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Design Strategies and Application Potential of Multifunctional Hydrogels for Promoting Angiogenesis

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Abstract: Hydrogels can be rationally designed as multifunctional platforms with structures and functions for various biomedical applications. Because of their excellent biochemical and mechanical properties, hydrogels have shown great potential for promoting angiogenesis, and an increasing amount of research has been devoted to designing and developing new hydrogels. However, a systematic and detailed review of hydrogels that promote angiogenesis is lacking. This paper comprehensively summarizes the design strategies of different kinds of functional hydrogels that promote angiogenesis, with anti-oxidant, substance-delivery, stimulus-responsive, self-healing, conductive, and wound-monitoring properties. The applications of hydrogels in wound healing, bone regeneration, and treatment of myocardial ischemia are discussed. Finally, future development directions of functional hydrogels promoting angiogenesis are proposed along with new strategies for the treatment of related diseases.

Keywords: Hydrogel, angiogenesis, bioactive materials, wound healing, intelligent hydrogel, review

Introduction

Angiogenesis is the formation of new blood vessels from existing blood vessels. When triggered by tissue injury, inflammation, ischemia, and hypoxia, stimulated vascular endothelial cells release matrix metalloproteinases (MMPs), which break down the basement membrane. This process activates endothelial cells as tip cells that detach from the original vessel wall and move to the surrounding matrix. The endothelial cells then proliferate, forming new vascular cavities. Finally, they inhibit cell proliferation by releasing VE-cadherin, a primary adhesion molecule, and stabilize neovascularization by recruiting pericytes.[1] This process plays a crucial role in maintaining physiological function and facilitating tissue repair and regeneration. However, under pathological conditions, such as tissue damage, infection, or the release of inflammatory factors, angiogenesis can be severely obstructed, which can lead to tissue ischemia and hinder regeneration in various systems. Poor angiogenesis poses significant threats to human health and quality of life while imposing substantial economic burdens on patients and society.[2,3]

Hydrogels consist of three-dimensional porous networks formed through the chemical or physical crosslinking of hydrophilic polymer chains. Because hydrogels exhibit exceptional biocompatibility, degradability, and tunable mechanical properties,[4,5] they are ideal for the encapsulation and delivery of bioactive molecules and cells. Recently, novel hydrogel types have emerged that can effectively promote angiogenesis by enhancing the extracellular matrix (ECM) microenvironment, facilitating drug and bioactive substance delivery, regulating vascular-related gene expression, and improving the release of angiogenesis-related factors.[6–8] Innovative hydrogels offer a promising avenue for addressing the limitations associated with traditional angiogenic methods, such as substance inactivation, poor targeting efficiency,

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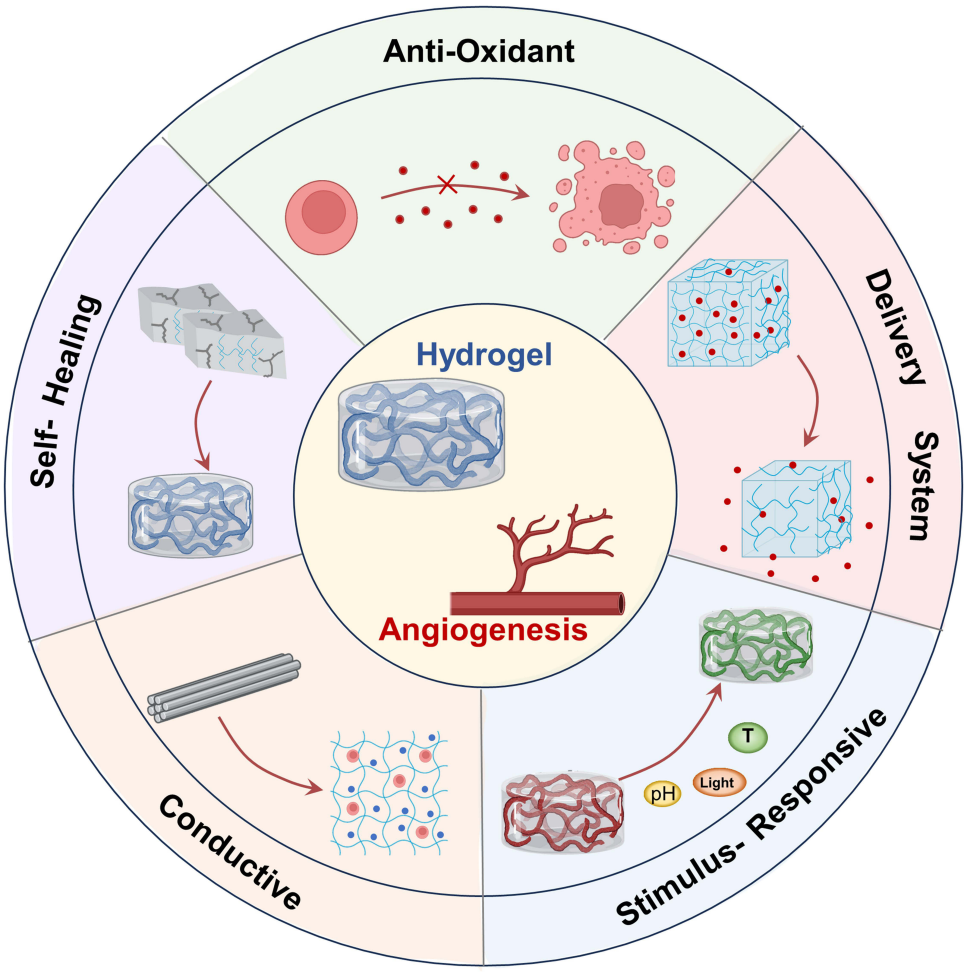
Graphical Abstract



low utilization rates, and immune reactions. Furthermore, they overcome the inherent drawbacks of conventional hydrogels, including their low strength, limited toughness, low viscosity, and insensitivity to external stimuli.[9–11]

This review provides a comprehensive summary and discussion of the design aspects of new angiogenic hydrogels with diverse functionalities, including antioxidant properties, controlled substance delivery, stimulus-responsive behavior, self-repair capabilities, conductivity, wound-monitoring abilities, and enhanced ECM functionality. Furthermore, this review describes the applications of hydrogels in wound healing bone regeneration and highlights their potential in ameliorating myocardial ischemic conditions. Finally, to address the clinical translation challenges encountered during the application of these hydrogels, we propose future research directions for the development of advanced angiogenic hydrogels.

Design of Angiogenic Hydrogels

Anti-Oxidant Hydrogels

Following injury, organs or tissues undergo a state of heightened oxidative stress, leading to the excessive production of reactive oxygen species (ROS), which impair the functionality of VECs and subsequently impede angiogenesis.[12] Previous studies have verified the ability of hydrogels to promote angiogenesis by enhancing antioxidant effects through free-radical neutralization and the regulation of oxidation-related enzyme activity.[13–15]

Various natural substances with antioxidant properties, such as polyphenols, ketones, natural pigments, vitamins, and active polysaccharides, can be incorporated into the hydrogel to prepare antioxidant hydrogels capable of scavenging free radicals and promoting angiogenesis.[14,16–18] For example, a pure puerarin hydrogel can downregulate the level of malondialdehyde and inhibit fat peroxidation owing to the reaction of its phenylcyclohydroxyl substituents with free radicals, providing a suitable microenvironment for angiogenesis.[19] To enhance the antioxidant effect of the puerarin hydrogels, a study incorporated ferulic acid into the formulation to create multiple antioxidant hydrogels. This approach promotes nicotinamide adenine dinucleotide phosphate (NADP) production, leading to improved DPPH clearance rates and reduced ROS levels while significantly enhancing angiogenesis.[20] Recent studies have found that injectable hydrogels prepared using melanin nanoparticles (NPs) extracted from cuttlefish ink and synthetic alginate exhibit a significant reduction in dihydroethidium fluorescence-labeled ROS, enhance the viability of endothelial cells, and promote an increase in vascular density.[14] However, natural antioxidants have unstable chemical properties, which reduces their bioavailability and hinders their ability to neutralize free radicals. To address this issue, using common curcumin as an example, recent studies have prepared NP microspheres, micelles, or curcumin-derived carbon point re-synthetic hydrogels to enhance their stability and sustained release.[21–23] It is worth noting that taxifolin, an excellent antioxidant, has limited bioavailability due to its poor water solubility. To address this issue, some researchers have innovatively used liposomes with a phospholipid-like bilayer structure to encapsulate taxifolin (TL), thereby preparing TL, a purified drug with high drug bioavailability, stability, sustained release, and targeting properties. By loading TL onto nanocomposite membranes, excellent antioxidant effects and enhanced angiogenesis have been achieved. These findings serve as a reference for improving the bioavailability and promoting the angiogenesis of other substances using similar methods and materials.[24] In addition, some studies have added the traditional iron ion chelator deferoxamine (DFO) to the hydrogel to improve the redox reaction caused by iron ion accumulation, thereby reducing the oxidative damage caused by the release of hydroxyl radicals, increasing the level of vascular endothelial growth factor (VEGF) in blood vessels, and significantly improving the ability to promote angiogenesis and improve tissue blood supply.[25] In addition to conventional iron ion chelators, it has been discovered that the synthesis of a three-dimensional porous hydrogel by grafting protocatechuic acid onto carboxymethyl chitosan through freeze-drying and secondary crosslinking can significantly enhance the chelation activity of iron ions, thereby reducing oxidative stress.[26] In addition, recent studies have found that the natural plant extract mulberry polysaccharide can chelate with iron ions to form polysaccharide-iron complexes, which show stronger antioxidant activity than ordinary iron chelators, can effectively remove hydroxyl radicals, and is highly safe for biological use.[27] However, there is no research report on the addition of mulberry polysaccharides to hydrogel preparations; therefore, the synthesis of mulberry polysaccharide hydrogels could be feasible for improving the local blood supply and promoting angiogenesis (Figure 1).

