory responses. The synthetic polymers can be designed and synthesized to offer exceptional chemical, mechanical and degradation tunability to meet the specific requirements of diverse soft tissues. Notably, mechanical properties such as elasticity and toughness, can be precisely tailored by selection of synthetic polymers, adjustment of the compositional ratios and engineering of the crosslinking network, minimizing mechanical mismatch at the material-tissue interface [36,37]. As an example, polyurethane (PU) has become an ideal material for fibrous membranes that endure cyclic deformation owing to its exceptional toughness, elasticity, and biocompatibility [38]. Poly(L-lactide-*co*-ε-caprolactone) (PLCL) has been readily electrospun into nanofibrous scaffolds as soft tissue-compatible bioresorbable materials [39]. Similarly, synthetic materials composed of polyacrylamide (PAAm) or poly(ethylene glycol) (PEG) provide inert networks and highly tunable mechanical properties.

Stimuli-responsive polymers play an essential role in creating active interfaces. For example, poly(N-isopropylacrylamide) (PNIPAM) represents a typical thermoresponsive material, with a lower critical solution temperature (LCST) close to body temperature [40]. Upon warming to 37 °C, PNIPAM chains embedded in the hydrogels or fibers undergo a hydrophilic-to-hydrophobic transition, generating considerable contractile force [41]. The body temperature-responsive contraction property has been widely used to construct materials that actively apply mechanical tension to wound edges for promoting wound closure [27]. The responsive mechanisms based on reactive oxygen species (ROS)-or pH-sensitive dynamic bonds, such as boronate esters and Schiff bases, have been employed for microenvironment-stimulated drug delivery. In addition, enzyme-responsive materials have been designed to react with specific enzymes in the microenvironment for on-demand drug delivery [42]. A typical example is the pH- and enzyme- dual-responsive microgel, which enables on-demand release of antibiotics [43]. Another example involves photo-responsive systems for on-demand drug delivery or detachment [32]. Collectively, the stimulus-responsive platforms enable the construction of programmable interfacial materials for adaptive and dynamic therapeutic interventions.

In practical applications, natural and synthetic materials are often hybridized to combine their specific advantages, such as biocompatibility, mechanical properties, biodegradability, etc. By tailoring the key behaviors, the interfacial interactions between the biomaterials and surrounding biological environment can be effectively optimized.

2.2. Structural Design

Apart from material selection, the structural design plays a critical role in engineering interfacial interactions. Biofunctional materials can be rationally engineered by designing the structure to provide interfacial interactions such as mechanical signal transmission, exudate management, and biological signal delivery. The structural design transforms the materials into active platforms, which is beneficial for the construction of favorable interfacial microenvironment for soft tissue repair.

As a representative strategy, a "stiff-elastic" binary component fibrous tape with body temperature shrinkage behavior was developed via electrospinning for providing tensile force for wound closure [44]. In this study, highly elastic PU and stiff poly(vinyl butyral) (PVB) were used for electrospinning, during which PU chains could be stretched under the electrostatic field followed by fixation within the rigid PVB network, resulting in considerable elastic energy storage (Figure 1Ai). A rapid and large isotropic shrinkage of the fibrous membrane was observed upon exposure to 37 °C, due to the retraction of the PU/PVB molecular chains (Figure 1Aii). Notably, the shrunk membrane was able to be highly stretched, and an almost full recovery could be achieved after exposure to 37 °C (Figure 1Aiii). The thermal-triggered shape recovery was attributed to the mobility of polymer chains and exchanges of H-bonds (Figure 1Aiv). The generated contractile force was capable of inducing significant wound closure and promoting wound healing. In addition, the contraction directionality of dressings can be readily adjusted by controlling the fiber alignment. As an example, a nanofibrous membrane with biaxial orientation was fabricated by regulating the collector geometry during electrospinning. Interestingly, a distinct centripetal contraction was achieved upon thermal stimulation, providing favorable peripheral-to-center mechanical drawing of wound edges [45]. Alternatively, controlled wound contraction can be achieved by hydration-based shape-memory mechanism. Zhao et al. developed a strain-programmed patch, which was pre-stretched and maintained, and the adhesive layer of the patch recovered from the glassy state to the rubbery state after absorbing water, releasing the predetermined strain value, thereby providing contraction force [46].

Alternatively, the rational structural design endows the materials with a liquid-triggered self-expansion behaviors, generating interfacial compression, which facilitates rapid hemorrhage control in the irregular and deep wounds. For instance, Ding et al. developed a highly porous bioactive glass nanofibrous cryogel (BGNC), which was composed of flexible BG electrospun fibers and citric acid crosslinked poly(vinyl alcohol) (PVA) via homogenization of electrospun fibrous membranes and freeze-drying (Figure 1Bi) [47]. The cryogel could be injected into a deep cavity, followed by a rapid expansion triggered by fluid absorption, resulting in a full filling of the cavity (Figure 1Bii). The expansion stress was measured during fluid absorption. Upon water absorption, BGNC exhibited an ultrafast expansion within 3 s and generated a substantial expansion stress of 2.72 kPa, which was about 4.7 times that of PVA cryogels (Figure 1Biii). Moreover, BGNC exhibited underwater resilience with near zero Poisson's ratios during compression (Figure 1Biv). These findings indicated that BGNC holds great potential for treating the deep bleeding wounds, even under dynamic conditions such as movement. Alternatively, *in situ* gas foaming provides a robust approach for generating expansive pressure within injectable hydrogels. Specifically, the hydrogels containing calcium carbonate and acetic acid are able to generate carbon dioxide bubbles due to the decomposition reaction, resulting in hydrogel expansion and self-propelling (Figure 1Ci) [48]. Figure 1Cii shows the changes in stress during expansion process. The hydrogels with self-expanding and self-propelling action would access deep perforating and conform to the irregular wound cavities.

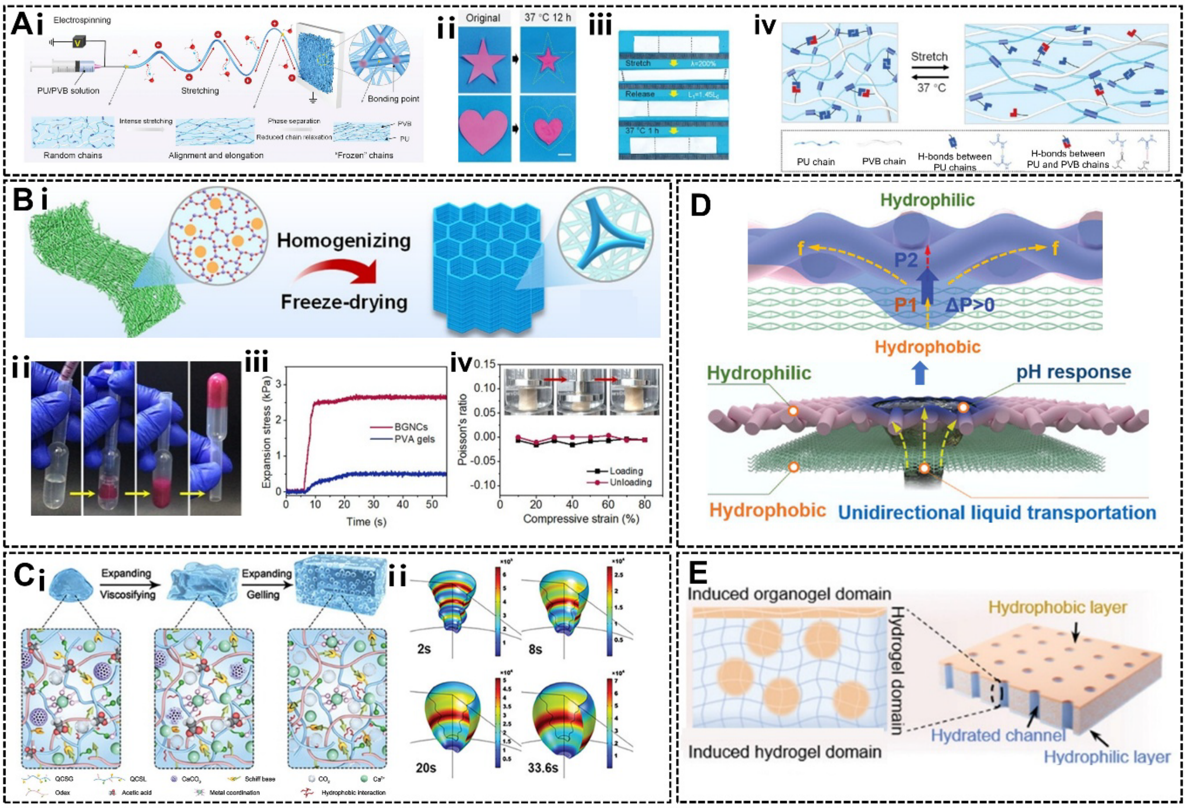


Figure 1. Structural design of interface-engineered biomaterials. (**A**) The electrospun "stiff-elastic" binary-component fibrous membrane with thermal-triggered shrinkable capability. (**i**) Schematic showing the stretching process of PU/PVB chains followed by fixation induced by phase separation during electrospinning. (**ii**) Shrinkage behavior at 37 °C. Scale bar indicates 1 cm. (**iii**) The stretching-release-thermal recovery behavior and (**iv**) mechanism of the shrunk membrane. Reproduced with permission [44]. Copyright 2024, Wiley-VCH. (**B**) Highly porous fibrous cryogels with self-expanding behavior. (**i**) Schematic showing fabrication process by homogenization of electrospun membranes and freeze-drying. (**ii**) Injectability and fluid absorption triggered self-expansion performance. (**iii**) Expansion stress upon water absorption. (**iv**) Cyclic compressive capability under water. Reproduced with permission [47]. Copyright 2023, American Chemical Society. (**C**) Carbon dioxide bubble generating hydrogel with self-expanding performance. (**i**) Schematic showing the hydrogel expansion mechanism. (**ii**) Stress during expansion. Reproduced with permission [48]. Copyright 2024, Wiley-VCH. (**D**) Janus fibrous dressing with unidirectional fluid transportation capability. Reproduced with permission [49]. Copyright 2024, Wiley-VCH. (**E**) Self-pumping organohydrogels with aligned hydrated hydrogel channels. Reproduced with permission [50]. Copyright 2024, Wiley-VCH.

