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Review

Progress in the Application of Multifunctional Composite Hydrogels in Promoting Tissue Repair

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Cite This: *ACS Omega* 2024, 9, 47964−47975

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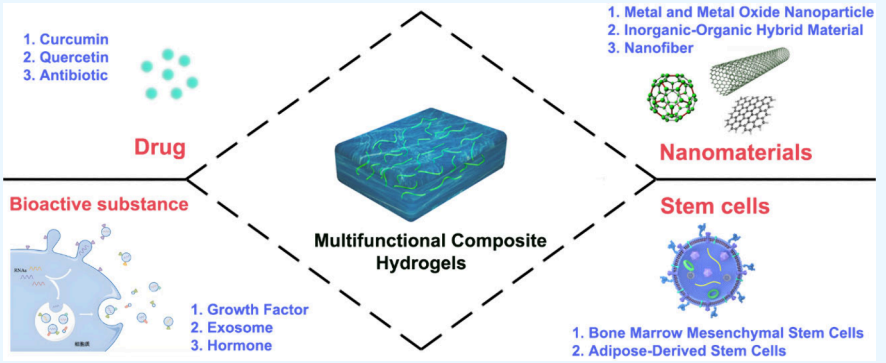

ABSTRACT: Tissue repair is an extremely complex process, and effectively promoting tissue regeneration remains a significant clinical challenge. Hydrogel materials, which exhibit physical properties closely resembling those of living tissues, including high water content, oxygen permeability, and softness, have the potential to revolutionize the field of tissue repair. However, the presence of various complex conditions, such as infection, ischemia, and hypoxia in tissue defects, means that hydrogels with simple structures and functions are often insufficient to meet the diverse needs of tissue repair. Researchers have focused on integrating multiple drugs, nanomaterials, bioactive substances, and stem cells into hydrogel matrices to develop novel multifunctional composite hydrogels for addressing these challenges, which have superior antibacterial properties, hemostatic abilities, self-healing capacities, and excellent mechanical properties. These composite hydrogels are designed to enhance tissue repair and have become an important direction in the current research. This review provides a comprehensive review of the recent advances in the application of multifunctional composite hydrogels in promoting tissue repair, including drug-loaded hydrogels, nanomaterial composite hydrogels, bioactive substance composite hydrogels, and stem cell composite hydrogels.

1. INTRODUCTION

The repair of tissue defects resulting from severe trauma, tumor resection, infection, degenerative diseases, and other pathological conditions remains a significant challenge in contemporary surgical practice, imposing a considerable economic burden on patients.[1] Traditional repair methods, including autologous transplantation, allogeneic transplantation, wound dressings, and surgical reconstruction, are often associated with inherent risks such as limited donor availability, donor site morbidity, immune rejection, disease transmission, and potential complications of repeated surgeries. Thus, there is a pressing need for a safe and highly regenerative repair method with superior biocompatibility that not only fills the defect area but also promotes tissue regeneration and restores the normal physiological function of the damaged tissue. Recent research indicates that novel tissue engineering biomaterials, designed to mimic the structure, mechanical properties, and biological characteristics of natural tissues, hold significant promise for improving treatment outcomes in patients with tissue defects.

Clinically common tissue defects include skin, nerve, and bone defects, and so on. The skin, as the largest organ of the human body, comprises three interconnected layers: the epidermis, dermis, and subcutaneous tissue, arranged sequentially from the outermost to the innermost layer. It has been found to play vital roles in protection, sensation, secretion, and metabolism.[2,3] The advancement of tissue engineering and regenerative medicine has resulted in the development and clinical application of various artificial skin products, including

Received: September 3, 2024
Revised: November 4, 2024
Accepted: November 18, 2024
Published: November 21, 2024