To date, antioxidant hydrogels have been shown to reduce oxidative stress by regulating the activity of oxidation-related enzymes. Hydrogels can be prepared by directly combining enzymes with antioxidant activity, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), with natural or synthetic polymers.[28,29] For example, a new type of heat-sensitive hydrogel loaded with SOD can maintain up to 85% SOD in vitro activity, effectively catalyze SOD anions, and improve the microenvironment for angiogenesis.[30] Other studies have prepared multifunctional glucose oxidase (GOx) and CAT nanoenzyme–chitosan hydrogels, which can decrease ROS levels via efficient enzyme cascade reactions and increase the proliferation and migration speed of endothelial cells as well as the length of tube formation.[29] However, the activity of the enzyme directly added to the hydrogel is easily affected by the external environment. To solve this problem, selenium NPs have been used in the synthesis of hydrogels to improve GPx activity, and CeO2 NPs and carotene have been used to improve SOD and CAT activities, enhance antioxidant capacity, and promote angiogenesis.[31–33] In contrast, antioxidant hydrogels can effectively mitigate elevated levels of oxidative stress by inhibiting the activity of prooxidative enzymes. For instance, a hydrogel derived from willow herb extract was shown to suppress the activities of fat oxidase and protease, thereby reducing ROS levels and consequently mitigating oxidative stress-induced damage to VECs while promoting angiogenesis.[34] Consequently, there is a significant potential for developing and applying hydrogels that modulate oxidation-related enzymes to promote angiogenesis.

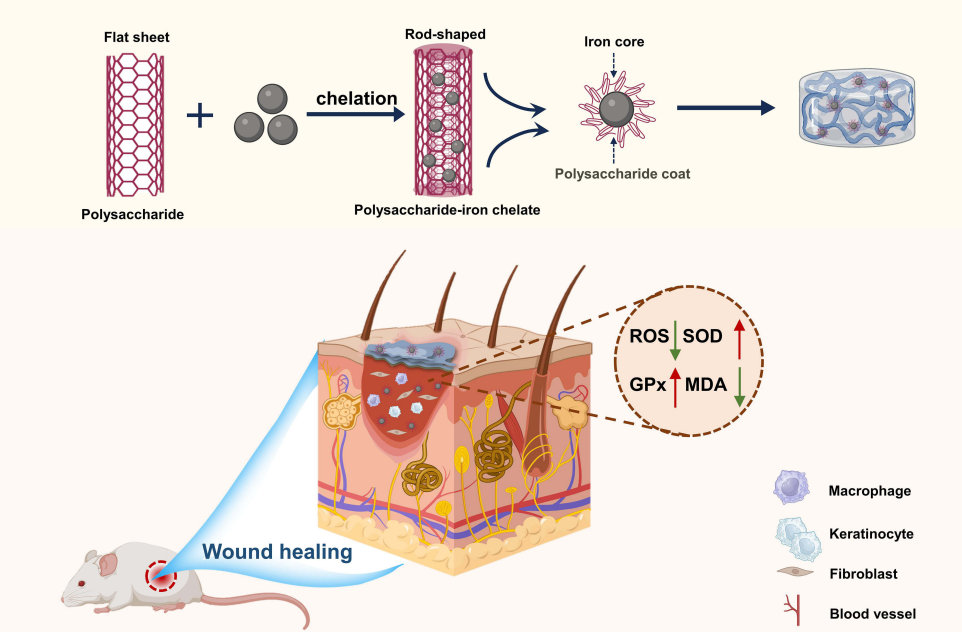


Figure 1 The polysaccharide-iron hydrogel exhibits a pronounced anti-ROS effect.

Delivery Hydrogels

Owing to their three-dimensional porous network structure, hydrogels are well-suited for the controlled delivery of substances with angiogenic effects, including cells, cytokines, exosomes, gases, genes, and proteins. Compared with the direct local administration of these substances, hydrogels can effectively maintain their activity levels while prolonging their half-life and enabling sustained release over time. Consequently, hydrogels significantly enhance the efficacy of angiogenesis.[35–39]

Hydrogels can effectively deliver specific cells, such as mesenchymal stem cells (MSCs) and VECs, along with cytokines, including VEGF, angiopoietin, and fibroblast growth factors (FGFs), to targeted sites, thereby overcoming the inherent instability and low efficacy of the cells and ultimately enhancing their capacity to promote angiogenesis.[40,41] Hydrogels serve as effective material-delivery systems that can create suitable microenvironments for cells and cytokines, relying on the careful selection of polymers, physical properties of the matrix, and microstructure of the synthetic hydrogels. Natural polymers with exceptional biocompatibility such as chitin, collagen, silk fibroin, and hyaluronic acid (HA) were chosen to encapsulate cells and cytokines because of their superior support for cell survival compared with synthetic polymers.[42] Hydrogel scaffolds with a specific strength can effectively shield cells from compression deformation and cytokine inactivation. However, the use of natural polymers alone often fails to achieve the desired mechanical strength. Therefore, researchers tend to use synthetic polymers such as poly ε-caprolactone (PCL) and gelatin methacrylate (GelMA) as internal structures, which are incorporated with natural polymers to fabricate hydrogels with high biocompatibility and adequate mechanical strength.[43,44] Furthermore, several studies have demonstrated that the porous three-dimensional architecture of 3D printed hydrogels promotes superior cell and cytokine adhesion, proliferation, and differentiation compared with two-dimensional network microenvironments, thereby achieving optimal angiogenesis-promoting effects.[45] Furthermore, the controlled release capability of hydrogels plays a pivotal role in facilitating the delivery of cells and cytokines. Currently, grid degradation–controlled release hydrogels are widely used to regulate drug-release kinetics. For instance, by modulating the pore size through grid degradation, HA hydrogels loaded with VEGF nanoparticles could sustain active VEGF release for 42 days, thereby promoting accelerated VEC migration and significantly enhancing vascular branching and density.[46]

Exosomes (Exos) exhibit the advantages of low immunogenicity, reduced immune rejection, manageable production costs, and convenient transportation and storage. Exos can modulate angiogenesis by transferring specific proteins,

genetic information, or other molecules, making them an appealing strategy for cell-free angiogenesis.[47,48] Recent studies have indicated that hydrogels are the optimal materials for Exo delivery. Hydrogels capable of delivering Exos can effectively modulate local immune responses, including Exo secretion by adipose-derived stem cells. ADSC-Exo hydrogels facilitate macrophage polarization by activating the JAK/STAT2 pathway, thereby enhancing the local inflammatory microenvironment and subsequently promoting angiogenesis.[49] Moreover, exosomal hydrogels enhanced the expression of angiogenesis-related miRNAs. Specifically, the MSC exosome hydrogel was shown to elevate the levels of VEGF-A and HIF-1α by upregulating the miRNA21/NOTCH1/DLL4 pathway, thereby promoting angiogenesis.[50] Recent studies have revealed that Exos derived from Schwann cells can facilitate the dominance of peripheral functional nerve fibers during the fibrovascular phase, thereby stimulating the release of neurotransmitters and neuropeptides (such as vasoactive intestinal peptide, substance P, CGRP, SEMA3A, and Netrin), which are intricately associated with angiogenesis promotion.[51,52] Given that a multitude of regulatory mechanisms governing Exo-mediated angiogenesis remain unexplored, there is a need to develop superior and more efficient angiogenesis-promoting Exos.

Long-term hypoxic environments, such as diabetic wounds and myocardial ischemia, pose challenges for VEC regeneration owing to the difficulty in controlling oxygen levels.[53] Hydrogels offer a novel strategy to address local hypoxia. Hydrogels can provide sustained oxygen release at specific sites, thereby improving the hypoxic microenvironment and promoting angiogenesis.[54] For instance, oxygen-containing microsphere hydrogels, hemoglobin-based oxygen carrier hydrogels, and algae-based hydrogels capable of photosynthetic oxygen production have demonstrated excellent efficacy in releasing oxygen.[55,56] In contrast, damaged tissues often exhibit low oxygen partial pressure. However, by creating a moist environment that facilitates efficient skin penetration and increases tissue oxygen partial pressure, hydrogels can effectively enhance endothelial cell proliferation, migration, and angiogenesis.[57] Therefore, the development and application of oxygen-delivering hydrogels have significant potential for promoting angiogenesis in long-term hypoxic environments.