The material architectures can be engineered to harness fluidic forces, which facilitate wound exudate management. The wound exudate causes risks of delayed healing, wound degeneration, infection, and persistent inflammation. In clinical practice, the excessive exudate should be removed timely. However, traditional materials are extremely difficult to remove biological fluids with high viscosity on the surface of wounds. The Janus dressing with asymmetric wettability represents a typical example of driving fluid transport. As an example, a bilayered dressing consisting of a hydrophobic poly(ε-caprolactone) (PCL) electrospun membrane and a hydrophilic cellulose nonwoven was prepared, resulting in Laplace pressure difference (Figure 1D) [49]. Therefore, a unidirectional fluid transport was achieved from the wound-facing hydrophobic layer to the hydrophilic absorbent layer, effectively draining exudate from the wound beds. A step forward has been made by engineering fluidic pathways with improved capillary pumping effect. For instance, hydrogel dressings with directional hydration channels were prepared by 3D-templated wetting-enabled-transfer polymerization, followed by integration with hydrophobic/hydrophilic gel layers, achieving self-pumping of viscous-biofluids (Figure 1E) [50]. The synergistic effect of guided channels and Janus wettability gradient led to an exceptionally high unidirectional fluid drainage capability at a speed up to 41.67 $\mu L \cdot s^{-1}$, which far surpassed that of conventional asymmetric dressings (5.0 $\mu L \cdot s^{-1}$).

2.3. Functionalization with Bioactive Ions or Biomolecules

Biofunctionalization provides a pivotal strategy to endow the interfacial materials with biological capabilities. The addition of bioadhesive substances such as catechol derivatives is favorable for enhancing intermolecular bonding forces at the tissue interface [51]. The immobilization of therapeutic agents, such as active ions, antioxidants, anti-inflammatory drugs, and growth factors, offers rich opportunities to improve the hostile tissue microenvironment [52–54], including alleviating chronic inflammation [55], suppressing excessive oxidative stress [56], and promoting angiogenesis.

Bioactive metal ions can be directly integrated into material networks to impart multifunctionality. For example, zinc ions (Zn^{2+}) exhibit broad-spectrum antibacterial property while facilitating human umbilical vein endothelial cell proliferation and angiogenesis [57]. Iron ions (Fe^{3+}) can serve as crosslinking agents to form strong coordination complexes and participate in the Fenton reaction to clear ROS, thereby improving therapeutic outcomes [28,58]. Nanocarriers, including metal-organic frameworks (MOFs), nanoparticles, nanofibers and nanohydrogels, act as versatile reservoirs for controlled drug delivery. Diverse biomolecules and bioagents have beenhave been readily encapsulated into the nanocarriers for controlled release. It can be engineered in response to microenvironmental stimulus such as pH, ROS, and proteinases. Certain MOFs based on Zn^{2+}, Mg^{2+}, or Fe^{3+} possess superoxide dismutase (SOD)-like, or catalase (CAT)-like activities, showing great potential for ROS scavenging [59,60]. In addition, the released bioactive metal ions contribute to antibacterial and angiogenesis functions. The MOF hydrogel loaded with functional small molecules is able to regulate local immune response and accelerate wound healing [61]. Overall, owing to excellent drug delivery efficiency and outstanding antioxidant capacity, MOFs have shown great potential in soft tissue repair [62].

Polyphenols, such as tannic acid (TA) and its derivatives, serve dual roles as versatile interfacial adhesives and bioactive modulators [63,64]. The high density of catechol/pyrogallol groups facilitates strong adhesion through hydrogen bonding, hydrophobic interactions, and coordination bonds. The excellent ROS scavenging capability makes them effective antioxidants for tissue regeneration [65]. Furthermore, their metal-chelating ability allows the formation of functional complexes to achieve additional activities [66]. Curcumin, a polyphenolic compound, was encapsulated into microneedle patches to reshape the microenvironment and improve the repair of chronic soft tissue defects [67]. As another example, epigallocatechin gallate was introduced to the microneedle patches, which showed antibacterial and antioxidant capacity in healing process of infected diabetic wounds [68]. Various herbal preparations, including flavonoids and terpenoids, have been proven to reduce oxidative stress, regulate signaling pathways, and promote angiogenesis [69].

Overall, through diverse functionalization approaches, biomaterials can be endowed with tissue adhesion, specific bioactivates, and improved tissue-interfacing properties. More recently, the advancement of stimuli-responsive delivery system can provide more smart and intelligent systems, which are conducive to controlling cell response and improving tissue regeneration.

3. Regulatory Strategies of Material-Tissue Interfacial Interactions

The material-tissue interface represents a spatiotemporally dynamic system, involving interactions between biological components, such as proteins, cells, tissues, and the implanted material [70,71]. It has been widely recognized that interfacial molecular interactions are the fundamental basis underlying most biological processes in nature [72]. The interfacial interactions ultimately drive multi-level physical, chemical, and biological events. Thus, the material-tissue interfacial interactions are of importance for modulating cell behavior and tissue function. The basic regulatory strategies include biophysical modulation, intermolecular interaction regulation, and microenvironment tuning, which collectively influence the cell adhesion, migration and differentiation, and consequently govern tissue adhesion, integration and regeneration. Notably, biophysical modulation delivers physical force cues, including tension and compression, as well as mediates capillary action, to promote wound closure, hemostasis, and exudate drainage. The intermolecular interactions, including hydrogen bonds and dynamic chemical bonds can directly mediate the interface between materials and tissues. Notably, strong intermolecular interaction leads to robust adhesion ability, whereas the repulsive force results in superior anti-adhesion performance. Furthermore, increasing evidence suggests that engineered interfaces capable of modulating microenvironment exhibit a powerful ability to recapitulate the *in vivo* microenvironment through biochemical cues, such as pH, ROS, factor expression, cell phenotypes, etc.

3.1. Biophysical Modulation

As a non-invasive strategy, the mechanical modulation harnesses biophysical cues to promote the healing process. For instance, the interfacial materials can be engineered to generate tensile forces through contraction, apply compressive pressure via expansion, and drive fluid transport by capillary action. By delivering such active biophysical cues, these materials guide critical repair outcomes, including wound closure, hemostasis, and exudate drainage, in a direct and effective way.

Contractile forces can be generated by engineering the materials to undergo programmable dimensional changes. For instance, a composite fiber composed of sodium alginate, gelatin and hydroxyl-rich silica nanoparticles was prepared by Di et al. [73]. The composite fiber knitted textile showed moisture-adaptive contraction performance, which relied on the disruption of intermolecular hydrogen bonds upon fluid absorption, causing molecular chain relaxation and fiber elongation (Figure 2Ai). Subsequent drying triggered the reconstruction of hydrogen bonds, forcing the polymer chains into a contracted conformation and generating substantial uniaxial contractile force, which actively drawn wound edges together in a simulated wound model (Figure 2Aii). Alternatively, thermal activation provided a facile approach for providing contractile forces [74]. Hydrogels formulated with temperature-sensitive polymers exhibited volume shrinkage upon reaching their LCST. When bridged across a wound, the contraction generated a continuous closing force. The stress-shielding effect directly relieved mechanical tension at wound edges, effectively promoting healing and mitigating scar formation (Figure 2B).

In addition to contractile forces, the interfacial materials can be engineered to offer controlled expansion for providing compression pressure, which is beneficial for hemostasis. To this end, shape memory materials that undergo liquid-triggered self-expansion have been developed to deliver interfacial compression. For instance, a porous scaffold composed of carboxymethyl cellulose (CMC) fibers and acetalized PVA exhibited more than 20 times its original volume within seconds upon blood contact, attributed to the volumetric expansion of the porous network and the swelling of embedded hydrophilic fibers [75]. The expansion forces exerted mechanical compression to the bleeding blood vessels at the lesion sites, similar to manual pressure for stopping bleeding. As another example, Wu et al. developed a self-expanding cuttlefish bone elastomeric sponge (CBES) with ordered microchannels, which composited with poly-(glycerol sebacate) (PGS) and PCL by 3D-printing (Figure 2Ci) [76]. It was found that the sponges were able to absorb fluid rapidly upon blood contact, leading to red blood cell enrichment for blood clotting, along with shape recovery for exerting expansion pressure at the bleeding sites. Moreover, the ordered microchannel architecture provided guiding cues for blood flow and the incorporated bioactive cuttlefish bone powder was capable of enhancing the coagulation cascade (Figure 2Cii).