https://doi.org/10.1021/acsomega.4c08103
ACS Omega 2024, 9, 47964−47975

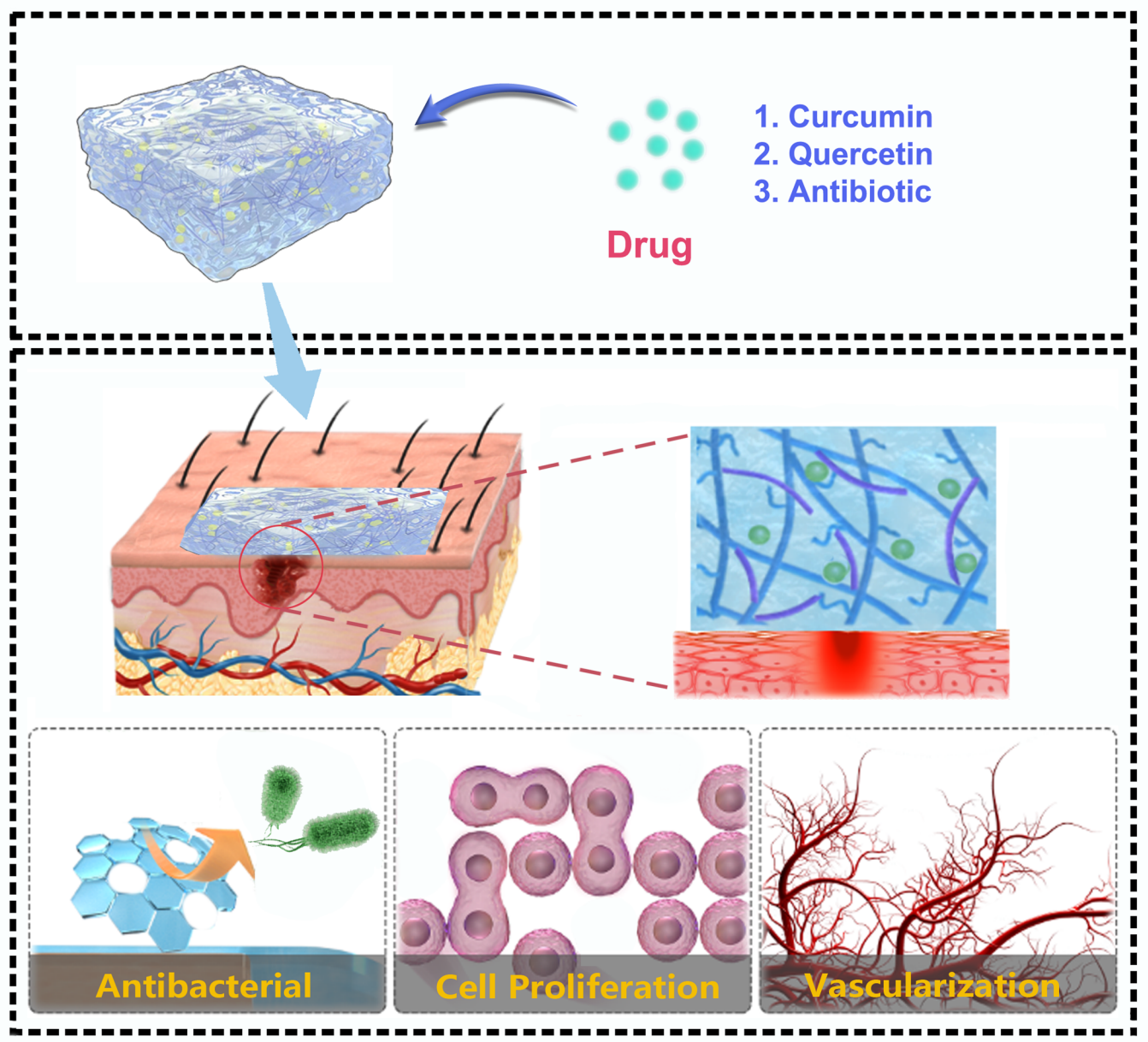

Figure 1. Schematic diagram of the synthesis of drug-loaded hydrogels and their roles in wound tissue repair.

epidermal substitutes, dermal substitutes, and composite skin substitutes.[4] However, inadequate functionality of these products, such as the inability to fully reconstruct the skin's structure and function, as well as the risk of infection from bacteria and airborne particles during the healing process, severely limits practical clinical applications. Effective strategies to promote wound healing and repair damaged skin remain a significant clinical challenge.[5] Nerve tissue is difficult to repair, mainly due to the limited regenerative capacity of neurons, the inhibitory environment of the central nervous system, the complexity of neural circuits, and the slow rate of regeneration. In recent years, the rapid advancement of neural tissue engineering technologies has provided a novel therapeutic approach for nerve injury repair. The healing of bone tissue is primarily dependent on three factors: osteoconduction, blood supply, and osteoinduction.[6,7] Bone defect repair is categorized into primary and secondary bone healing, with the latter involving multiple processes, including blood clotting, inflammatory response, the formation of fibrocartilaginous callus, intramembranous and endochondral ossification, and bone remodeling.[8] Tissue engineering materials intended for filling bone defects and promoting in situ bone regeneration should ideally mimic the structure, mechanical properties, and biological characteristics of natural bone.

Hydrogels are three-dimensional network polymers synthesized from natural or synthetic materials, and they are highly regarded in the field of tissue regeneration due to their excellent biocompatibility, hydrophilicity, biodegradability, and nonimmunogenicity.[9] However, conventional hydrogels primarily serve as physical barriers, fillers, and moisture-retaining agents and are inadequate for repairing damaged tissues under complex conditions. For instance, in scenarios involving ischemia, infection, oxidative stress, and inflammation or in areas subjected to mechanical stress and movement, higher mechanical strength is required to provide sufficient support. Consequently, conventional hydrogels fall short of meeting the

https://doi.org/10.1021/acsomega.4c08103
ACS Omega 2024, 9, 47964−47975

increasingly stringent clinical demands for wound dressings, tissue scaffolds, and grafts. To overcome these challenges, the development of novel multifunctional composite hydrogels, which integrate various drugs, nanomaterials, bioactive substances, and stem cells, has become a prominent trend in tissue repair material design. These advanced hydrogels not only offer essential physical support but also continuously release antimicrobial agents and growth factors to prevent infection, enhance mechanical strength and stability, and further promote rapid tissue repair and regeneration.