Stimulus-Responsive Hydrogels

Stimulus-responsive hydrogels are a class of hydrogels that undergo significant physical and chemical changes in response to various environmental factors including temperature, light, electricity, ultrasound, pH, solvent composition, ionic strength, enzymes, and sugars.[58–60] These hydrogels exhibit the ability to respond to both external and internal stimuli to regulate the pathological microenvironment by releasing angiogenesis-promoting substances (Figure 2). Some commercial hydrogel dressings used for wound healing have tremendous potential to promote angiogenesis, as summarized in Table 1.

pH-responsive hydrogels release substances through Schiff bonds in acidic environments and phenyl borate cleavage in alkaline environments, thus playing an indispensable role in microenvironments with varying pH values.[62,78] Mangiferin (MF), a natural plant extract, exerts a protective effect on the vascular endothelium by enhancing SOD activity in VECs. An MF-based hydrogel incorporating phenyl borate can effectively respond to the acidic environment associated with acute infections or inflammatory wounds, ensuring the sustained release of MF and facilitating angiogenesis.[62] Previous studies have utilized the property of Mg2+ to promote ECM synthesis under acidic pH conditions for the preparation of a poly (hydroxypropyl acrylate-co-acrylic acid)-magnesium ion (poly-(HPA-co-AA)-Mg2+) gel, which induces a significant release of Mg2+ in an acidic environment and promotes ECM growth to enhance endothelial cell adhesion through integrin, providing a suitable microenvironment for VEC proliferation and migration.[79] However, the pH of chronic inflammatory wounds (such as chronic burns and vasculitis wounds) becomes alkaline, which is unfavorable for angiogenesis. To address this issue, researchers have developed alginate sulfate (AlgS-Ph) pH-responsive hydrogels loaded with FGF-2 by leveraging the ionizability of the hydroxyl group of alginate in alkaline environments. These hydrogels exhibit enhanced swelling rates under alkaline conditions and facilitate the accelerated release of FGF-2 to achieve therapeutic effects by promoting angiogenesis.[80] Furthermore, a PRP-based alginate hydrogel was engineered to respond to alkaline environments for the controlled release of growth factors, thereby recruiting stem cells and inducing angiogenesis. Hence, careful consideration should be given to selecting appropriate pH-responsive hydrogels based on different acid-base microenvironments.[81]

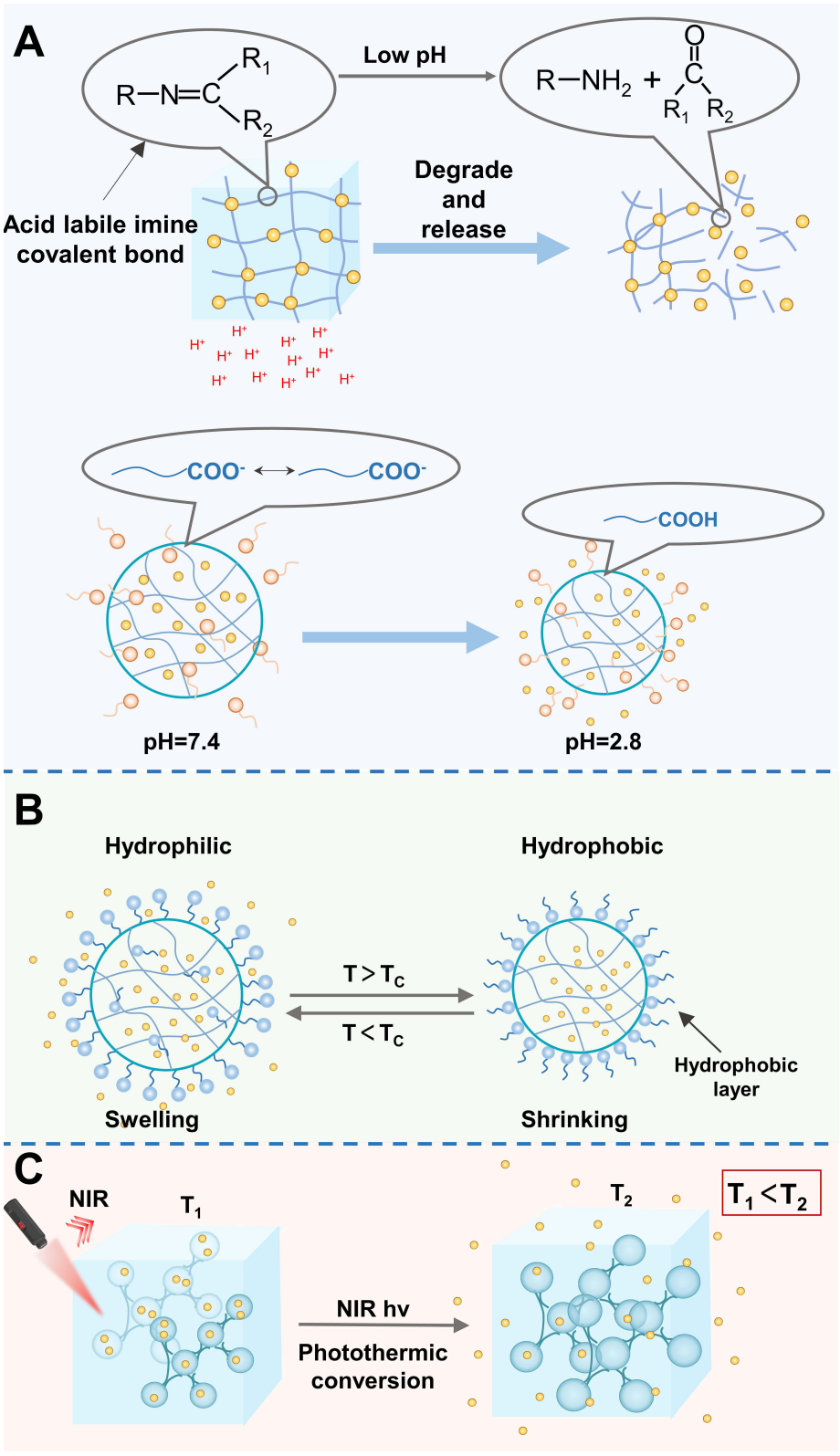


Figure 2 Sustained release principle of stimulus-responsive hydrogels: (**A**) pH-responsive hydrogels; (**B**) Temperature-responsive hydrogels; (**C**) Light-responsive hydrogels.

Table 1 Application of Different Types of Stimulus-Responsive Hydrogels

Hydrogel	Stimulator	Cargo	Effects/Results	Time of Assessment (in vivo)	References
PDAP@Alg/Cs	pH	POSS	Simultaneously accelerate intraosseous vascularization and decrease bone resorption	8 weeks	[61]
MF-Lip@PEG	pH	MF	Neovascularization-promoting and multifunctionality for the dynamic healing process of skin flap regeneration	7 days	[62]
HAMA/PAA and GOD-CP MCPS	pH	Copper peroxide	Angiogenesis-promoting and wound healing	9 days	[63]
The multifunctional fish gelatin hydrogel IOFs	pH	VEGF	Improve its angiogenesis capability and report the wound healing status	9 days	[64]
DS&MIC@MF embedded POD/CE	pH/ROS	DS, MF	Promoted angiogenesis and accelerated wound repairing	14 days	[65]
F127-COS/A-HA/COS/BA (FCAB)	Temperature / pH	DFO	Promoted migration and angiogenesis of HUVEC, enhanced therapeutic effects for diabetic foot ulcer	14 days	[66]
Poly(N-isopropylacrylamide)-based copolymer, functionalized gelation	Temperature	QK peptide	Tissue vascularization and angiogenesis	14 days	[67]
HA/Gel-R-Ag hybrid gel	Temperature	Ag^{+}	Boosted skin regeneration by inhibiting inflammation and promoting collagen deposition and angiogenesis	14 days	[68]
Que-SLNs@PCLA-HA	Temperature	Que	Angiogenesis and anti-osteoclastic differentiation	8 weeks	[69]
PCGA-b-PEG-b-PCGA (tri-PCG)	Temperature	ADSC	Longer retention of the cells and recovery from the ischemic condition	28 days	[70]
VEGF@MX-HF	NIR	VEGF	Promoting angiogenesis, decreasing inflammation, and attenuating apoptosis in skin flaps	9 days	[71]
Gel/SA/CeO2 hydrogel	NIR	CeO2NPs	Quickening the healing of diabetic wounds	14 days	[72]
Alginate and nanotubes hydrogel	NIR	Ca^{2+}	Promoting angiogenesis and collagen deposition to accelerate wound regeneration	21 days	[72]
rGO@PDA/Ag-PF127 hydrogel	NIR	Ag NPs	Eliminating bacteria, promoting collagen deposition and angiogenesis, as well as reducing inflammation	14 days	[73]
HA-PBA-FA/EN106 hydrogel	Glucose	FNIP1	Stimulated angiogenesis through FEM1b-FNIP1 axis regulation	21 days	[74]
GelMA-CPBA/EGCG hydrogel	Glucose	EGCG	Eliminate reactive oxygen species, reduce the inflammation, and promote angiogenesis	14 days	[75]
Met@CuPDA NPs/HG	pH/Glucose	Cu2+	Improving angiogenesis and accelerating the deposition of ECM and collagen	14 days	[76]
PC/GO/Met hydrogels	pH/Glucose	Metformin	Enhancing angiogenesis in a rat type II diabetic foot	21 days	[77]

Photoresponsive hydrogels consist of polymers and photoresponsive nanogroups that convert light signals into physical or chemical signals, thereby controlling the physical or chemical properties of the hydrogels. Hydrogels have been extensively used in the field of biomedicine.[82] Near-infrared (NIR) light can be converted into heat through the plasma-resonance effect of NPs by using metal- and carbon-based NPs and polymers. This process accelerates vascular expansion by increasing the local tissue temperature, subsequently triggering an increase in vascular permeability to NO and activating the Notch pathway, ultimately promoting vascular sprouting.[76,83] Studies have confirmed the exceptional photosensitivity and angiogenic capabilities of CuS NPs. Photothermal hydrogels incorporating CuS NPs were developed to achieve controlled release of Cu2+ under NIR, thereby activating HiF-1α to simulate a hypoxic microenvironment for promoting angiogenesis.[84] Furthermore, by utilizing photosensitive carbon nanomaterials such as carbon nanoenzyme sponge carbon spheres (N-SCS), which exhibit remarkable quasi-enzymatic activity towards diverse enzymes, researchers have synthesized N-SCS photothermal hydrogels that enhance peroxidase activity upon NIR irradiation. This effectively catalyzes superoxide anions, prevents excessive ROS-induced damage to VEC function, and facilitates angiogenesis.[85] Graphene quantum dots exhibit remarkable photothermal properties and can target integrin receptors.[86] Hence, a composite hydrogel comprising graphene quantum dots and integrin α3β1 can be designed for the light-triggered delivery of integrin, thereby facilitating the formation of tubular structures in endothelial cells and promoting angiogenesis.