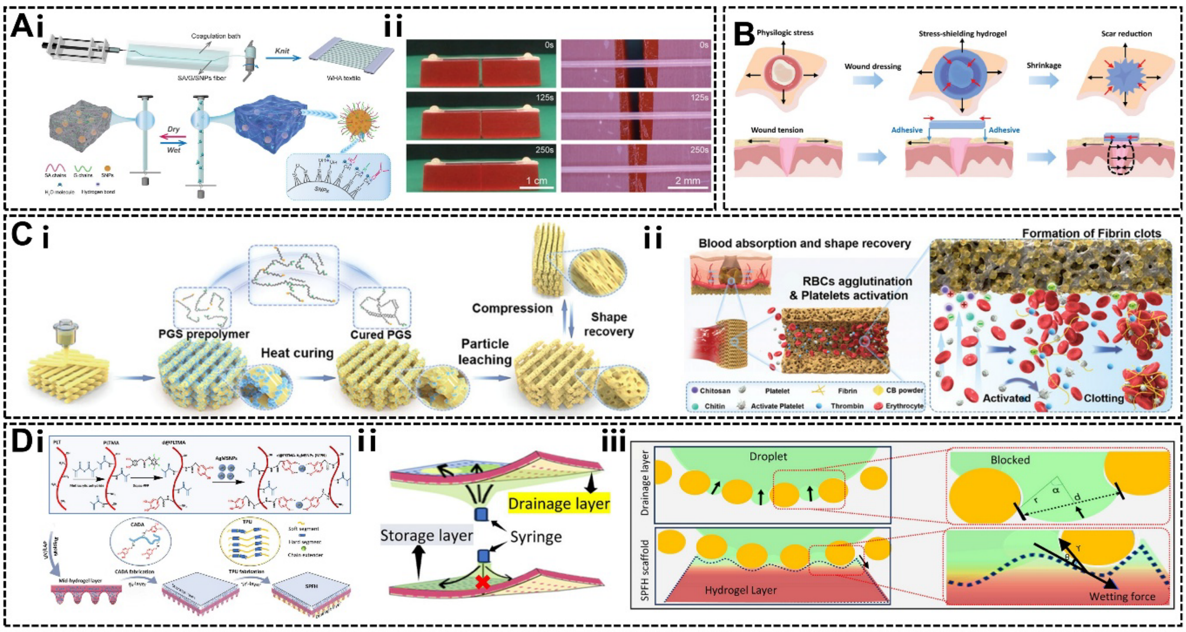


Figure 2. Interfacial biomaterials for biophysical modulation. (**A**) Contractile force provided by the humidity-responsive textile. (**i**) Schematic showing fabrication of the textile knitted by the composite fibers. (**ii**) The simulated contraction process by using an agarose model. Reproduced with permission [73]. Copyright 2023,

Wiley-VCH. (**B**) Schematic illustrating contractile force provided by the stress-shielding hydrogel for reducing scar formation. Reproduced under the terms of the CC BY 4.0 license [74]. Copyright 2024, the authors, published by Wiley-VCH. (**C**) Compressive pressure provided by the self-expanding elastomeric sponge. (**i**) Schematic showing fabrication process of the sponge with ordered channels and porous structures. (**ii**) Schematic illustrating the hemostatic mechanism of the sponge, combining mechanical compression by rapid self-expansion, red blood cell aggradation, and Ca^{2+} triggered coagulation. Reproduced with permission [76]. Copyright 2023, Wiley-VCH. (**D**) Capillary force provided by the tri-layered Janus scaffold integrating hydrophobic/hydrophilic asymmetric wettable layers and aligned hollow microneedle channels. (**i**) Schematic showing fabrication of the mid-layer featuring aligned hollow microneedle channels. (**ii**) Schematic showing transport process when droplet contacts with different layer. (**iii**) The schematic showing the self-pumping mechanism of SPFH scaffolds in which the wetting force generated by the hydrogel layer pulled the droplet from the contacting points. Reproduced with permission [77]. Copyright 2025, Wiley-VCH.

The capillary force of the materials based on the Laplace pressure gradients, offers a simple and versatile strategy for guiding fluid transport, which is beneficial for wound exudate drainage. The dressings constructed by depositing a hydrophilic layer on a hydrophobic layer create asymmetric wettability, offering a directional capillary force [78,79]. The principle was further amplified in an advanced design by integrating aligned hollow hydrophilic microchannels or microneedle arrays with the hydrophilic/hydrophobic Janus dressing. As shown in Figure 2Di, Pei et al. fabricated a tri-layer self-pumping Janus fibrous hydrogel scaffold (SPFH) composed of an inner hydrophobic electrospun drainage layer, an outer hydrophilic storage layer, and a middle supramolecular hydrogel layer with hollow microneedle channels [77]. The combination of hydrophobic/hydrophilic asymmetric wettability and microchannels synergistically enhanced the drainage performance (Figure 2(Dii,Diii)). In addition to highly efficient exudate drainage, the superhydrophobic surface is able to repel the wound fluid and minimize adhesive contact, facilitating easy and non-traumatic removal [80].

3.2. Intermolecular Interaction Regulation

The dynamic, molecularly engineered interfaces have attracted considerable attention. Interfacial biofunctional materials for soft tissue repair rely on sophisticated intermolecular interactions to modulate the biological response at different stages. For example, Cao et al. developed a timescale-dependent bio-adhesive, enabling strong wet adhesion, along with fault-tolerant convenient surgical operations (Figure 3Ai) [81]. In the initial stage which lasts only seconds, the hydrogel formed instant and reversible physical interactions with wet tissue surfaces, allowing reposition or detachment of misplaced adhesives without causing secondary tissue damage, superior to the conventional covalent-based tapes (Figure 3(Aii,Aiii)). Subsequently, a transition from physical interactions to strong covalent linkages occurred in hours, and an interfacial toughness of approximately 1268 J m^{-2} was achieved.

The interface water layer, which mediates the material-tissue interactions dramatically, poses a significant challenge to the adhesion effect [82]. To overcome this challenge, various strategies have been developed, including disruption of hydration layer, enhancement of intermolecular interactions, introduction of covalent bonds, and design of water absorption structures [83]. For example, self-gelling coacervate powders were developed to achieve robust adhesion on wet tissue surface, through a liquid-liquid phase separation process mediated by intermolecular hydrogen bonds and hydrophobic interactions between TA, CS, and PEG (TCP) [84]. Upon absorption of interfacial water, *in situ* self-gelling occurred for the powders, leading to a tight adhesion to various material surfaces, attributing to the formation of hydrogen bonding, cation-π interactions, and coordination bonding (Figure 3Bi). A higher adhesion strength was achieved for the TCP gel compared with fibrin sealant (Figure 3Bii). Moreover, loading of bioactive substances such as platelet-rich plasma and deferoxamine was beneficial for wound healing. Apart from adhesion materials, the anti-adhesive materials play a crucial role in preventing postoperative adhesions. For example, Wang et al. developed a self-fused, antifouling, and injectable hydrogel to prevent postoperative peritoneal adhesions [85]. The hydrogel was constructed through reversible hydrogen-bonding networks between methacrylate hyaluronic acid (HA-GMA) and ultra-hydrophilic N-(2-hydroxypropyl) methacrylamide (HPMA) side chains (Figure 3Ci). Interestingly, the dense hydrated layer consisting of ultra-hydrophilic HPMA chains functioned as an antifouling barrier, effectively repelling proteins and fibroblasts (Figure 3Cii). The hydrogel facilitated peritoneal repair by modulating mesothelial-to-mesenchymal transition. In another example, a microgel assembly with programmable self-contraction, robust adhesiveness, and triggerable detachment, was developed to provide a mechanically active interface for wound healing by activating mechanotransduction [86]. Specifically, the self-contraction N-isopropyl acrylamide (NIPAM)-*co*-acrylic acid (AAC) microgel assembly with robust tissue adhesion featured a secondary network of polyacrylic acid and calcium ions (Figure 3Di). Interestingly, the adhesion decreased dramatically after spraying of sodium bicarbonate solution, allowing noninvasive removal of the dressings (Figure 3(Dii,Diii)). Importantly, the microgel was capable of temperature-triggered self-contraction, which enabled mechanical traction directly to the wound surface. The mechanical cue activated mechanotransduction pathways, such as Hippo and TGF-β/Smad, to promote cell conversion and collagen synthesis. Simultaneously, the contraction of exosomes-laden microgel assembly (SMART-EXO) facilitated the on-demand release of exosomes to accelerate re-epithelialization through PI3K/AKT and MAPK/Erk signaling, indicating transition from passive barriers to active mechanical and biochemical regulators.