This review focuses on the latest advancements in multifunctional composite hydrogels, particularly those incorporating diverse drugs, nanomaterials, bioactive substances, and stem cells. It will summarize their advantages in tissue repair and discusses future research directions, providing new insights for the development of the next generation of tissue repair materials.

2. DRUG-LOADED HYDROGELS

The development of drug-loaded hydrogels harnesses the inherent porous architecture of hydrogels to encapsulate therapeutic agents, thereby achieving desirable drug release profiles and enhanced physicochemical properties. It is challenging to solubilize hydrophobic drugs due to their poor aqueous solubility and limited bioavailability. Currently, the hydrogel matrix has been widely applied in drug delivery because of its amphiphilic characteristics, which enable the effective solubilization of these drugs. Additionally, the gradual degradation of hydrogels facilitates sustained drug release, maintaining therapeutic concentrations over extended periods, which is crucial for effective tissue regeneration. This section delves into three drug-loaded composite hydrogels: curcumin-loaded hydrogels, quercetin-loaded hydrogels, and antibiotic-loaded composite hydrogels (Figure 1).

2.1. Curcumin-Loaded Hydrogels. Curcumin, a polyphenolic compound derived from *Curcuma longa*, exhibits a broad spectrum of biological activities, including anti-inflammatory, antimicrobial, and antiaging effects, which have garnered significant interest for its therapeutic applications. Studies have shown that curcumin not only modulates the inflammatory response through the downregulation of enzymes, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and lipoxygenase, but also inhibits the activation of nuclear factor kappaB (NF-κB), which can exert anti-inflammatory and antioxidant effects.[10] Furthermore, antimicrobial efficacy is demonstrated through multiple mechanisms, including the inhibition of bacterial DNA replication, reduction of bacterial motility, and alteration of bacterial gene expression.[11] Additionally, curcumin promotes collagen synthesis and accelerates the maturation of collagen fibers, thereby facilitating wound healing.[12] However, the clinical application of curcumin is significantly hindered by its low bioavailability, poor water solubility, rapid metabolism, and swift clearance from the body.[13]

Innovative drug delivery systems and controlled release strategies have been developed to address these challenges. For instance, Lei et al. engineered a curcumin/rhein emulsion encapsulated within a hydrogel matrix for oral administration in the treatment of inflammatory bowel disease.[14] This formulation markedly improved curcumin's solubility and bioavailability. The hydrophilic three-dimensional network of the hydrogel further enabled the targeted and controlled release of the drug specifically in the colon. Jia et al. designed a functional composite hydrogel incorporating curcumin and CuS nanoparticles, utilizing the amphiphilic properties of Pluronic F127 as both the hydrogel's drug carrier and cross-linking agent, thereby enhancing curcumin's solubility.[15] The resulting hydrogel exhibited potent anti-inflammatory and antimicrobial activities, effectively reducing wound inflammation and promoting skin regeneration. Moreover, Luo et al. developed an Fmoc-grafted chitosan (FC)/Fmoc peptide (FI)-curcumin composite hydrogel, wherein curcumin was encapsulated within a hybrid hydrogel structure.[16] This formulation enabled sustained drug release and modulated inflammatory responses, facilitating the repair of spinal cord injury in a rat model. Collectively, these studies represent significant advancements in the design and application of curcumin-loaded hydrogels for tissue regeneration and repair.

2.2. Quercetin-Loaded Hydrogels. Quercetin, a flavonol recognized for its diverse biological activities, plays a pivotal role in preventing oxidative damage through the scavenging of reactive oxygen species (ROS) and the inhibition of lipid peroxidation, thus maintaining oxidative homeostasis and mitigating inflammatory responses.[17] Furthermore, it has been confirmed that quercetin plays a role in antibiosis by altering bacterial cell permeability, disrupting cell wall integrity, and inhibiting nucleic acid synthesis.[18] These bioactivities position quercetin as a promising candidate for tissue repair applications. However, its development for use in wound healing is limited by poor solubility and low skin permeability, primarily due to the presence of polar hydroxyl groups.[19]

To overcome these limitations, researchers have developed quercetin-loaded hydrogel dressings that enhance their application in tissue repair. A water-in-oil nanoemulsion incorporating quercetin, embedded within a Carbopol hydrogel matrix (QCN-NE-GEL), was constructed by Jee et al., significantly improving quercetin's water solubility and skin permeability.[20] Their findings demonstrated that the quercetin hydrogel facilitated fibroblast proliferation, suppressed inflammation, and promoted collagen synthesis, thereby accelerating the healing of diabetic wounds. Wang et al. engineered a highly adhesive, self-healing, antioxidant, and antimicrobial hydrogel dressing composed of quaternized chitosan, quercetin, and dopamine.[21] The phenolic hydroxyl groups present in dopamine and quercetin were utilized to enhance the hydrogel's adhesive properties. This hydrogel dressing exhibited robust antioxidant activity and substantial antibacterial efficacy against *Staphylococcus aureus* and *Escherichia coli*. Yu et al. developed an injectable quercetin−gelatin composite hydrogel characterized by an optimal swelling ratio, which significantly improved quercetin bioavailability and allowed for sustained release due to the hydrogel's controlled degradation.[22] This composite hydrogel was shown to preserve the chondrocyte phenotype, impede extracellular matrix degradation, attenuate inflammation, and facilitate cartilage regeneration. Collectively, the studies underscore the significant potential of quercetin-loaded hydrogels in the advancement of tissue repair strategies.