Owing to their unique thermal-response characteristics, thermally responsive hydrogels play a crucial role in angiogenesis through their solution-gel conversion mechanism and thermally sensitive sustained release.[87] The thermally sensitive material PF-127 exhibits liquid properties at low temperatures, transforms into a hydrogel at high temperatures, and is widely employed in the preparation of hydrogels. For instance, by utilizing the solution-gel conversion mechanism, a hydrogel composed of PF-127 and MSC-exos was injected into diabetic foot wounds to achieve an optimal fit with the wound site.[88] The biocompatibility, injectability, and high drug-loading rate of hydrogels made from heat-sensitive materials such as polyethylene glycol (PEG) and poly(lactic-co-glycolic acid) (PLGA) have been reported. Upon gelation, PLGA–PEG–PLGA hydrogels loaded with VEGF exhibited enhanced local adhesion and prolonged concentration and retention time of VEGF at the site, effectively stimulating endothelial cell proliferation and migration.[89] Furthermore, an injectable heat-sensitive DFO–gelatin microsphere hydrogel was developed to continuously release DFO through heat-responsive swelling at femoral defect sites, significantly enhancing endothelial cell proliferation and migration while promoting blood-vessel formation.[90] Therefore, heat-sensitive hydrogels have promising applications in the promotion of angiogenesis.

In recent years, ultrasound has emerged as a promising modality for promoting angiogenesis owing to its vasodilatory effect, ability to enhance blood circulation, and stimulation of VEC regeneration.[91] Ultrasound-responsive hydrogels have attracted considerable attention in the medical field. For instance, researchers have developed ultrasonic hydrogels using SiO2 NPs as acoustic crosslinking agents for biosensing applications aimed at wound monitoring.[92] Additionally, recent studies have shown that magnetic nanoparticle hydrogels can undergo mechanical deformation under the influence of an external magnetic field, releasing specified substances and exhibiting great potential for angiogenesis promotion.[93] However, ultrasound and magnetic hydrogels have not been developed for or applied to angiogenesis; therefore, we propose the design of ultrasound/magnetic hydrogels loaded with angiogenic substances such as VEGF and FGF for use in localized ischemic areas. For example, gold cluster–HA ultrasound hydrogels loaded with VEGF may be used to achieve ultrasound sensing in biological systems. The responsive, sustained release of VEGF may be realized while monitoring the wound, thereby achieving an ideal angiogenic effect. Similarly, the design of magnetic nanoparticle hydrogels loaded with VEGF may be achieved by applying an external magnetic force to realize mechanical deformation and release the aggregated substance, thereby enhancing angiogenesis.[94]

Conductive Hydrogels

Using electrically active substances such as carbon nanomaterials, conducting polymers, or metal-based materials incorporated into polymer matrices, water-based gels with unique electrical properties can be prepared. These gels can be electrically stimulated to mimic endogenous electric fields, thereby regulating cell behavior during angiogenesis, such as endothelial cell proliferation and directed migration and tube formation. This technique can be used to optimize the

distribution of cell factors, enhance cell-to-cell signaling and electrical coupling, and stimulate neural and vascular regeneration pathways and neurotransmitter release, offering great advantages in promoting angiogenesis.[95–98]

Microelectric fields in damaged tissues can guide the directional migration of VECs and augmentation of the microelectric field can effectively promote angiogenesis. Previous studies demonstrated that a conductive hydrogel prepared by incorporating gold nanowires into alginate and subsequently crosslinking it with calcium ions can faithfully mimic the electroactive physiological microenvironment of tissues. This hydrogel enhanced local endogenous electric fields and stimulated directed migration and regeneration of VECs, thereby promoting local angiogenesis.[99] Furthermore, tissue damage impedes the transmission of electrical signals between neighboring cells. Conductive hydrogels, such as tetraaniline (TA) NP-modified hydrogels, exhibit conductivities comparable to those of the natural myocardium. The composite conductive hydrogels synthesized with HIF-1α stabilizer DPCA can augment the expression of myocardial connective protein 43 (Cx43), thereby enhancing intercellular signal communication and electrical coupling, upregulating the expression level of HIF-1α, and promoting angiogenesis.[100] In addition to augmenting the endogenous electric field and intercellular communication, hydrogels synthesized using conductive materials with electron-transfer abilities such as polyaniline (PANI), TA, and polypyrrole exhibit distinctive electrochemical redox properties. For instance, conductive hydrogels comprising PANI-grafted chitosan and polyester effectively scavenge excess free radicals, thereby attaining excellent antioxidant performance and enhancing angiogenesis.[101,102] Recently, the potential of conductive hydrogels in facilitating neurovascular regeneration and neurotransmitter release has garnered significant attention. Conductive hydrogels synthesized from gelatin, methyl acrylate, chondroitin sulfate oxide, and polypyrrole can enhance nerve cell migration and axon growth by augmenting cellular Ca^{2+} influx under endogenous electric fields. Additionally, they upregulate the PI3K/AKT and MEK/ERK pathways to promote the proliferation and migration of VECs.[103] Previous studies demonstrated that the incorporation of Mg-modified black phosphorus into methacrylic gelatin to prepare conductive hydrogels can augment the endogenous electric field, thereby enhancing Schwann cell migration and secretion. Furthermore, this material promotes nerve synapse growth and facilitates the release of neurotransmitters and neuropeptides such as vasoactive intestinal peptide, substance P, CGRP, and Sema3A, which are closely associated with angiogenesis promotion.[104]

In addition, conductive hydrogels exhibit electrical stimulation response capabilities. Bone morphogenetic protein (BMP) has been found to promote angiogenesis. Studies have been conducted on the preparation of GO/PVP-PCL conductive hydrogels loaded with BMP, aiming to enhance their electrical conductivity and bioactivity. Under the influence of an external electric field, the concentration of released BMP increases because of the periodic lattice vibration caused by oscillating eddy currents, which is dependent on the intensity of the electric field. Consequently, this phenomenon effectively facilitates angiogenesis.[105] However, the application of this method is hindered by its complex procedure for applying an electric field. Therefore, in recent years, there has been growing interest in stimulus-responsive conductive hydrogels based on dynamic wound environments. Some studies have employed flexible electric patches composed of conductive hydrogels synthesized from silver nanowires and methacrylic acid alginate, thereby enhancing the local electric field effect through the conductivity of the silver nanowires. In future research, it is envisioned that connecting silver nanowires to microelectric-field devices could enable the remote control of the strength of the electric field, thereby regulating the release of electrical stimulants and promoting angiogenesis.[106] To further investigate the miniaturization of electrical stimulation devices, researchers have developed a flexible miniature Zn-MnO_2 (mZMB) battery-based wound dressing for wound management.[98] They demonstrated that the use of a ring electric field is more advantageous in promoting cell migration and angiogenesis compared to a traditional parallel electric field. In the future, the combination of these flexible microbatteries with hydrogels and annular electric fields holds great promise for advancing angiogenesis research.

Self-Healing Hydrogels

Common hydrogels exposed to the external environment are susceptible to fracturing, which compromises their angiogenic performance. Hence, ensuring the structural integrity of therapeutic hydrogels is of paramount importance. Self-healing hydrogels are regarded as intelligent materials capable of autonomously repairing both functional and structural damage and exhibit significant potential for promoting angiogenesis.[107,108]

Physical self-healing hydrogels achieve self-healing through the dynamic formation of non-covalent interactions, such as hydrogen bonding, π-π interactions, ion interactions, host–guest interactions, and metal coordination bonding.[109] Some researchers have utilized self-healing hydrogels containing acryloyl-6-aminohexanoic acid (AA) and AA-g-N-hydroxysuccinimide (AA-NHS), which exploit the terminal carboxyl group of AA to establish hydrogen bonds with other terminal carboxyl or amide groups within the hydrogel. This approach enables rapid self-healing of the hydrogel, facilitating prompt adhesion and hemostasis at the damaged site while enhancing α-smooth muscle actin expression levels, type-I collagen production, and vascular density.[110] Melamine with a π-π conjugated ring as the core can be crosslinked with thiol-modified hyaluronic acid (HA-SH) and GO to form hydrogels. The incorporation of π-π interaction enables self-repair while enhancing polymer conductivity, thereby enhancing the promotion of angiogenesis.[111] Recently, a novel self-healing conductive hydrogel was designed by crosslinking four-armed SH-PEG with Ag and coordinating Ag–S to produce a dynamic PEG hydrogel.[112] In addition to achieving self-repair through dynamic metal coordination bonds, these hydrogels provide a stable three-dimensional matrix for loaded substances, effectively enhancing VEGF expression and stimulating the proliferation of VECs and angiogenesis. Recent studies have revealed that self-healing hydrogels based on the host–guest interaction between N-isopropylacrylamide and cyclodextrin, amantadine, or silk fibroin exhibit NIR-responsive substance release in addition to intrinsic self-repair; however, their potential applications in angiogenesis remain unexplored.[113] Therefore, we intend to design N-isopropylacrylamide–cyclodextrin self-healing hydrogels loaded with angiogenesis-related substances to promote angiogenesis in our future research.