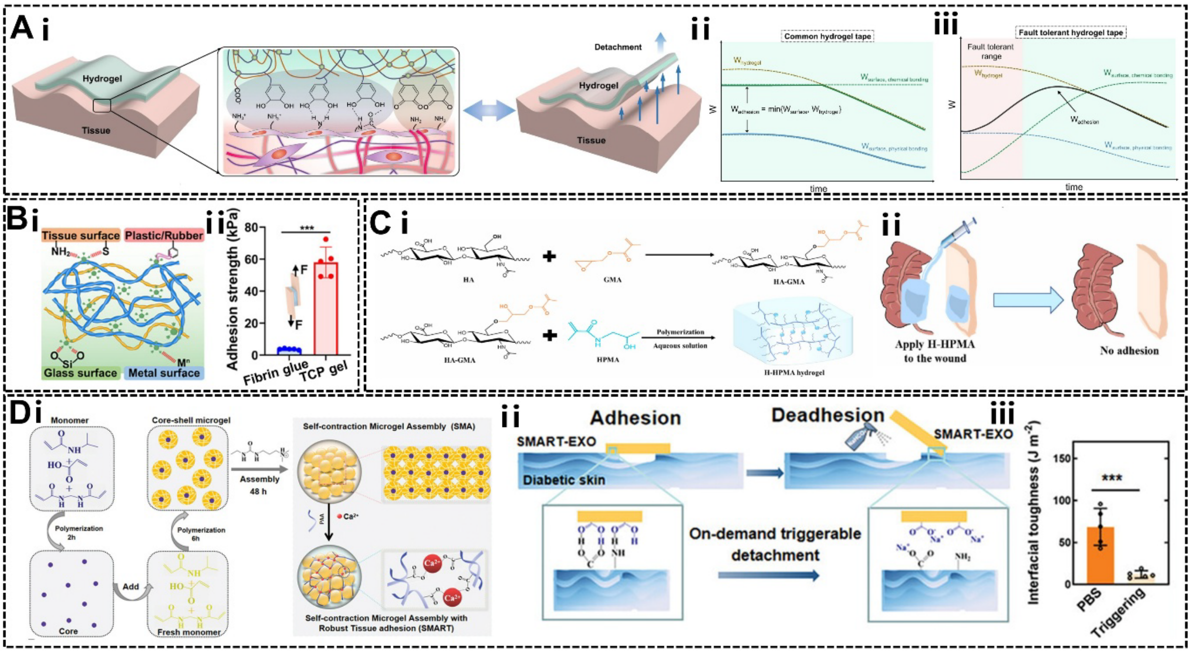


Figure 3. Interfacial biomaterials for intermolecular interaction regulation. (**A**) The fault-tolerant hydrogel tape with reversible adhesion at the initial stage and long-term strong adhesion capability. (**i**) Schematic showing the fault-tolerant mechanism due to the formation of non-covalent interactions in seconds. The time-dependent adhesion strength of (**ii**) common hydrogel tapes and (**iii**) fault-tolerant hydrogel tapes. Reproduced under the terms of the CC BY 4.0 license [81]. Copyright 2021, the authors, published by Springer Nature. (**B**) Coacervate powder-derived adhesive hydrogel. (**i**) Schematic showing adhesion mechanism to different substrates. (**ii**) Adhesion strength on porcine skin. Reproduced with permission [84]. Copyright 2025, Wiley-VCH. (**C**) Hydrogel with anti-adhesion capability. (**i**) Schematic showing hydrogel preparation. (**ii**) Schematic showing its application on a rat cecum-abdominal wall adhesion model. Reproduced under the terms of the CC BY 4.0 license [85]. Copyright 2022, the authors, published by KeAi Publishing. (**D**) Microgel assembly with self-contraction, adhesive, and triggerable detachment capabilities. (**i**) Schematic showing the fabrication process of the microgel. (**ii**) Schematic showing the wet adhesion and triggerable detachment of the microgel. (**iii**) The interfacial toughness of the microgel on wet porcine skin decreased significantly upon application of triggering solution for 5 min. Reproduced with permission [86]. Copyright 2024, Wiley-VCH.

3.3. Microenvironment Tuning

Beyond biophysical modulation and intermolecular interaction regulation, advanced interfacial material functions as an active platform that dynamically regulates the local biochemical and cellular microenvironment of the lesion sites. Significant efforts have been devoted to the development of biofunctionalized materials to regulate hostile microenvironment with excessive ROS, dysregulated inflammation, and aberrant cellular signaling, creating a conducive niche for promoting efficient regeneration. The active intervention strategy is capable of addressing the pathological imbalances of chronic or impaired healing, offering a sophisticated approach for microenvironmental reprogramming.

ROS scavenging and oxidative stress alleviation have been recognized as critical and primary issues for mitigating the deleterious ROS-inflammation cascade in injured tissues. Thus, the antioxidative materials that can protect cells from oxidative damage and activate pro-survival and pro-migration pathways have been widely used as interfacial agents. Nanomaterials engineered with enzyme-mimicking nanozymes can directly scavenge multiple types of ROS [87]. For instance, metal-polyphenol coordination nanoparticles not only exhibit SOD-like activity to catalyze the conversion of superoxide anions, but also upregulate endogenous antioxidant enzymes (e.g., SOD, CAT) in cells. The dual-action, at the material-tissue interface, effectively decreases the local oxidative burden, protects mitochondrial integrity from damage, and subsequently downregulates harmful pathways such as AGE-RAGE, thereby rescuing cellular function and creating a redox-balanced microenvironment conducive to healing [88].

The sustained inflammation and compromised angiogenesis pose major obstacles for soft tissue regeneration. It has been reported that the nuclear factor-κB (NF-κB) signaling pathway is the key mechanistic target of ROS-inflammatory cascade. Therefore, a tetrahedral framework DNA hydrogel (TDH) was prepared for effective ROS scavenging (Figure 4Ai), which could inhibit the activation of NF-κB pathway, leading to downregulated expression of pro-inflammatory cytokines such as TNF-α and IL-1β and improved macrophage switching from a pro-inflammatory (M1) to an anti-inflammatory (M2) state (Figure 4(Aii–Aiv)) [89]. The precise immunomodulation at the tissue interface is capable of eliminating chronic inflammation and fostering a restorative microenvironment.

Integration of biochemical regulation and biophysical stimulation provides a comprehensive strategy for promoting wound healing. For example, an antioxidative and thermosensitive active shrinking hydrogel was constructed to enhance re-epithelization and skin constriction [90]. It was found that the gel activated the mechanosensitive epidermal growth factor receptor/Akt pathway, thereby promoting cell proliferation. Furthermore, electrical stimulation offers robust regulatory cues to modulate cell proliferation and migration. A self-powered thermoelectric hydrogel Ag_2Se@GelMA was developed to generate stable electrical stimulation at the material-tissue interface by taking advantage of the natural temperature difference between the skin and the environment (Figure 4Bi) [91]. Electrical stimulation activated voltage-gated calcium channels on adjacent cells, triggering Ca^{2+} influx (Figure 4Bii). Subsequently, the increase of free Ca^{2+} levels in the cytoplasm activated Ca^{2+}/calmodulin dependent protein kinase β (CaMKKβ), which phosphorylated AMP activated protein kinase (AMPK) at the threonine 172 (Thr172). Modulation of AMPK activity through Ca^{2+} signaling enhanced mitochondrial function and dynamics, significantly promoting key cellular activities including proliferation, migration, and angiogenesis. Therefore, interfacial materials can transmit biochemical and biophysical signals that directly regulate the cellular activities necessary for tissue repair. The active regulation of cell behavior through favorable interfacial interactions provides essential support for guiding soft tissue repair.

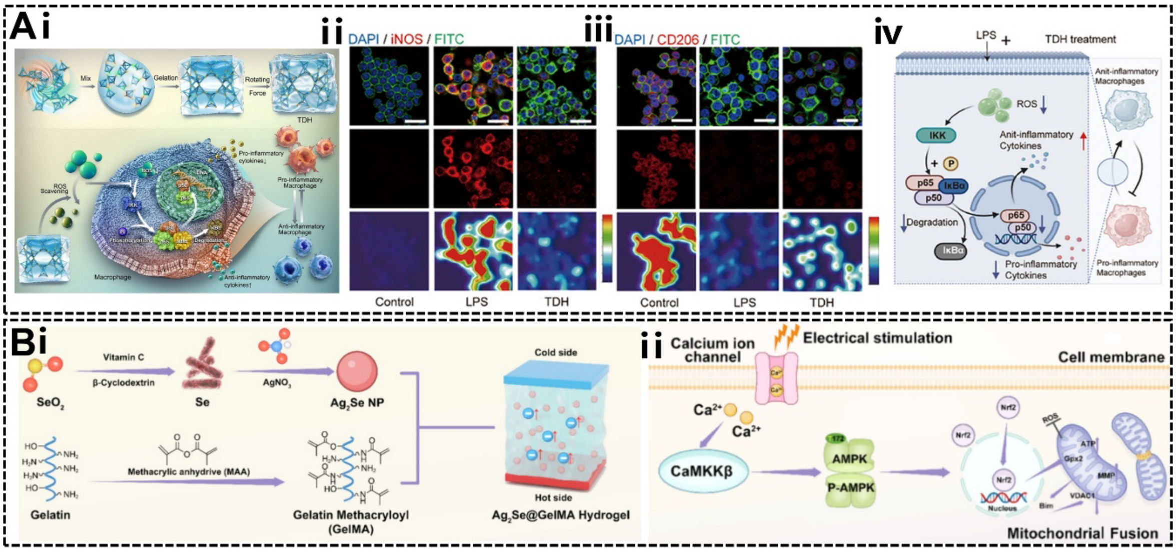


Figure 4. Interfacial biomaterials for microenvironment tuning. (**A**) DNA hydrogel with inflammation regulation capability. (**i**) Schematic showing hydrogel formation via cross-linking of tetrahedral DNA nanostructures based on complementary base pairing. Representative immunofluorescence images and heatmaps of (**ii**) iNOS and (**iii**) CD206 staining. (**iv**) Schematic showing that the hydrogel disrupted the ROS-inflammatory cascade in macrophages via downregulation of NF-κB pathway. Reproduced with permission [89]. Copyright 2025, Wiley-VCH. (**B**) The thermoelectric hydrogels with cell behavior regulation capability. (**i**) Schematic showing the fabrication of hydrogel-based electrical stimulation device. (**ii**) Schematic showing the mechanism and pathway of hydrogels for promoting wound healing. Reproduced with permission [91]. Copyright 2025, American Chemical Society.

4. Applications in Soft Tissue Repair

The repair of severe soft tissue defects remains a huge challenge. Interfacial biomaterials are designed to serve as temporary yet instructive matrices for actively guiding tissue regeneration. The ultimate goal is long-term integration followed by functional restoration. Thus, these constructs are engineered to not only fill the defect but also interact dynamically with the host tissues, directing key processes such as stem cell fate, tissue-specific regeneration, or the prevention of pathological adhesions. Up to date, the biomaterials have been constructed in the forms of injectable hydrogels, electrospun patches, decellularized matrix composites, etc., for the applications in repair of various soft tissues including skin, tendon, nerve, muscle, fascia, etc.