2.3. Antibiotic-Loaded Hydrogels. Antibiotics, secondary metabolites derived from microorganisms or higher organisms, play a crucial role in inhibiting pathogenic growth by hindering bacterial cell wall synthesis, interacting with bacterial cell membranes, disrupting protein synthesis, and impeding bacterial nucleic acid replication and transcription.[23] Although silver ions have been widely applied as broad-spectrum antimicrobial agents, silver nanoparticles can induce

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ACS Omega 2024, 9, 47964−47975

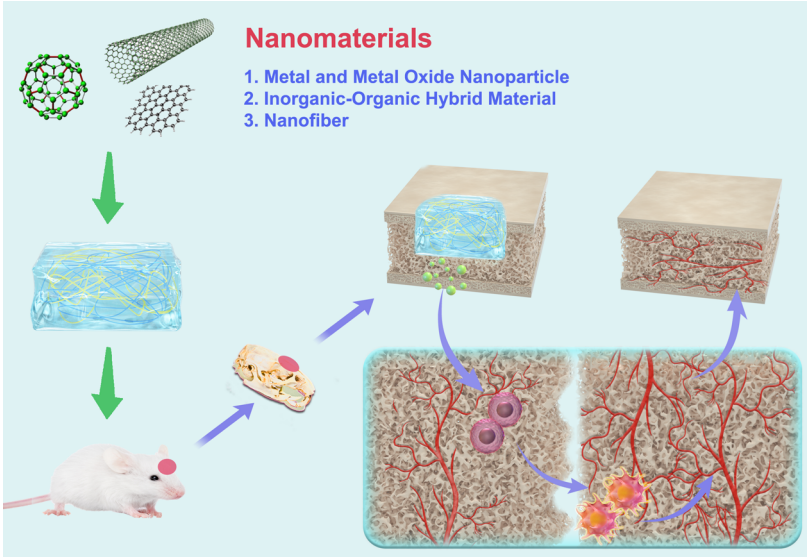

Figure 2. Schematic diagram of the synthesis of nanomaterial composite hydrogels and their roles in bone tissue repair.

cytotoxicity, leading to potential adverse effects, including cell membrane damage, DNA disruption, and oxidative stress.[24] As a result, antibiotics have received considerable attention as alternatives for preventing infections, particularly in post-operative wounds or tissue injuries. While systemic use of antibiotics often leads to undesirable drug reactions and side effects, localized antibiotic delivery can minimize these adverse effects and provide targeted antimicrobial action.[25]

Recent advancements in antimicrobial material research have led to the development of antibiotic-loaded hydrogel systems for tissue repair. For instance, Cai et al. utilized the porous structure of an injectable extracellular matrix hydrogel to adsorb vancomycin and ensure its timely release, enabling rapid antimicrobial activity.[26] In addition to its bactericidal properties, this composite hydrogel effectively managed wound bleeding and accelerated healing. Similarly, Hu et al. developed a gelatin/doxycycline composite hydrogel that exhibited broad-spectrum antibacterial efficacy against both Gram-positive and Gram-negative bacteria and efficiently absorbed wound exudate due to the porous architecture, which attenuated inflammatory responses and promoted wound healing.[27] Additionally, Zhang et al. fabricated a hydrogel-based dual-drug delivery scaffold incorporating the small-molecule drug FTY720 and vancomycin by 3D printing technology.[28] This drug delivery system demonstrated both high antibacterial efficacy and osteoinductive properties, showing exceptional bone regeneration capabilities in a rat femoral infection defect model. In conclusion, an antibiotic-loaded hydrogel for tissue repair represented a promising avenue for the development of next-generation antimicrobial materials. These innovative hydrogels offered enhanced localized drug delivery, potent antibacterial activity, and accelerated wound healing, holding significant potential in clinical application in the medical field.

3. NANOMATERIAL COMPOSITE HYDROGELS

Nanomaterial composite hydrogels are formed by uniformly dispersing nanoparticles or nanostructured materials within a polymer network, where the hydrogel network is established through physical or covalent cross-linking. Among the various developed composite hydrogels, they have garnered considerable attention due to their superior mechanical, optical, swelling, and contraction properties, significantly enhancing the strength and mechanical performance of traditional hydrogel materials.[29] A variety of nanomaterials have been utilized in the preparation of nanomaterial composite hydrogels, such as metal and metal oxide nanoparticles (e.g., gold, silver, and iron oxides), organic−inorganic hybrid materials (such as MOFs and POSS), and nanofibers. These nanomaterials can reinforce the hydrogel network structure while imparting unique functionalities, which enable the development of multifunctional nanomaterial composite hydrogels. Such materials possess considerable potential not only for applications in tissue repair research but also for the development of next generation biomedical materials (Figure 2).