Chemical self-healing hydrogels with superior mechanical stability are now more widely used than physical self-healing hydrogels, as they form reconstruction networks through dynamic covalent bonds such as amide, disulfide, imine, and Diels–Alder reversible covalent bonds.[114] For instance, the incorporation of dynamic imine bonds between GelMA and dextran oxide imparts self-repairing capability and shear-thinning behavior to GMO hydrogels loaded with angiogenic peptides, thereby exhibiting remarkable angiogenic potential.[115] However, the strong adhesion of self-healing hydrogels to body tissues makes their replacement and removal challenging. To address this issue, soluble self-healing hydrogels have been developed by condensing the amine groups of water-soluble CMC with the aldehyde groups of rigid rod-shaped aldehyde-modified cellulose nanocrystals (DACNC) to form imine bonds. The hydrogel can be dissolved using glycine as a competitor for CMC and the aldehyde group on DACNC, thereby avoiding pain and wound damage caused by replacing or removing the hydrogel.[116] The construction of a self-healing hydrogel incorporating insulin and fibroblasts was achieved through the formation of phenyl borate bonds to treat diabetic wounds. Leveraging the pH-dependent nature of dynamic phenyl borate bonds, this hydrogel demonstrated both self-repair capabilities and sustained release of insulin and fibroblasts under low pH conditions, effectively promoting angiogenesis.[117] Furthermore, using alpha-lipoic acid as an exceptional antioxidant agent with dynamic disulfide bond properties, researchers have successfully developed antioxidant self-healing hydrogels via heat- and concentration-induced ring-opening reactions involving alpha-lipoic acid and NaHCO polymerization.[118] This advancement has significantly enhanced the ability of hydrogels to promote angiogenesis. Consequently, chemical self-healing hydrogels have tremendous potential to facilitate angiogenesis.

In recent years, poly-dopamine (PDA) has emerged as a significant angiogenic agent. By leveraging the coexistence of hydrogen and dynamic imine bonds between PDA and polyacrylamide, we successfully developed an exceptionally robust self-healing hydrogel with tissue adhesion properties and remarkable cell affinity. This hydrogel exhibited an impressive extensibility, reaching up to eight times its initial length, while also achieving fragmented healing.[119] MXenes are a novel class of non-enzymatic antioxidant nanomaterials and extensive research has demonstrated that the antioxidant capabilities of MXenes can be further enhanced through PDA coatings.[120] Based on these findings, we propose that the design of a PDA-coated MXene/polyacrylamide composite be investigated to develop an antioxidant self-healing hydrogel specifically tailored to promote angiogenesis in tissues subjected to frequent activities and friction.

Application of Angiogenic Hydrogels

Figure 3 summarizes the applications of angiogenic hydrogels, which are discussed in the following sections in detail.

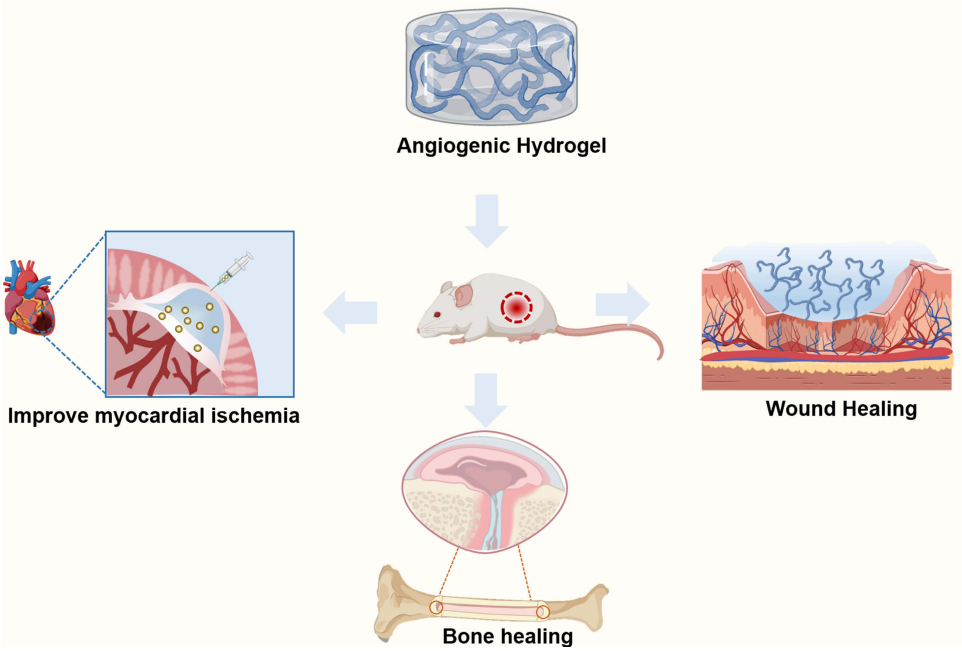


Figure 3 Application of hydrogels in promoting angiogenesis.

Skin-Wound Healing

Skin-wound healing is a complex phenomenon involving hemostasis, inflammation, proliferation, and remodeling. Angiogenesis plays a pivotal role in the cell proliferative phase.[5,121] However, variations in environmental parameters such as ROS, temperature, pH, glucose concentration, and oxygen availability can significantly influence angiogenesis.[122] Consequently, there is considerable interest in the development of novel angiogenic hydrogels with responsive or monitoring capabilities.[123]

Excessive ROS in wounds can impair the functionality of the VECs, thereby impeding angiogenesis. The hydrogels for skin-wound applications are ROS responsive, and the timely response to elevated ROS levels in the wound microenvironment and their elimination are focal points of research.[12] For instance, the incorporation of natural antioxidants such as puerarin, curcumin, and ferulic acid into the hydrogel enables the neutralization of ROS within the wound site, consequently reducing oxidative stress and promoting angiogenesis.[14–16] Recently, a polyvinyl alcohol-based hydrogel crosslinked with amphoteric phenylboronic acid was developed for the real-time monitoring of ROS during low-temperature cell preservation. The borate bond within this hydrogel undergoes oxidation by ROS, leading to slight swelling and resulting in changes in the overall gel resistance. These resistance variations reflect the ROS content through an externally connected power supply and display system.[124] Inspired by this concept, a polyvinyl alcohol-based hydrogel crosslinked with amphoteric phenylboronic acid that incorporates natural antioxidants may be realized. This novel formulation will possess both ROS-monitoring capabilities and an efficient ability to remove ROS, while providing valuable insights for treatment plan adjustments.

In the process of wound healing, both temperature and pH value exert a certain impact on angiogenesis at the wound surface. Monitoring the temperature and pH value of the wound surface can provide valuable insights into the microenvironment of the wound.[62] For instance, some studies have incorporated a microenvironment temperature-sensing chip into a prepolymer solution to fabricate biomimetic nanofiber membranes. By employing in situ UV crosslinking, a microenvironment sensor and gelatin methyl acrylate (GelMA + β-cd) hydrogel containing β-cyclodextrin were prepared. This enables the real-time monitoring of the wound surface temperature, facilitating the evaluation of wound inflammation when connected to image acquisition equipment to enable informed treatment decisions.[125] Although sensor monitoring is convenient for clinical wound temperature monitoring, it does not achieve synchronous drug delivery. Consequently, researchers have dedicated efforts to developing hydrogels capable of

releasing responsive substances during wound monitoring. For instance, N-acryloylglycine and 1-vinyl-1,2,4-triazole mixed supramolecular hydrogels have been employed as opal scaffolds, whereas temperature-responsive polyisopropyl acrylamide hydrogels loaded with VEGF serve as filling materials for temperature-responsive hydrogels. A novel pH-responsive opal film patch (IOF) based on a photocrosslinked fish gelatin hydrogel was constructed using fish gelatin methyl acrylate, CS, and pH-sensitive polyacrylic acid (PAA). The distinctive structural color of these two hydrogels undergoes a transition from red to green upon increasing the temperature and pH levels, facilitating the release of VEGF, and promoting angiogenesis and wound monitoring.[64,126] However, this type of hydrogel cannot transmit visual data to remote electronic devices. Recently, researchers have shown great interest in NIR fluorescence probes owing to their exceptional imaging capabilities. A multifunctional chitosan hydrogel based on a polymerized ionic liquid and a NIR fluorescent probe was investigated, enabling the real-time visualization of wound pH values through NIR fluorescence imaging in vivo, while also exhibiting pH-responsive continuous drug release.[127] This novel approach prevents the transition from acute to chronic wounds and promptly responds to changes in the microenvironment of chronic wounds, offering a new strategy for enhancing wound healing and facilitating real-time monitoring of skin recovery.