4.1. Skin Repair

As a critical component of soft tissue, the skin repair faces several challenges of rapid hemostasis, accelerated wound closure and complete restoration of skin function. Biofunctional interfacial materials have emerged as a versatile platform to manage bleeding or modulate wound microenvironment. Consequently, these materials demonstrate enormous potential beyond traditional wound dressings.

As the first stage of wound healing, uncontrollable bleeding remains the main cause of preventable death. Additionally, hemostasis establishes a provisional matrix enriched with activated platelets, which subsequently play a critical role in tissue repair and regeneration [92,93]. Therefore, hemostasis represents a crucial step that lays the foundation for subsequent soft tissue regeneration. Rapid and effective hemostatic materials should be capable of minimizing blood loss, preventing rebleeding, and facilitating wound healing.

The asymmetric dressing features a self-pumping action that unidirectionally transports excessive serum from the hydrophobic layer to the hydrophilic layer, concentrating coagulated factors and promoting hemostasis. As an example, a Janus amphipathic Fiber@Gel/Ca^{2+}/KL dressing was developed by combining multiple hemostatic mechanisms to enhance the efficiency [94]. Upon application to the bleeding wounds, the dressing enabled unidirectional self-pumping of serum, which effectively concentrated red blood cells and platelets while simultaneously releasing calcium ions to activate the coagulation cascade (Figure 5Ai). The multifunctional interfacial action promoted a rapid formation of stable clots in the rabbit ear artery bleeding models, resulting in reduced blood loss and hemostatic time (Figure 5(Aii,Aiii)). Notably, the anti-adhesive property of its hydrophobic surface allowed for easy and safe removal of the dressing without causing secondary hemorrhage.

Non-compressible hemorrhage control in deep wound represents a significant challenge. The self-expanding porous materials have been extensively studied to provide interfacial compression for physical tamponade, and absorb liquid for concentrating coagulation factors, resulting in improved blood clotting [95]. Freeze-drying offers a straightforward approach to develop interconnected porous sponges. The porous sponges, fabricated via freeze-drying, could rapidly absorb blood and expand within seconds to exert mechanical pressure on damaged vessels (Figure 5Bi) [96]. The hemostasis time of the hemostatic sponges in the mouse liver injury model was 41 s, which was much shorter than that of the commercial chitosan sponge group (77 s) (Figure 5Bii). Furthermore, on-demand removal was achieved via a simple rinsing that disrupted the ionic crosslinks, enabling safe debridement without disrupting the fresh clot. Moving forward, an approach combining cryogelation, solvent exchange and ambient-temperature drying has been developed to offer a potential strategy for reducing production costs (Figure 5Ci) [97]. By using this approach, chitosan fiber (CSF)-based cryogel with fast expanding capability has been fabricated. When applied in the rabbit axillary artery and vein complete transection model, the compressed CSF sponge rapidly absorbed blood, expanded, and sealed the cross-section of the artery, leading to reduced blood loss and hemostatic time (Figure 5Cii).

In addition to hemorrhage control, the main challenges facing skin wound healing include exudate management, persistent inflammation, and tissue regeneration disorders. Through precise engineering of interfacial interactions, including rapid exudate drainage, delivery of mechanical forces, and spatiotemporal modulation of the biochemical signals, the advanced wound dressings enable transformation of the hostile wound bed into a regenerative microenvironment. The dressings have been designed in various forms, including film, hydrogel, sponge, and nanofibrous scaffold, demonstrating superior efficacy in accelerating wound closure, enhancing tissue regeneration, and restoring function across diverse wound models.

Management of hostile wound microenvironments combines multiple interfacial functions to address co-existing challenges such as heavy exudation and persistent inflammation. For treatment of burn wounds with massive exudates, Wang et al. developed a self-pumping organohydrogel dressing with hydrophilic fractal microchannels [98]. By utilizing creaming-assistant emulsion interfacial polymerization, the dressing was constructed with gradient-distributed poly-laurel methacrylate (PLMA) organogel particles embedded within PAAm hydrogel networks (Figure 6Ai). Attributed to the multilevel capillary effects, the organohydrogel dressing enabled ~30 times enhancement in fluid drainage compared to the pure hydrogel. In a murine burn model, a ~42.5% reduction in dermal cavity was achieved compared to that of commercial Tegaderm dressings (Figure 6Aii). Moreover, microenvironment regulation via bioactive agent delivery focuses on governing pathological imbalances and directing cellular behavior. For treatment of diabetic wounds, a double-layered dressing composed of a ROS-degradable conjugated polymer poly(deca-4,6-diynedioic acid) (PDDA) and CS was employed for microenvironment modulation [99]. The dressing continuously scavenged ROS to alleviate inflammation, in parallel with sustained succinic acid delivery to promote angiogenesis and tissue regeneration. The double-layered dressing significantly promoted wound healing in both diabetic mouse and porcine. In another example, a wound dressing composed of radially aligned nanofibers and near-infrared responsive microparticles was developed for spatiotemporal release of growth factors [100]. The nanofiber scaffolds facilitated wound healing by activating PI3K-Akt, MAPK, and immune pathways in a porcine model.

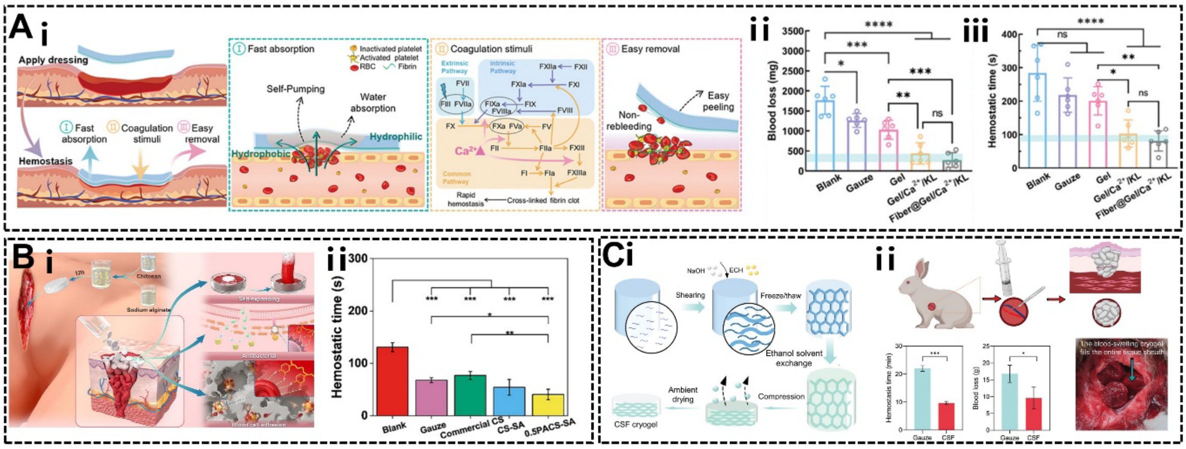


Figure 5. Applications of interfacial biomaterials for hemostatic management. (**A**) Janus self-pumping dressing for hemostasis. (**i**) Schematic showing the hemostasis mechanism. (**ii**) Blood loss and (**iii**) hemostatic time in the rabbit ear artery bleeding model. Reproduced with permission [94]. Copyright 2024, Wiley-VCH. (**B**) Self-expanding sponge prepared by freeze-drying method for non-compressible hemorrhage. (**i**) Schematic showing the self-expansion, blood cell adhesion and aggregation processes. (**ii**) Hemostatic time of the sponges in the mouse liver injury model. Reproduced with permission [96]. Copyright 2025, Wiley-VCH. (**C**) Self-expanding fibrous cryogels prepared via a non-freeze-drying strategy for non-compressible hemorrhage. (**i**) Schematic showing the fabrication of cryogels by assembling micro-hydrogels. (**ii**) Hemostatic capability of the self-expanding fibrous cryogels. Reproduced with permission [97]. Copyright 2023, Wiley-VCH.

To meet the demands of strong adhesion and painless removal for wound dressing, a multifunctional thermoresponsive hydrogel dressing (DA-Hyd-Doxy) was developed by copolymerization of N-isopropylacrylamide and dopamine-modified zwitterionic poly(amidoamine)s as the matrix, loaded with doxycycline [101]. The hydrogel exhibited smart interfacial adhesion, providing strong attachment to the dynamic wound site at body temperature, while allowing painless removal upon cooling (Figure 6Bi). In addition, antibacterial activity was mediated by doxycycline delivery, and antioxidant and anti-inflammatory effects were provided by the dopamine moiety directly. In the infected skin wound model established on the nape and dorsum of diabetic rats, this multifunctional interfacial strategy significantly promoted wound healing with a near-complete closure (wound area of 1.1 ± 0.4%) at day 15, which markedly outperformed conventional gauze (Figure 6Bii).