3.1. Metal and Metal Oxide Nanoparticle Composite Hydrogels. Metal and metal oxide nanoparticles display a diverse range of distinctive physical properties, such as the electrical conductivity of gold nanoparticles, antimicrobial properties of silver nanoparticles, magnetic properties of iron oxide nanoparticles, and optical and electrochemical properties of chalcogenide oxide nanoparticles. Additionally, the shape and size of metal and metal oxide nanoparticles exert considerable influence on their properties. For instance, nanoparticles with diameters smaller than 20 nm can more easily penetrate cell membranes and organelles.[30] Nanoparticles ranging from 10 to 50 nm in size, especially those with surface coatings, tend to retain their magnetic properties longer when subjected to an external magnetic field.[31] Due to their unique properties and functionality, nanoparticles of metals such as iron, zinc, and copper have been widely used in the fabrication of hydrogel wound dressings and tissue engineering scaffolds.

Magnetic-responsive nanoparticles (MNPs), such as Fe_3O_4 nanoparticles, can be aggregated and positioned under specific magnetic field conditions. Coupled with their excellent cell surface binding capabilities, MNPs enable the regulation of cellular behaviors, such as differentiation and proliferation, in a magnetic field. Ma et al. utilized Fe_3O_4 nanoparticles modified with poly(acrylic acid) (Fe_3O_4 NPs) as a magnetic material combined with silk fibroin (SF) hydrogel for bone tissue repair.[32] Their experiments demonstrated that mesenchymal

https://doi.org/10.1021/acsomega.4c08103
ACS Omega 2024, 9, 47964−47975

stem cells (MSCs) cultured on SF hydrogels loaded with Fe_3O_4@PAA NPs exhibited enhanced alkaline phosphatase activity, collagen secretion, and mineralization potential, indicating the composite material's potential for promoting bone tissue repair. The mechanisms by which MNPs and the magnetic field promote cell proliferation and differentiation at injury sites have been proposed based on experimental characterization and analysis, including the following main types: cells interacting with MNPs can experience nanoscale stress akin to mechanical forces, stretching cell membranes and regulating channels and receptors;[33,34] magnetic fields not only alter the activity and expression levels of cellular enzymes[32,35] but also can influence the shape and orientation of extracellular matrix (ECM) proteins;[34,36] and magnetic nanoparticles (MNPs) exposed to a magnetic field can trigger specific cellular signaling pathways, such as the epidermal growth factor receptor (EGFR), phosphoinositide 3-kinase (PI3K/Akt), Wnt/β-catenin signaling, and the bone morphogenetic protein (BMP) Smad1/5/8 pathways.[37−40] Incorporating MNPs into hydrogel systems holds significant research value for enhancing cell proliferation and differentiation at injury sites.[41]

Nanoparticle composite hydrogels incorporating metal and metal oxide have demonstrated considerable potential in promoting organizational repair, in addition to their outstanding antibacterial, anti-inflammatory, and antioxidant characteristics. Thanuasha et al. developed a hydrogel platform composed of biopolymers such as gelatin, hyaluronic acid, and chondroitin sulfate, incorporating asiatic acid and nanoparticles (zinc oxide and copper oxide).[42] The primary antibacterial mechanism of these metal oxide nanoparticles is the generation of reactive oxygen species (ROS), which disrupt the negatively charged bacterial cell walls, leading to their rupture. Moreover, the bioactivity and biocompatibility of copper oxide nanoparticles within the composite material facilitate collagen production by fibroblasts, thereby promoting the healing of burn wounds. Yang et al. reported an anti-inflammatory and antioxidant hydrogel primarily composed of small molecule lipoic acid, biocompatible glycine, and nanomagnetic iron oxide (γ-Fe_2O_3) nanoparticles.[43] The results showed that the hydrogel effectively reduces intracellular reactive oxygen species, directs macrophage polarization toward the M2 phenotype, and alleviates inflammation. Zhou et al. reported that the covalent bonding between methacrylated gelatin (GelMA) and carbon−carbon double-bond modified Fe_2O_3 nanoparticles is significantly stronger compared to common noncovalent bonds or physical mixtures.[44] The robust bonding can influence the cross-linking degree of the hydrogel by modulating stiffness with varying nanoparticle content, thereby enhancing the mechanical strength and stability of the composite.

Chen et al. utilized cellulose nanocrystals (CNCs) to reinforce a poly(*N*-isopropylacrylamide) (PNIPAM) hydrophilic polymer matrix.[45] Magnetic Fe_3O_4 nanoparticles, attached to the CNCs, were uniformly dispersed throughout the network, resulting in a highly stretchable, near-infrared (NIR) responsive thermosensitive hydrogel (Fe_3O_4/CNCs@PNIPAM). This composite hydrogel achieves a remarkable tensile strength of 2200%, with Fe_3O_4 nanoparticles serving as effective photothermal agents, demonstrating high biocompatibility and efficient photothermal conversion. This enhancement in NIR-triggered on-demand drug delivery and controlled drug release significantly improves tissue repair in wounds.