In the context of diabetic wounds, elevated glucose levels impede angiogenesis, necessitating the monitoring of wound glucose concentrations.[128] Several studies integrated insulin-, fibroblast-, and glucose-responsive hydrogels into a comprehensive approach. These hydrogels respond to the hyperglycemic wound environment by releasing insulin to enhance the microenvironment, and fibroblasts to stimulate angiogenesis. This multifaceted strategy significantly surpasses conventional drugs and cell therapies for promoting wound healing.[129] To enable the real-time monitoring of wound glucose concentrations, researchers have developed an enzyme electrochemical microfluidic biosensor for precise detection by incorporating GOx within the hydrogel matrix. Additionally, nonenzymatic electrochemical and optical methods have been employed for the accurate measurement of glucose levels in hydrogels. These versatile wound dressings hold great potential for treating chronic wounds and guiding the clinical management of diabetic wounds.[130,131]

Bone-Tissue Regeneration

Bone tissue is highly vascularized, and during the process of bone regeneration, osteogenic and angiogenic cells collaborate. The promotion of angiogenesis is advantageous for bone regeneration.[132] Hydrogels are increasingly employed in the field of bone-regeneration tissue engineering because of their biocompatibility, resemblance to ECM characteristics, distinctive swelling properties, easy accessibility, and enhanced ability to promote angiogenesis compared with biological materials such as simulated cement and scaffolds.[133]

Currently, conventional approaches to promoting angiogenesis in bone tissue rely on the utilization of diverse growth factors and stem cells. Hydrogels, which are water-soluble materials with a 3D network structure, offer superior alternatives for direct MSC applications. Researchers have successfully developed chitosan hydrogels loaded with VEGF and collagen hydrogels loaded with MSCs, which effectively enhanced the loading efficiency and viability of VEGF, while improving the proliferation, adhesion, and differentiation characteristics of MSCs. These advances have significantly increased the efficacy of angiogenesis.[134] Based on this premise, the incorporation of mineral ions (eg, iron, copper, zinc, calcium, and magnesium) that facilitate angiogenesis can augment the osteogenic efficacy of hydrogels.[135] For instance, 3D hydrogels composed of hydroxyapatite/MgO nanocrystals have demonstrated the ability to upregulate osteogenic gene expression, stimulate vascular regeneration, and effectively promote bone-tissue repair.[136] In addition to achieving efficient material loading, bone regeneration is a lengthy process that requires the controlled sustained release of materials. Consequently, hydrogels responsive to light, temperature, and electrical stimulation have been extensively developed and applied.[137] Owing to the irregularity of fracture sites, topical agents and dressings often fail to completely cover the bone defect surface, thereby affecting drug efficacy. The unique solution–gel conversion mechanism of thermally responsive hydrogels enables complete coverage at the injection site within the bone defect area while facilitating adhesion and fixation of the fracture site. Studies have utilized MgO NPs infused with phosphocreatine-functionalized chitosan to form injectable hydrogels that respond to local temperature increases after injection at the bone defect site, thus achieving sustained drug release.[136] Furthermore, collagen hydrogels comprising carbon nanoparticles or cadmium selenium quantum dots (CdSe QDs) are photosensitive, enabling the sustained release of substances under NIR irradiation, while the hardness of the NPs and QDs augment the mechanical properties of the hydrogel, providing

structural support for bone tissue. These materials accelerated the differentiation of bovine MSCs and enhanced angiogenesis by regulating the TGF-β/SMAD signaling pathway, thereby promoting bone regeneration in defects.[138,139] In addition to thermal and light responsivity, electrical stimulation-responsive hydrogels, such as GO/PVP-PCL loaded with BMP, can augment local endogenous electric fields and induce the directional migration of VECs. Moreover, the concentration of BMP released increases in an intensity-dependent manner under the influence of electric fields, thereby promoting angiogenesis and osteogenesis.[105]

Excessive free radicals within the inflammatory milieu of bone defects can impede angiogenesis by damaging cellular membranes and proteins, thereby necessitating the application of anti-free-radical hydrogels to regulate this environment. For instance, HA can be crosslinked with manganese carbonyl (MnCO) and BMP-2 to form hydrogels that exhibit decomposition properties and release Mn2+, CO, and BMP-2 upon binding with free radicals. This mechanism effectively promotes angiogenesis and osteogenesis.[140] In addition to attenuating free radicals, the modulation of macrophage polarization is a commonly employed strategy for regulating inflammation. In the field of bone-regeneration tissue engineering, hydrogels based on mineralized materials such as hydroxyapatite, fluorapatite, and bioactive glass are frequently used. For instance, PCL/nanohydroxyapatite hydrogel scaffolds and bioglass hydrogels have demonstrated the ability to induce M1-to-M2 macrophage polarization, ameliorate the inflammatory microenvironment, and facilitate bone defect regeneration.[141] However, these mineralized materials possess potential cytotoxicity and macrophages exhibit high sensitivity towards them, which can result in the persistent activation of M1 macrophages and the initiation of uncontrolled inflammatory responses. Consequently, contemporary tissue engineering has primarily focused on developing biomaterials with reduced sensitivity to regulate immune responses by modulating macrophage polarization from M1 to M2.[142] As novel RNA-active materials, imRNAs exhibit reduced cytotoxicity and enhanced immunomodulatory properties compared to mineralized materials. Previous studies have demonstrated that imRNAs stabilize calcium phosphate ion clusters, resulting in the formation of imRNA-ACP, which can modulate macrophage polarization from M1 to M2 via the JAK2/STAT3 signaling pathway and aid collagen fiber mineralization. However, there are currently no imRNA-based hydrogels for bone regeneration.[143] Motivated by this gap in the knowledge, we intend to design imRNA-ACP RNA-active hydrogels capable of regulating the immune microenvironment while promoting collagen fiber mineralization, thereby offering promising applications in the field of bone formation.

Improved Myocardial Ischemia

Myocardial ischemia can lead to various cardiovascular disorders including atherosclerosis, myocardial infarction, and heart failure. Currently, clinical treatment predominantly relies on drug administration and the use of other therapeutic agents (eg, stem cells and growth factors).[144,145] However, drug therapy encounters challenges such as limited targeting ability and susceptibility to inactivation, which significantly diminish the efficacy of the drugs. Therefore, the development of novel materials that enhance the management of myocardial ischemia is imperative. Novel proangiogenic hydrogels offer substantial advantages in ameliorating myocardial ischemia owing to their injectability, self-healing capability, conductivity, and sustained drug-release properties.[146]

Minimally invasive injectable hydrogels have demonstrated remarkable efficacy in the treatment of cardiovascular diseases. Among the natural hydrogels, ECM-based injectable hydrogels are particularly noteworthy. For instance, silk-based hydrogels containing cECM (ECM derived from cardiac tissue) were injected into the ischemic site of the myocardium and formed a network structure gel state through heat induction. This approach provides a biocompatible microenvironment for angiogenesis.[147] However, the complex preparation process involved in extracting the ECM poses challenges such as limited extraction methods and high costs. Consequently, current efforts to develop natural injectable hydrogels have focused on alternatives, such as chitosan, HA, sodium alginate, and silk fibroin hydrogels, that possess characteristics resembling those of the ECM. These substitutes offer advantages such as high availability, affordability, and ECM-like properties.[148] Additionally, the beating of the heart may lead to fracture or shedding of the encapsulated hydrogel, which hinders the effective repair of myocardial ischemia. To address this concern, injectable self-healing hydrogels must be applied to the heart. For instance, a chemically self-healing hydrogel formed through a Schiff base reaction between xanthan gum and gelatin exhibited excellent ductility and rapid fracture repair capabilities, thereby effectively preserving both the morphology and functionality of the hydrogel.[149]

When myocardial hypoxia and ischemia occur, elevated levels of ROS can induce the apoptosis or necrosis of myocardial cells and VECs. Hydrogels with ROS scavenging capabilities, such as PANI-grafted chitosan–polyester and N-isopropylacrylamide–PEG–methyl-methacrylate copolymer hydrogels, effectively scavenge excessive ROS through electron transfer. This scavenging action not only protects the myocardium from oxidative damage but also enhances angiogenesis, thereby improving myocardial ischemia.[101] Furthermore, following myocardial ischemia-reperfusion (I/R), an imbalance in ROS/NO levels and the release of damage-associated molecular patterns can lead to increased ROS production, which negatively affects angiogenesis. To address this issue, borate-protected ammonium dibenzo-p-nitroso (CS-B-NO)-modified chitosan injectable hydrogels were developed. These hydrogels are capable of releasing NO in response to ROS stimulation and regulate the ROS/NO ratio after I/R injury. Thus, these hydrogels inhibit oxidative stress and inflammatory responses induced by I/R injury and promote angiogenesis.[150] In contrast, damage-associated molecular patterns activate TLR4 to induce NADPH oxidase expression in immune cells, thereby facilitating ROS production. To disrupt this pathway, we designed and prepared an injectable hydrogel system composed of epigallocatechin-3-gallate (EGCG) and Rhein hydrogel, which effectively impedes the detrimental cycle of ROS through ROS clearance and TLR4 inhibition, promoting angiogenesis, and ameliorating myocardial ischemia.[151]

Myocardial infarction results in extensive myocardial cell death and collagen fiber deposition, leading to impaired electrical signal conduction in the myocardium, which subsequently causes cardiac systolic and diastolic dysfunction as well as arrhythmia. Previous studies have utilized the gelatin-grafted polypyrrole as a conductive material to fabricate highly water-soluble hydrogels with excellent biocompatibility and conductivity that matches that of the heart. These hydrogels effectively reduce resistivity in myocardial fibrous tissue, increase the conduction velocity within myocardial tissue, attenuate ventricular remodeling, inhibit infarct expansion, and facilitate the regeneration of myocardial blood vessels.[100,101] Furthermore, composite conductive hydrogels were developed by incorporating tetraphenylamine NP-modified hydrogels with 1,4-dihydrophenylthiourea-4-keto-3-carboxylic acid.[97] This approach improves the expression of Cx43 to enhance intercellular signal communication while upregulating HIF-1α factor expression levels. Consequently, it promotes the proliferation and migration of ECM proteins, ultimately facilitating angiogenesis.