Active mechanical intervention for wound closure involves materials that provide physical forces directly to the wound edges, counteracting skin tension and promoting contraction. For example, a core-ring structured hydrogel (CR-gel) was fabricated via two-step photopolymerization, in which the C-gel was composed of methacrylate hyaluronic acid (HAMA) and N-isopropylacrylamide (NIPAAm) and the R-gel consisted of N, N'-methylene bisacrylamide (MBA), acrylic acid (AA) and TA (Figure 6Ci) [102]. The CR-gel exerted localized functions, with a temperature-responsive core generating a contractile force (~3.4 kPa), and an adhesive ring transferring the stress to the wound periphery edge. The dressing provided effective mechanical force while resisting exudate-mediated swelling, leading to an accelerated epidermal closure of 85% on day 8 in miniature swine skin (Figure 6(Cii,Ciii)). The gel group exhibited shorter epidermal gap and denser collagen fibers, indicating better healing quality (Figure 6(Civ,Cv)). Furthermore, a mechanically active adhesive and immune regulative dressing was fabricated, to provide strong adhesion, temperature-triggered contraction, and immune regulation. The mouse and porcine wound models validated the synergistic effect of contractile and immunomodulatory functions for promoting wound healing [103].

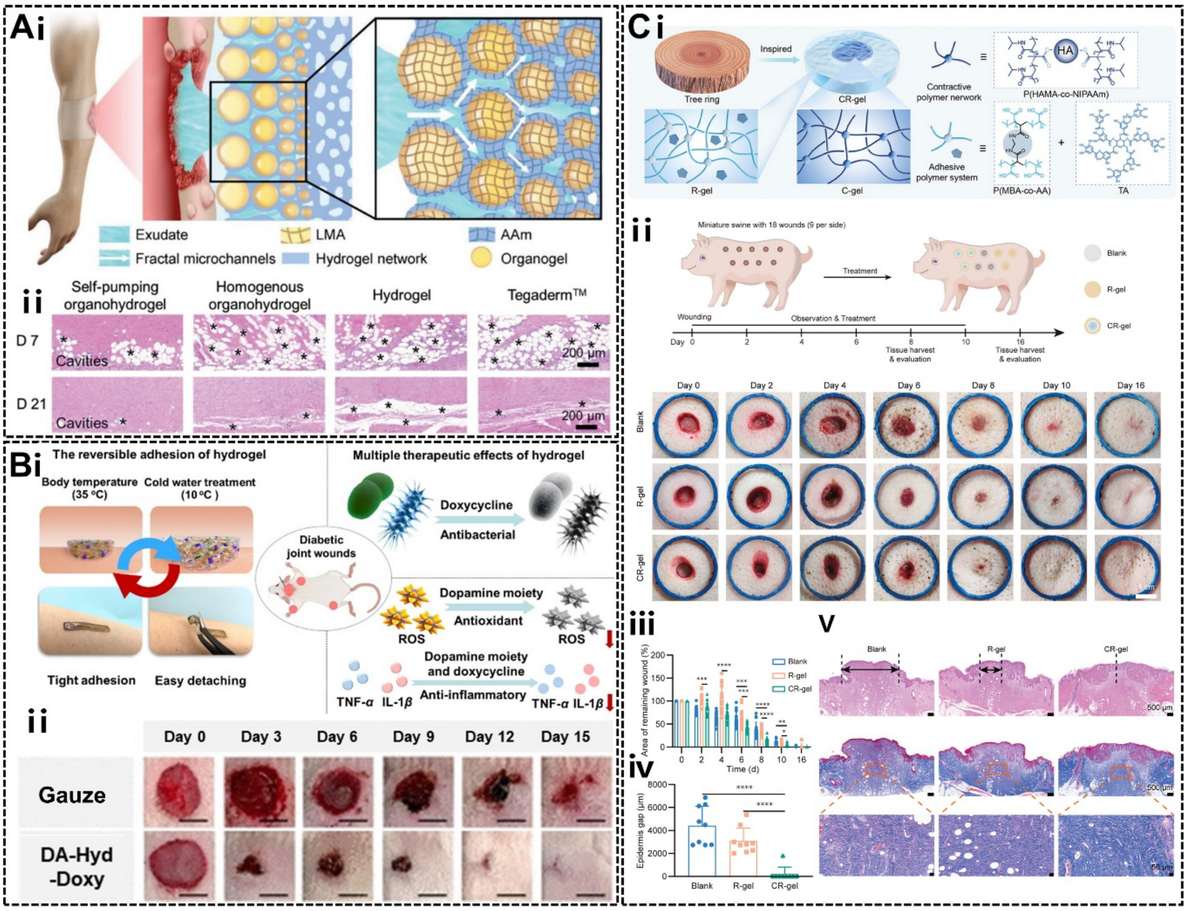


Figure 6. Applications of interfacial biomaterials for wound healing. (**A**) Dressing with self-pumping capability for burn wound healing. (**i**) Schematic showing the design of dressing with hydrophilic fractal microchannels. (**ii**) H&E staining image of burn wounds showing dermal cavities marked by black asterisks. Reproduced with permission [98]. Copyright 2023, Wiley-VCH. (**B**) Reversible adhesive hydrogel for infected diabetic joint wound healing. (**i**) The schematic showing reversible adhesion based on a thermo-stimulated autoshrinkage mechanism and the multiple therapeutic effects of hydrogel for wound healing. (**ii**) Photographs of the infected diabetic joint wounds on the nape area of rats. Scar bar indicates 5 mm. Reproduced with permission [101]. Copyright 2025, American Chemical Society. (**C**) Core-ring structured hydrogel with mechanical regulation capability to promote skin wound repair. (**i**) Schematic showing the hydrogel fabrication. (**ii**) Hydrogel treatment of full-thickness skin wounds in miniature swine: experimental protocol and representative wound photographs. (**iii**) Quantified remaining wound area of wounds. (**iv**) Epidermis gap on day 8. (**v**) H&E and Masson staining images of wound tissues on day 8. Reproduced with permission [102]. Copyright 2024, Wiley-VCH.

4.2. Tendon Repair

As a typical soft tissue, tendons including rotator cuff and Achilles tendon, play an important role in force transmission and joint movement. However, given the limited regenerative ability, effective tendon repair remains a significant challenge. Since the sliding behavior of tendon relies on a low friction, the engineered interfacial materials are highly desirable for tendon repair. Moreover, it is crucial to modulate the microenvironment by scavenging ROS, mitigating inflammatory response and promoting tenogenic differentiation, to facilitate functional regeneration.

The substantial presence of ROS causes acute oxidative stress, collagen degradation, and M1 macrophage polarization. With the aim of improving tendon repair, the scaffolds with ROS scavenging capability have been developed. As shown in Figure 7Ai, Li et al. developed a decellularized tendon (DT) fibrous membrane decorated with MnO_2 with the aid of TA as the cross-linking and reducing agent [104]. MnO_2@DT efficiently scavenged excessive ROS, significantly accelerating the proliferation and remodeling stages during repair of injured tendon.

In the rat model of patellar tendon defect, the arrangement of collagen fibers was enhanced under treatment of MnO_2@DT, showing a significant promoting effect on tendon tissue repair (Figure 7Aii).

A motion lubrication layer can be formed by the hydrogel, which is able to form abundant hydrogen bondswith water molecules, to enable interfacial lubrication during tendon movement. Thus, the hydrogel patches with lubrication and drug delivery properties have been developed to provide anti-adhesion and regenerative capability [105]. Mooney et al. developed a tough hydrogel with tissue adhesion side, sliding surface and high drug-loading performance [106]. The tough hydrogel, comprising calcium ion crosslinked alginate along with covalently crosslinked PAAM, functioned as the high-capacity depot for local drug release. And CS adhesive on one side generated strong adhesion with the tissue, while the other non-adhesive side supported tendon sliding. In a rat model of Achilles-tendon rupture, the hydrogel promoted healing along with reduced scar formation, while in a rat model of patellar tendon injury, it inhibited inflammation, improved chemokine secretion, and promoted tendon stem and progenitor cell recruitment.

Electrical stimulation has emerged as a promising approach for tissue repair. A piezoelectric injectable anti-adhesive hydrogel (PE-IAH) composed of cross-linked carboxymethyl chitosan (cCMCS) and HA, incorporating piezoelectric poly-L-lactic acid (PLLA) electrospun short fibers, was developed (Figure 7Bi) [107]. This implant acted as a physical barrier against peritendinous adhesion while providing piezoelectric stimulation that facilitated proliferation and differentiation of tendon stem/progenitor cells (TSPCs), as well as the expression of tenascin C (TNC) and secretion of collagen I under ultrasound (US) excitation. A clear boundary with the surrounding tissues, and dense collagen fibers were found in the PE-IAH group on day 8 in a rat ruptured Achilles tendon model (Figure 7Bii). Moreover, a significant improvement in tendon functional recovery was achieved with enhanced Achilles Functional Index (Figure 7Biii).