3.2. Inorganic−Organic Hybrid Material Composite Hydrogels. Inorganic−organic composite nanomaterials formed by integrating rigid inorganic nanoparticles into flexible organic polymer matrices, which represented a class of materials with unique structures and broad application potential.[46] The resulting inorganic−organic networks exhibit synergistic properties that enhance their performance in optics, electronics, magnetism, sensing, catalysis, and more. Recently, they have also attracted significant attention in the field of regenerative medicine. Inorganic−organic hybrid materials such as metal−organic frameworks (MOFs) and polyhedral oligomeric silsesquioxane (POSS) have proven effective in enhancing the physical, chemical, and biological properties of hydrogels, thereby facilitating the advancement of functional and stimuli-responsive composite hydrogels.[47−49]

MOFs are a versatile class of three-dimensional porous materials characterized by a well-defined coordination structure, high surface area, and tunable porosity, which endow them with broad application in many fields.[50,51] The lattice of MOFs consists of alternating metal ions and organic ligands, forming a series of channels and micropores of varying sizes and shapes that provide numerous adsorption sites for MOFs to efficiently adsorb molecules. Furthermore, the MOF-based hydrogels can achieve efficient drug and metal ion loading with controlled release due to the high adsorption capacity of MOFs and the structural framework of hydrogels. The zeolitic imidazolate framework-8 (ZIF-8) is a specific type of MOF. Li et al. produced a sodium alginate (SA) hydrogel incorporating ZIF-8, which has curcumin (CCM) as a ligand and Zn^{2+} as the central ion.[52] The encapsulation of CCM within the micropores of the ZIF-8 framework enabled a slow and sustained release, imparting long-lasting antibacterial properties to the composite hydrogel. Similarly, Yang et al. developed a wound dressing based on decellularized pomelo peel (DPP), where gallic acid/copper MOFs were incorporated into a poly(vinyl alcohol)-tripolyphosphate-benzyl acid (PVA-TSPBA) hydrogel and coated onto the DPP.[51] The MOFs delivered copper ions and gallic acid, exerting antibacterial and anti-inflammatory effects and thus promoting tissue healing. Xiao et al. embedded copper-based MOF nanoparticles (HKUST-1) into a thermoresponsive citrate-based hydrogel containing antioxidants, to slow the release of copper ions and to help ensure that the MOFs did not degrade too rapidly.[53] Beyond promising drug delivery capabilities, the inherent tunability in the structure and composition of MOF−hydrogel composites has led to further innovative advancements. Zhang et al. created a bilayer hydrogel in combination with a dry film, which was then utilized as a wound dressing.[54] The upper layer consisted of a Ag@MOF-encapsulated chitosan nanoparticle film, which, despite its limited biocompatibility, exhibited strong bactericidal activity to effectively prevent microbial infection. The lower layer, a polymerized and cross-linked system (PACS) hydrogel, was in direct contact with the skin, offering good biocompatibility while promoting blood clotting and cell proliferation, thus effectively aiding in wound tissue repair.

Among the most promising organic−inorganic hybrid materials is polyhedral oligomeric silsesquioxane (POSS), known for its biocompatibility, nontoxicity, and ability to induce phase separation, which are fundamental properties required in modern biomedical applications.[55,56] The silsesquioxane clusters in POSS molecules can significantly enhance the mechanical strength and tensile resistance of the hydrogel

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ACS Omega 2024, 9, 47964−47975