Due to the insufficient cardiac revascularization effect of a single natural or synthetic hydrogel, there is an urgent need for the development of injectable hydrogels with enhanced intervention capabilities for clinical treatment. For example, composite injectable hydrogels that incorporate NPs, drugs, and stem cells have been prepared.[152] Another study proposed an injectable hydrogel based on nanodiamond that exploits the effective interaction between VEGF and chemical functional groups on the nanodiamond surface to achieve sustained release of VEGF, thereby promoting vascular repair.[153] Most current stem-cell hydrogels face challenges related to the low migration rates of stem cells across the endothelium towards injured tissue, which significantly impacts their efficacy. Recent studies have designed biomimetic hydrogels combined with stem cell-homing factor (SDF-1) to treat chronic myocardial infarction. Compared with simple stem-cell hydrogels, this approach improves the migration rate of stem cells and greatly enhances myocardial vascular repair and regeneration.[154]

Because the heart is an internal organ, it cannot be directly observed with the naked eye, unlike skin wounds. Previous studies on efficacy have often relied on dissection analysis of isolated hearts in animal experiments, utilization of in vitro cardiac myocytes to induce structural color changes after hydrogel application, and in vitro bioadhesive ultrasound hydrogel imaging.[155] Nevertheless, the real-time monitoring of living hearts remains a challenging task. Effective real-time monitoring of cardiac-related indicators would facilitate the optimization of treatment strategies. Recently, researchers have developed a bionic wrinkle-enhanced adaptive nanoclay interlocking soft-strain sensor based on a high-tensile elastic ionic conductive hydrogel.[156] This hydrogel enables the sensing of layered ordered structures and has been demonstrated to accurately localize myocardial infarction areas by detecting early-stage electrophysiological changes after implantation. If the controlled release of proangiogenic substances, such as VEGF, could be integrated into this hydrogel, it could potentially serve as a novel strategy for the real-time monitoring of cardiac pathological alterations and improvement of myocardial ischemia.

The application of some angiogenesis hydrogels in wound healing, bone regeneration, and improvement of myocardial ischemia is summarized in Table 2.

Table 2 Applications of Angiogenesis Hydrogels

Application	Hydrogel	Effects/Results	Time of Assessment (in vivo)	Reference
Wound healing	(PDLLA-PEG-PDLLA) hydrogel (PLEL)-based wound dressing	Improved diabetic wound healing, decreased ROS production, angiogenesis promotion, and reduced IL-6 and TNF-α levels within diabetic wounds	28 days	[15]
	Puerarin/ferulic acid/polydopamine incorporated hydrogel	Improved activity of superoxide dismutase and glutathione peroxidase, reduced levels of ROS and malondialdehyde; promotion of tissue regeneration and collagen accumulation	15 days	[16]
	GelMA + β-cd UV-crosslinked hydrogel	Increased VEGF expression through HIF-1α to promote neovascularization and wound healing; monitoring changes in the wound microenvironment in real time	7 days	[125]
	N-acryloyl glycinamide (NAGA) and 1-vinyl-1,2,4-triazole (VTZ) mixed supramolecular hydrogel	Color-sensing behavior suitable for wound monitoring and management as well as guiding clinical treatment	10 days	[126]
	Novel inverse opal film (IOF) patch based on a photo-crosslinking fish gelatin hydrogel	Monitoring of the wound healing status through real-time structural color or reflectance spectra variations.	9 days	[64]
	PIL-CS hydrogel	Real-time visualization of wound pH through in vivo NIR fluorescent imaging and pH-responsive sustained drug release	28 days	[127]
	Phenylboronic acid-hydrogels	Long-term, remote read-out of glucose	45 days	[129]
Bone regeneration	GelMA/TCS/POSS-Mg hydrogels	The introduction of POSS and Mg^{2+} stimulates the osteogenic differentiation of BMSCs and promotes angiogenesis	14 days	[134]
	CSMP-MgO injectable hydrogels	Regulated Mg^{2+} release in a stable and sustained manner; promotion of new bone formation	21 days	[135]
	Collagen–genipin–quantum dot (CGQ) composite hydrogels	Simultaneous triggering of photodynamic provocation (PDP) to produce ROS; promotion of BMSC proliferation, induced cartilage-specific gene expression	21 days	[139]
	Graphene oxide/polyvinylpyrrolidone hydrogel	The concentration of released BMP increases in an intensity-dependent manner under the influence of electric fields	5 days	[105]
	Osteoimmunity-regulating biomimetically hierarchical scaffold	Activation of the hypoxia-inducible factor-1α pathway; Mn^{2+} and DFO@PCL NP further promote angiogenesis	28 days	[140]
	PCL/nHA@GRgel	Increased percentage of anti-inflammatory M2 macrophages and osteoblasts, and high-level vascularization	12 weeks	[141]
Treatment of myocardial ischemia	Melanin nanoparticles (MNPs)/alginate (Alg) hydrogels	Elimination of ROS to reduce the impact of oxidative stress injury on cardiomyocytes; regulation of the inflammatory MI microenvironment and promotion of angiogenesis	28 days	[14]
	Cardiac extracellular-matrix-derived hydrogel	Both human cardiomyocytes and mesenchymal stem cells could maintain high cell viability	-	[147]
	Self-healing OGGP3 (3 wt% GP) hydrogel	Reduction of the electrical resistivity of myocardial fibrous tissue and increased conduction velocity of the myocardial tissue	4 weeks	[149]
	Alg-P-AAV hydrogel	Continuously VEGF expression, which significantly promoted the proliferation, migration, and tube formation of endothelial cells	28 days	[101]
	Injectable chitosan-based hydrogel (CS-B-NO)	Modulation of the ROS/NO disequilibrium after ischemia/reperfusion (I/R) injury	21 days	[150]
	EGCG@Rh-gel	Efficient blocking of the ROS-inflammation cycle by ROS scavenging and TLR4 inhibition	28 days	[151]
	SDF-1α-encapsulated puerarin (PUE) hydrogel	Enhanced endogenous stem cell homing, simultaneously polarization of the recruited monocyte/macrophages into a repairing phenotype	28 days	[154]
	Nanoclay-composite hydrogel	Real-time monitoring of pathological changes in heart disease.	28 days	[156]

Limitations and Prospects

As promising materials for promoting angiogenesis, the incorporation of diverse proangiogenic agents represents a key design strategy for hydrogels. In recent years, anti-inflammatory and antioxidant drugs, extracellular matrices, exosomes, and nanomaterials such as nanoclay have attracted widespread attention.[11] Such hydrogels have been fully developed and applied in clinical practice. With the proliferation of gene therapy, hydrogels may be used as carriers of gene fragments with angiogenic effects to achieve precise and efficient treatment.[157] In addition, improving the loading rate of these hydrogels may serve to improve the promotion of angiogenesis. This may be achieved by optimizing the pore structure of the hydrogel, enhancing the force between the hydrogel and loading material, selecting appropriate loading materials and morphologies, and developing and adopting more advanced preparation techniques.[158] However, while striving to enhance the loading efficiency, excessive addition of substances may compromise the mechanical properties of the hydrogels, potentially resulting in deformation damage and functional loss during their application.[159] To address this issue and increase the mechanical strength of hydrogels, current investigations are focused on leveraging natural and synthetic polymers, integrating nanomaterials, and optimizing structural designs. The energy dissipation of dynamic fractures in metal-ligand hydrogels has emerged as an effective approach for enhancing their mechanical properties. Recently, a strategy based on the formation of robust coordination complexes between acylhydrazone ligands and zinc ions was reported, demonstrating significant toughening of the hydrogels.[160] Furthermore, the introduction of sulfonic acid groups into the hydrogel skeleton enabled reversible mechanical enhancement through the addition or removal of Zr^{4+} ions. The resulting metal complex-enhanced polyelectrolyte hydrogel exhibited remarkable resistance to slippage under 3–4 times higher forces.[161] However, it is crucial to consider that, while optimizing mechanical properties, this approach may potentially impact the proangiogenic effect of hydrogels. Therefore, future studies should focus on developing preparation strategies to ensure high biocompatibility and mechanical strength.