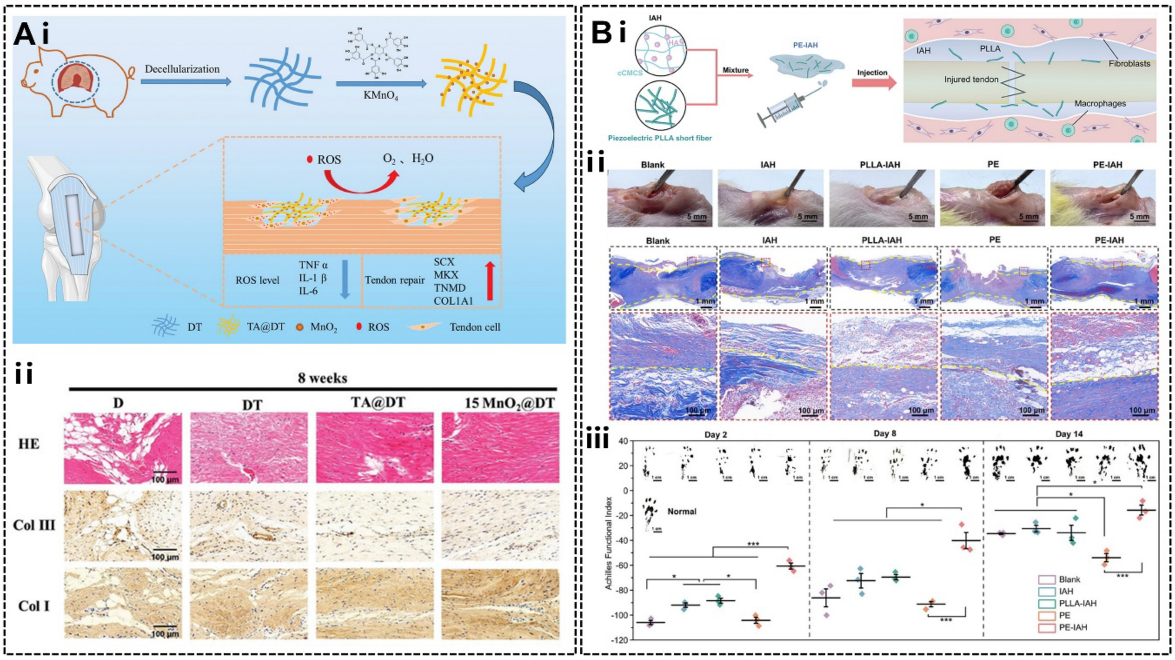


Figure 7. Applications of interfacial biomaterials for tendon repair. (**A**) MnO_2-modified decellularized tendon membrane with ROS scavenging ability to promote tissue regeneration. (**i**) Schematic showing the preparation process. (**ii**) H&E staining and immunohistochemical staining images of patellar tendon after surgery at 8 weeks post-surgery. Reproduced with permission [104]. Copyright 2024, Wiley-VCH. (**B**) Injectable piezoelectric anti-adhesive hydrogel to improve tendon functional recovery. (**i**) Schematic showing the preparation of hydrogels. (**ii**) Photographs and Masson staining images of hydrogel treated Achilles tendon on day 8. (**iii**) Paw prints and Achilles Functional Index of rats. Reproduced with permission [107]. Copyright 2025, Wiley-VCH.

4.3. Nerve Repair

Nerve presents one of the most challenging soft tissues to repair. Natural nerves feature a hierarchical structure composed of parallel myelinated axon bundles and multi-layered sheaths, offering electrical conduction. The repair of nerve injury has evolved from suturing of nerve stumps to microenvironment reconstruction. Thus, the biomaterial interfaces can be engineered with topographical guidance for axonal extension, electrical signals for stimulating Schwann cell migration and myelination, and biomolecules for regenerative niche modulation.

In recent years, stem cell therapy has opened up emerging avenues for nerve repair. Aimed to modulate endogenous neural stem cells for facilitating nerve repair, Dai et al. developed an aligned collagen-fibrin fibrous hydrogel (Col-FB), consisting of collagen and fibrin, with superior adhesive, stretchable and spatiotemporal delivery abilities for the spinal cord injury repair (Figure 8Ai) [108]. The fibrous hydrogels with SDF1α gradient release and sequential delivery of SDF1α/paclitaxel (PTX) directed endogenous neural stem cells toward the lesion site at early stage (Figure 8Aii) followed by neuronal differentiation, resulting in restoration of hindlimb locomotion. In addition, nerve guidance conduit (NGC) engineered with US-triggered electrical stimulation and controlled drug delivery has been developed for peripheral nerve repair. For example, Chai et al. constructed an aligned piezoelectric nanofiber-derived hydrogel NGC, which was composed of barium titanate piezoelectric nanoparticles (BTNPs)-doped polyvinylidene fluoride-trifluoroethylene [BTNPs/P(VDF-TrFE)] electrospun nanofibers loading with nerve growth factor (NGF) (Figure 8Bi) [109]. The NGC utilized US-triggered electrical stimulation to facilitate directional neuronal extension along with neurite outgrowth, while enabling controllable release of NGF through hydrogel shrinkage upon heating, thereby actively accelerating nerve repair. The *in vivo* results of rat sciatic nerve defect repair model showed that the NGCs combined with US treatment exhibited significant nerve regeneration (Figure 8Bii). In another study, a self-healing electroconductive hydrogel composed of HA, cystamine, and pyrrole-1-propionic acid (HASPy) was developed [110]. HASPy promoted the expression of genes and proteins associated with Schwann cell myelination primarily by activating the interleukin 17 (IL-17) signaling pathway, thus facilitating nerve regeneration. Apart from axonal regeneration, supportive angiogenesis is another key challenge for nerve repair. To address this issue, an NGC consisting of polydopamine (PDA) modified GelMA hydrogel nanofibers with sustained drug release was developed to synergistically promote nerve regeneration and angiogenesis (Figure 8Ci) [111]. The interfacial platform enabled the loading and sustained release of Secreted Frizzled-Related Protein-2 (SFRP2) via π-π stacking and hydrogen bonding of the PDA modification. The *in vivo* findings demonstrated that the NGCs significantly enhanced angiogenesis and promoted peripheral nerve repair. A significant increase in myelin sheath thickness was achieved (Figure 8Cii), leading to functional recovery. Despite the considerable advances, the long-gap nerve regeneration with bridging of nerve stumps, effective electrophysiological signal transmission, and full restoration of motor function remains a critical challenge.

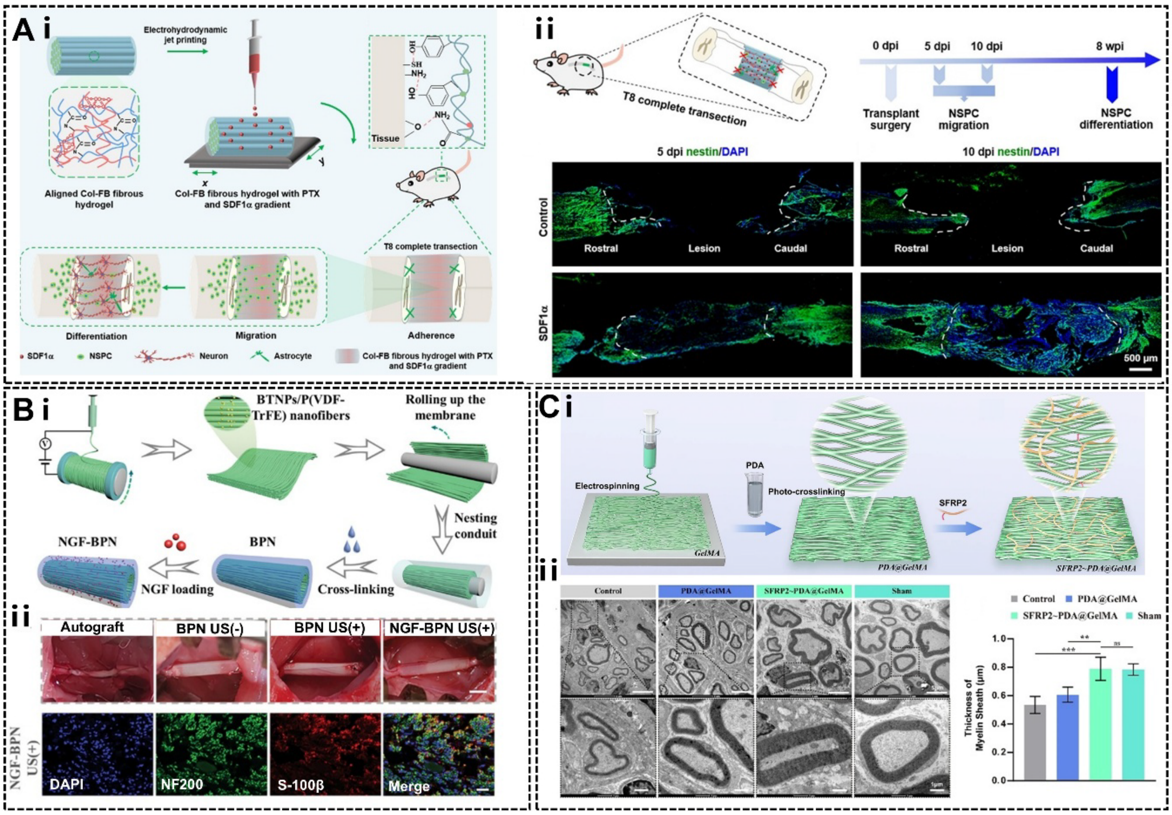


Figure 8. Applications of interfacial biomaterials for nerve repair. (**A**) Adhesive fibrous hydrogel with spatiotemporal delivery capability for spinal cord injury repair. (i) Schematic showing the fabrication process. (ii) The aligned fibrous hydrogels with gradient SDF1α induced endogenous NSPC migration after implantation in transected site of the spinal cord injury rats. Reproduced with permission [108]. Copyright 2021, American Chemical Society. (**B**) US-responsive piezoelectric NGC for peripheral nerve repair. (i) Schematic showing the

preparation process. (ii) Photographs of implantation after surgery (scar bar indicates 2 mm), and immunofluorescent staining images at 8 weeks post-surgery (scar bar indicates 20 μm). Reproduced with permission [109]. Copyright 2024, Wiley-VCH. (**C**) Hydrogel nanofiber-based NGC with sustained release of SFRP2 for angiogenesis and nerve regeneration in peripheral nerve injury repair. (i) Schematic showing the preparation process. (ii) TEM images of sciatic nerves and quantitative analysis of myelin sheath thickness in different groups. Reproduced under the terms of the CC BY 4.0 license [111]. Copyright 2025, the authors, published by Springer Nature.