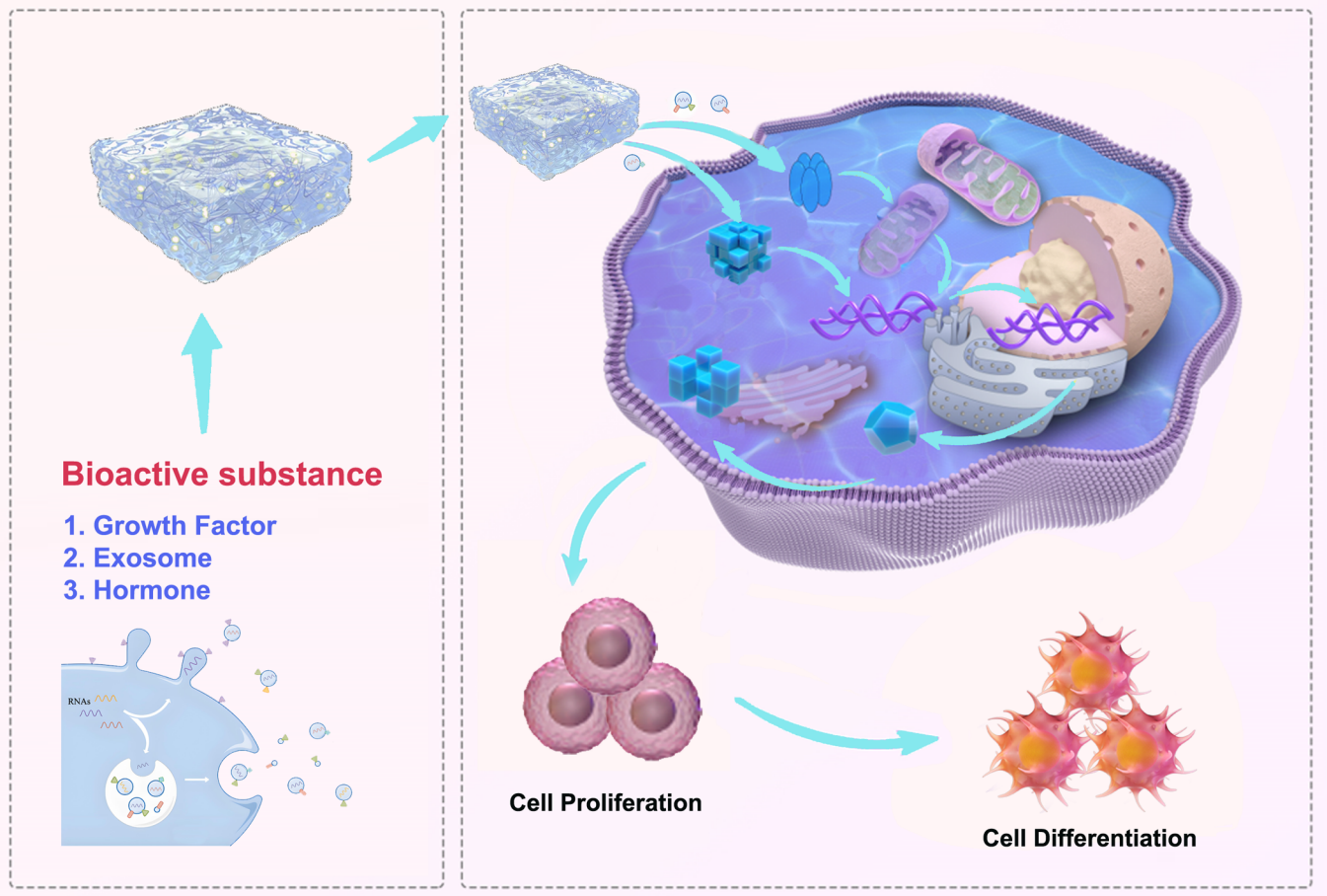

Figure 3. Schematic diagram of the synthesis of bioactive substance composite hydrogels and their roles in tissue repair.

through high rigidity and stability, when they are mixed uniformly and interact with the hydrogel matrix. Moreover, the material's inherent stiffness and corrosion resistance effectively improve the hydrogel's stability and durability under tensile loads. Cui et al. developed an injectable and degradable organic−inorganic hybrid hydrogel designed for cartilage scaffolding. This was achieved by cross-linking acrylated 8-arm star polyhedral oligomeric silsesquioxane (POSS-8) with poly(ethyl ethylene phosphate) (PEEP-AC) and thiolated hyaluronic acid (HA-SH).[57] The resulting POSS−PEEP/HA hydrogel adhered to rat cartilage tissue, effectively withstanding cyclic compression and promoting cartilage repair. Xu et al. employed polyethylene glycol (PEG) as the flexible component of the hydrogel, while using isobutyl-functionalized polyhedral oligomeric silsesquioxane diol (TMP POSS diol) as the rigid segment.[58] The hydrophilic soft segment (PEG) and the hydrophobic hard segment (POSS) underwent microphase separation, resulting in the formation of crystalline structures. Consequently, the POSS nanocrystals served as physical cross-linking points, thereby enhancing the stability and deformation resistance of the composite hydrogel.

Other organic−inorganic hybrid composite hydrogels also demonstrate remarkable potential for various applications. Liu et al. developed a biomimetic hybrid artificial periosteum by incorporating inorganic calcium phosphate nanoparticles (CAPs) into gelatin-methacryloyl hydrogels (GelMA-F) with the use of electrospun fibers.[59] This material exhibited favorable fiber morphology and mechanical properties, as well as the ability to induce in situ mineralization, which is expected to provide new strategies for bone regeneration. The application prospects and research progress of organic−inorganic hybrid composite hydrogels in tissue repair are highly promising. Although this field is still in its early stages, comprehensive consideration of their practical utility at this stage is expected to prove invaluable in the future development and application of organic−inorganic hybrid composite hydrogels.[60]

3.3. Nanofiber Composite Hydrogels. The fibrous structures in biological soft tissues, such as collagen and elastic fibers in the extracellular matrix and the orderly arranged collagen fiber bundles in skeletal muscle, provide biological tissues with excellent mechanical properties and specific biological functions. Traditional hydrogels lack the fibrous architecture and multilayered organization found in biological soft tissues like the extracellular matrix, muscle, and cardiac tissue, which limits their functional properties. Currently, several types of nanofibers are employed in the field of tissue repair: (1) Natural Nanofibers (e.g., collagen, cellulose, and gelatin): These are suitable for mimicking the natural extracellular matrix, supporting cell adhesion and growth. (2) Synthetic Nanofibers (e.g., poly(lactic acid), polycaprolactone, and poly(vinyl alcohol)): These are used to modulate the biodegradability and mechanical properties of hydrogels and can be tailored to influence cell behavior under specific conditions. (3) Functionalized Nanofibers: The introduction of bioactive molecules (such as growth factors and hormones) via chemical modification can facilitate specific cellular responses or inhibit the onset of infections.