Currently, the selection of materials for hydrogel design is primarily based on their proven ability to promote angiogenesis and detect common therapeutic signaling pathways, such as inflammation and angiogenesis. However, the current understanding of the mechanisms underlying the promotion of angiogenesis remains limited. For instance, studies commonly focus on the inflammatory pathway regulated by MMP-9 and TNF-α.[162] At present, it has been reported that GO can promote the formation of endothelial tip cells by coupling with lysophosphatidic acid in serum through the Hippo/yes-associated protein (YAP).[163] It has also been found that under hypoxia, the activation of the RhoA/ROCK signaling pathway promotes the proliferation and elongation of vascular endothelial cells and smooth muscle cells.[164] Although these pathways play an important role in angiogenesis, it has not been reported whether hydrogels can promote angiogenesis through the above pathways, and this mechanism requires further exploration. In addition, the key molecules and signaling pathways of hydrogel- and vascular-related cells (such as vascular endothelial cells, smooth muscle cells, and pericytes) should be investigated. These pathways include the PI3K-Akt and Notch pathways related to endothelial cells and vascular smooth muscle cells, which up-regulate the expression of CD31 and α-SMA to promote cell proliferation and differentiation. These systems play an important role in the growth and extension of new blood vessels. Moreover, the platelet-derived growth factor-β (PDGF-β) signaling pathway contributes to recruiting pericytes and smooth muscle cells to the vascular endothelium, which is essential for vascular stability.[165] In addition, recent studies have reported the role of hydrogels in the reprogramming of macrophages.[166] For example, the synergistic effects of hydrogels, magnesium ions, and engineered small extracellular vesicles have been demonstrated to promote the reprogramming of macrophages to M2 phenotype polarization, thereby promoting angiogenesis.[167] However, the specific mechanism of macrophage polarization remains unclear, and previous studies have focused on the classical oxidative stress pathway. For example, some studies have reported that a nanofiber scaffold–HA hydrogel can alleviate oxidative stress injuries and promote the M2 polarization of macrophages through the TLR4/NF-κB and MAPK pathways.[168] In addition to oxidative-stress-related pathways, the effect of hydrogels on macrophage lipid metabolism should be investigated, including up-regulating the expression of the cholesterol metabolism transcription factor PPAR, promoting fatty acid metabolism, and inducing M2 polarization. It has also been reported that inhibiting SAM-dependent PP2Ac methylation to block PINK1-mediated mitophagy flux antagonized the M1 polarization of macrophages.[169] However, whether hydrogels can promote the reprogramming of macrophages through the

aforementioned pathways to improve angiogenesis must be further explored. Nevertheless, considering that angiogenesis is a complex process and various hydrogels possess distinct characteristics, it is crucial to adopt a multifaceted approach when investigating the mechanisms that promote angiogenesis in future hydrogel development. Exploring deeper and more innovative mechanisms, such as the fundamental interactions between materials and biology, is expected to facilitate advancements in angiogenic hydrogels.

However, certain intraperitoneal hydrogels, such as injectable hydrogels for ischemic myocardium, exhibit limited degradation ability, and their residual substances may have adverse effects on the body. Therefore, enhancing the degradability of hydrogels is crucial to their design. Improvement in hydrogel degradability depends on the selection of synthetic raw materials for hydrogel synthesis. Natural polymers, such as collagen and silk fibroin, have better biocompatibility and biodegradability in the body than synthetic polymers. Hence, for internal and nonremovable dressing components, natural polymers are more suitable for hydrogel synthesis.[170] The biocompatibility and safety of hydrogels have attracted much attention in medical and biomedical applications. Some materials may cause allergic or toxic reactions. For example, the metal-based nanomaterials commonly loaded in hydrogels may cause skin allergies, and their entry into the human body may also cause adverse reactions such as neuropathy and cardiovascular diseases. To reduce adverse reactions toward such hydrogels, hydrophilic compounds such as poly(2-oxazoline) and zwitterionic polymers can be added to the surface of metal NMs to reduce the formation of protein coronas and reduce the toxicity of the materials.[171]

The replacement of hydrogels in skin wounds is susceptible to secondary injury. To facilitate the replacement process, researchers have recently utilized the strong affinity between polyacrylamide-based hydrogels and cellulose acetate to develop a reversible, viscous, double-layered hydrogel tape. The back layer of this tape can be easily detached after bonding with minimal residue without compromising the performance of the other side of the hydrogel layer.[172] Because such bilayer hydrogels can improve the shortcomings of traditional hydrogels, which are difficult to remove, they have great application prospects in promoting angiogenesis. For example, considering the ischemic components that require daily dressing changes, a dorsal-layer hydrogel can be loaded with antioxidant substances, cells, and cytokines, and this hydrogel can be replaced to realize the continuous supply and release of the dorsal-layer substances to promote angiogenesis. For patients with a positive Nikolsky sign, frequent changing of the wound dressing may aggravate skin erosion. In this case, double-layered hydrogels can be applied, and the dorsal hydrogel can be simultaneously loaded with pain relievers and antibiotics.

Although hydrogels can achieve a sustained and controlled release of angiogenic substances, the continuous stimulation of certain factors may lead to vascular proliferation, resulting in the formation of granulomas or even carcinogenesis. Therefore, the development of hydrogels that can monitor various indicators in real time and achieve precise material regulation is both a focus of current research and a direction for future research.[97,173] In recent years, some studies have reported the use of flexible MXene-based systems to realize electronic skin, such as intelligent multifunctional electronic skin composed of laser-scribed graphene and polyurethane nanogrids, which has enabled the transdermal detection of human skin temperature, humidity, pH, and electrolyte metabolites.[154,174] Furthermore, a wearable hemodynamic sensor that is thin, soft, and flexible has been reported for the easy, effective, and noninvasive monitoring of local blood vessel conditions.[175] We anticipate the integration of electronic skin with angiogenic hydrogels such as mechanically controlled sustained-release hydrogels containing VEGF. Upon detecting changes in pH or hemodynamics, physicians can apply external pressure to induce grid deformation and promptly release VEGF to promote angiogenesis (Figure 4).

At present, angiogenic hydrogels are mainly used for wound healing, bone regeneration, and improving myocardial ischemia. However, due to their good biocompatibility, excellent mechanical properties, loading capacity, and angiogenesis properties, they may be applied to various applications including cerebral angiogenesis, tissue engineering, and regenerative medicine. In particular, organoids are a current research hotspot in the field of regenerative therapy, especially in the field of vascularized tissue engineering. Organoids are in vitro 3D model systems with multi-cellular structures and functions that can mimic the key function, structure, and biological complexity of organs.[176] They have been widely used as developmental and disease models, as well as for high-throughput drug screening. However, the generation of functional vascular networks prevents the clinical use of organoids as it is difficult to ensure the perfusion

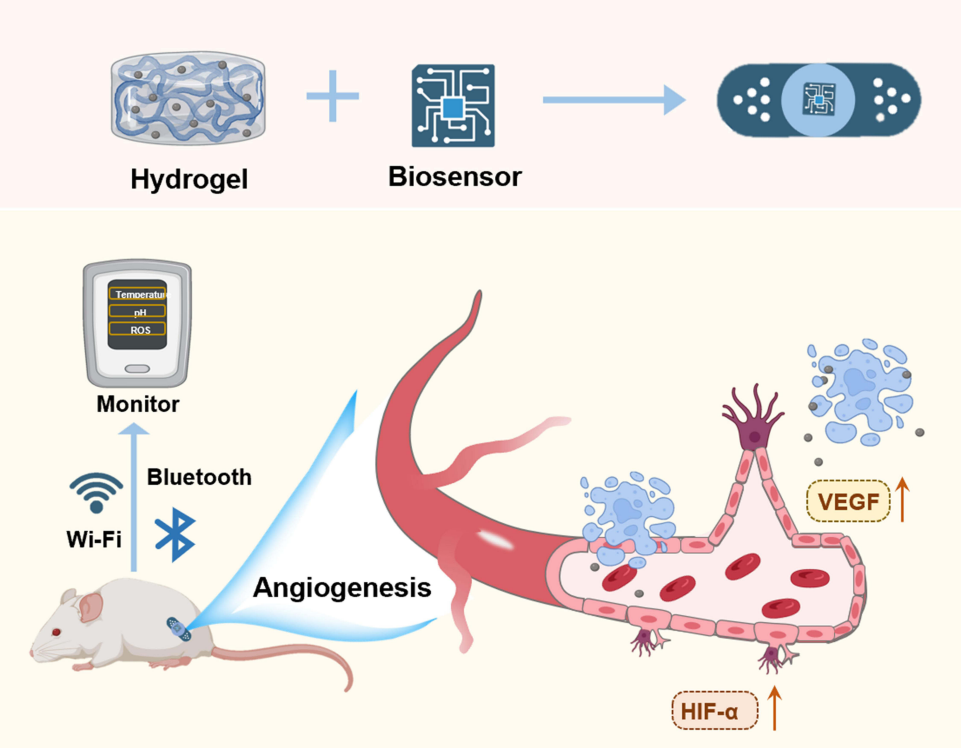


Figure 4 Intelligent hydrogels for the monitoring and regulation of vascular regeneration.

of the vascular system following organoid implantation to maintain the vitality of the organ.[177] To solve this problem, several studies have utilized the excellent biocompatibility of angiogenic hydrogels, mimicking the characteristics of natural matrices and achieving good angiogenesis performance. These systems have been used to construct organoid scaffolds, which can improve the shortage of blood vessels and the poor blood supply of organoids. 3D bio-printed hydrogels have also demonstrated promising application potential. Several studies have used this technology to prepare proangiogenic 3D hydrogels, which can create complex vascular patterns while building organoid scaffolds. Moreover, these hydrogels may be optimized to better address the insufficient perfusion of organoid vasculature.[178] Such hydrogels may be applied to promoting the development of organoids and overcoming the insufficient supply of clinical organ transplants.

Summary

With the advancement and refinement of clinical demands, hydrogels have evolved from their basic functionality into multifunctional compounds, making them the most competitive candidates for promoting angiogenesis. In this review, we comprehensively summarize the design strategies employed in the existing research on various types of functional hydrogels with angiogenic effects, encompassing antioxidant, sustained release, stimulus responsiveness, conductivity, and self-repairing properties. Furthermore, we provide novel insights for future enhancements and designs. We also explore the utilization of proangiogenic hydrogels in cutaneous wounds, osseous defects, and the amelioration of myocardial ischemia based on diverse application scenarios, offering novel therapeutic strategies for enhancing angiogenesis. Furthermore, we propose several approaches and innovative concepts for subsequent investigations, particularly addressing issues pertaining to the mechanical robustness, facile removal, precise regulation, and mechanistic elucidation of hydrogels. Ultimately, we anticipate that this review will further stimulate the advancement of proangiogenic hydrogels toward electronic and intelligent orientations while expanding their clinical applications.

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Disclosure

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