4.4. Other Soft Tissue Repair

Given the highly heterogeneous microenvironments of diverse soft tissue types, interfacial design employs spatiotemporally dynamic physical and biological signals to orchestrate complex tissue regeneration. Deep soft tissue injury refers to acute trauma involving all tissue layers from the skin to the bone, including muscles, ligaments, fascia, etc. Aimed to utilize traditional Chinese medicine external prescriptions for deep soft tissue injury, Mu et al. fabricated a hydrogel adjuvant composed of gallic acid coupled ε-poly-L-lysine (EPL-GA) and partially oxidized hyaluronic acid (OHA) for loading Chinese medicine ultramicro-powder (μCMP) (EG-OHA@μCMP) (Figure 9Ai) [112]. A deep soft tissue injury model was established by striking the thigh muscles of rats with a heavy hammer. It was found that EG-OHA@μCMP group exhibited almost complete disappearance of blood stasis, and dense and continuous muscle fibers (Figure 9(Aii,Aiii)).

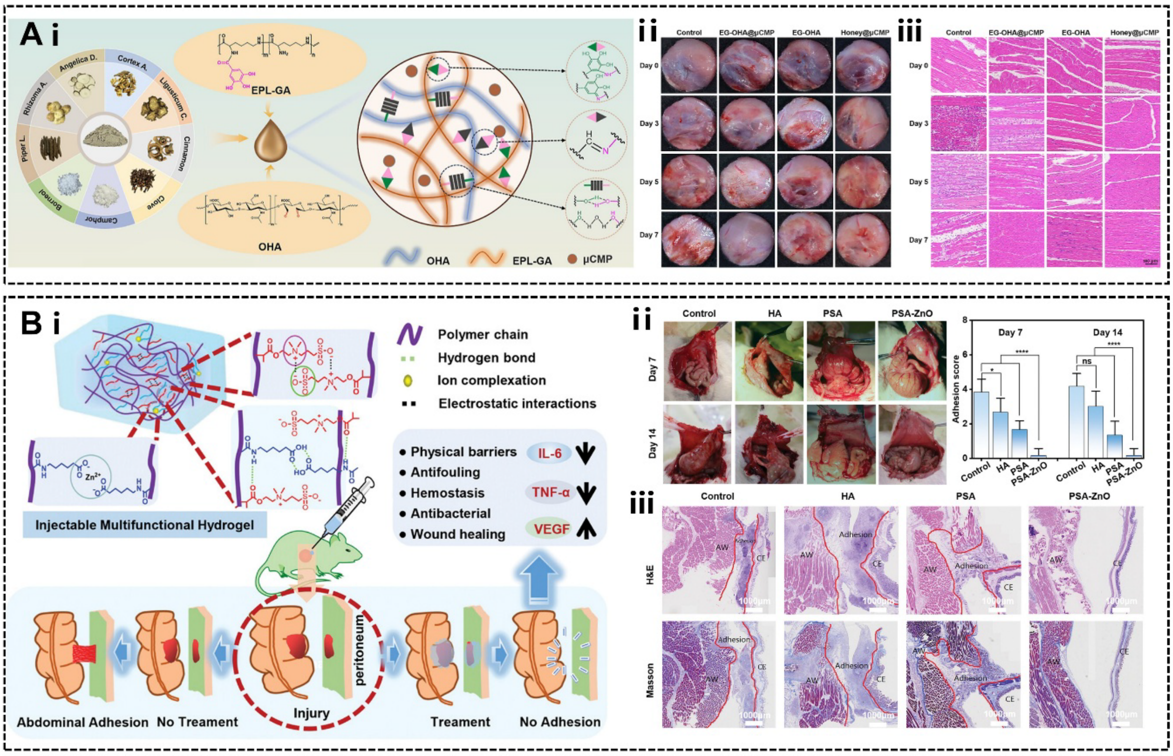


Figure 9. Applications of interfacial biomaterials for other soft tissue repair. (**A**) A hydrogel adjuvant combined with Chinese medicine external preparations for deep soft tissue injury repair. (i) Schematic showing the preparation of hydrogel. (ii) Representative photographs of the muscle tissue of the damaged area. (iii) H&E staining images of the muscle tissue. Reproduced with permission [112]. Copyright 2024, American Chemical Society. (**B**) Injectable zwitterionic hydrogel for prevention of abdominal adhesions. (i) Schematic showing the multiple intermolecular interactions of the hydrogel and its application for abdominal adhesion prevention. (ii) Photographs and scores of abdominal adhesions in different groups. (iii) H&E and Masson staining images on day 14. Reproduced under the terms of the CC BY 4.0 license [113]. Copyright 2025, the authors, published by Wiley-VCH.

Volumetric muscle loss (VML) refers to extensive and irreversible loss of skeletal muscle tissue caused by trauma or disease, resulting in permanent tissue deformity, impaired motor function, and long-term functional impairment. Although stem cell therapy shows great potential for VML repair, its therapeutic efficacy is limited by inadequate control over stem cell fate. With the aim of solving this issue, Rando et al. developed a decellularized extracellular matrix loaded with polymeric nanocapsules for sequential release of growth factors [114]. The transplanted muscle stem cells were stimulated to proliferate and differentiate by basic fibroblast growth factor and insulin-like growth factor 1, which were sequentially delivered by the bioinstructive scaffolds. In the murine VML defect model, the transplanted scaffolds restored muscle structure as well as functionality.

Peritoneum, a type of delicate soft tissue, is highly susceptible to damage during abdominal surgery, leading to postoperative adhesions. Various types of anti-adhesion barriers have been developed to prevent postoperative adhesions and promote peritoneal repair. For example, the body temperature activated in-situ gel barrier was prepared by sulfated hyaluronic acid, CS and thermal responsive polymer [115]. A wide spread to the damaged peritoneal wall was formed, followed by a significant reduction in adhesion and anti-inflammatory effect in the rat ischemic button model. Similarly, Huang et al. developed an injectable hydrogel (PSA-ZnO) containing sulfobetaine, modified aminocaproic acid (A6ACA) and ZnO nanoparticles to prevent adhesion and inhibit inflammation (Figure 9Bi) [113]. Importantly, PSA-ZnO prevented foreign body reaction through the inhibition of blood clot formation and pathological fibrin accumulation. In the side wall defect cecum abrasion model of rats, a hydration layer was established at the hydrogel surface for antifouling, while the released Zn^{2+} showed antibacterial and anti-inflammation performance, cooperatively leading to inhibited peritoneal adhesion and promoted peritoneal repair (Figure 9Bii). The H&E and Masson staining images validated that the inhibited peritoneal adhesion and promoted repair (Figure 9Biii). Moreover, a microneedle array with a double-layer structure was constructed to provide physical barriers and immune regulation [116]. Since calcium signaling plays a role in adhesion formation, poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles containing calcium channel blockers were loaded in the microneedle arrays to regulate the calcium concentration in cells and enhance anti-adhesion effects. The microneedle patch provided a promising strategy to prevent adhesion by destroying the fibrotic progress of adhesion.

5. Conclusions and Outlook

To improve the material-tissue integration and therapeutic efficacy, a variety of interfacial engineered biomaterials have been developed. In this article, we have discussed the optimization of material selection, structural design, and biofunctionalization to enhance the interfacial performances. Various regulatory strategies have been developed, such as biophysical modulation, intermolecular interaction regulation, and microenvironment tuning. As a result, the functional interfacial materials have been explored to promote diverse soft tissue repair.

With the deepening understanding of interfacial interactions and the advancement in of fabrication techniques, an increasing number of products based on interfacial engineering have been approved for clinical use. These products cover a range of soft tissue repair scenarios, including wound healing (Kerecis® Omega3 wound patch [117]), rotator cuff repair (Rotium® nanofiber scaffold [118]), nerve repair (NeuraGen® nerve conduit [119]), adhesion prevention (Seprafilm® adhesion barrier [120]), and soft tissue repair (NovoSorb® biodegradable temporizing matrix [121]), etc. Despite significant progress in engineering biomaterial interfaces, the clinical applicability of these materials remains limited. Several critical challenges, especially concerning biosafety, *in vivo* stability, and scale-up production, are yet to be addressed, which hinder their translations.

The biosafety concern of the interfacial materials is the primary issue. The toxic risks originate from not only the main materials and residual solvents, but also their degradation products. Therefore, the eco-friendly, non/low-toxic, sustainable materials and solvents should be selected, along with complete removal of monomers and residual solvents after material fabrication. Future work may consider development of fabrication methods with biocompatible solvents, such as water, ethanol, and ionic liquids, or solvent-free techniques such as melt-processing to reduce the toxicity.

The *in vivo* stability of interfacial materials poses a critical challenge, largely arising from the complexity of sophisticated engineering and advanced functionalization. For example, although mechanical actuation such as compression and tension, shows great potential in hemostasis and wound closure, their long-term effectiveness is significantly determined by their *in vivo* expansion, shrinkage and degradation features. In the complex pathological microenvironment, the engineered interfaces are susceptible to structural compromise and uncontrollable degradation due to body fluids, blood, enzymes and other biological factors. Thus, future researches may consider designing interfaces with superior biochemical resistance, and tuning the *in vivo* biodegradation profiles.

Another translational challenge is the scalable and reproducible manufacturing of complex interfacial materials. As an example, the intricate structural features, such as hierarchical porosity, Janus wettability gradients, and aligned multichannels, provide essential support for therapeutic outcomes. However, the advanced and complex designs pose huge challenges for production at scale. Future progress should be achieved by integrating artificial intelligence (AI) for process parameter screening, and real-time quality monitoring. The breakthrough in design of functionally active interfaces and the advancement of mass production systems will drive the development of next-generation of interfacial biomaterials for soft tissue repair.

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