https://doi.org/10.1021/acsomega.4c08103
ACS Omega 2024, 9, 47964−47975

As a result, research on nanofiber composite hydrogels has attracted significant attention in the scientific community. Sun et al. reported a tendon-mimicking hydrogel material platform where rigid aramid nanofibers (ANFs) and flexible poly(vinyl alcohol) (PVA) were assembled into a highly oriented network.[61] The anisotropic composite hydrogels (ACHs) produced demonstrated mechanical performance similar to that of natural tendons while retaining about 60% of the water content found in natural tendons. This material shows promise in advancing research in tissue repair. Vinikoor et al. developed an injectable, biodegradable composite hydrogel using low-temperature cut piezoelectric short nanofibers of poly-L-lactic acid (NF-sPLLA) combined with a collagen matrix.[62] This nanofiber composite hydrogel holds great potential in the field of tissue repair. Nanofibers can also be employed in assembling tissue-engineered nerve grafts to create a suitable microenvironment for nerve regeneration. For example, Liu et al. prepared composite hydrogel loaded functional self-assembling peptide (F-SAP) nanofibers, showing that this novel hydrogel of growth factors combined with F-SAP nanofibers can induce endogenous neurogenesis by locally reassembling the extracellular matrix.[63]

4. BIOACTIVE SUBSTANCE COMPOSITE HYDROGELS

Bioactive substance composite hydrogels are hydrogels that have been enhanced by incorporating bioactive molecules, such as growth factors and hormones, to augment their functionality. These hydrogels not only supported cell growth but also regulated cell behavior by releasing these bioactive molecules, which promoted cell proliferation, differentiation, and matrix synthesis, thereby accelerating the regeneration and repair of damaged tissues. When combined with hydrogels, the stability of the bioactive substance composite could effectively address several challenges: maintaining effective concentrations of bioactive molecules over time, ensuring uniform distribution within the treatment area, and improving bioavailability. Additionally, the direct application of bioactive substances could sometimes lead to localized adverse reactions; however, the controlled release and isolation properties of hydrogels could mitigate or prevent these negative effects.

The integration of bioactive substances with single hydrogels could also enhance the material's mechanical properties and resistance to degradation, beyond imparting biological functions. Those changes resulted from cross-linking reinforcement and structural modulation as the multiple functional groups present in bioactive substances can form chemical bonds with the matrix molecules of the hydrogel, increasing the cross-linking density between polymer chains. Therefore, bioactive substance composite hydrogels hold significant potential for applications in tissue repair (Figure 3).

4.1. Growth Factor Composite Hydrogels. Studies have reported the indispensable role of growth factors in regulating a multitude of biological procedures, where they can bind to particular receptors located on cellular membranes, which then activate intracellular signaling pathways that impact the behavior of cells including growth, differentiation, or survival. Thus, growth factors are considered potent therapeutic agents in tissue engineering and regenerative medicine. However, the clinical application of growth factors is constrained by their brief half-life in physiological environments and potential side effects. Growth factor composite hydrogels are promising for extending the half-life of growth factors, reducing rapid proteolysis and burst release.[64]

For example, Wathoni et al. developed a hydrogel membrane (Sac/EGF-HF) incorporating epidermal growth factor (EGF) using sacran, a polysaccharide derived from algae.[65] The presence of EGF significantly enhanced the thickness, tensile strength, and degradation resistance of the Sac/EGF-HF hydrogel. Moreover, this hydrogel demonstrated the ability to induce fibroblast migration, highlighting its potential for tissue repair applications. Gnavi et al. engineered a gelatin-based hydrogel system for the delivery of vascular endothelial growth factor (VEGF), which promoted the survival and regeneration of motor neurons and the growth of peripheral nerve fibers.[66] Rahman et al. constructed a platelet-derived growth factor (PDGF) hydrogel, which was shown to significantly enhance angiogenesis in wound healing.[67]

4.2. Exosome Composite Hydrogels. Exosome composite hydrogels primarily promoted the repair of damaged tissues by leveraging the paracrine-like functions of exosomes.[68] Exosomes, a type of extracellular vesicle (EV), are involved in various physiological processes by carrying bioactive components, such as RNA, microRNA (miRNA), and proteins. These processes encompass hemostasis, thrombosis, inflammation, immune interactions, angiogenesis, and wound healing.[69] Traditionally, exosomes have been administered via multiple subcutaneous injections around the wound area.[70] However, for more practical clinical applications, a simpler, more effective, and noninvasive delivery method is needed. Currently, combining exosomes with hydrogel materials to extend the retention time of exosomes on wound surfaces, without compromising their bioactivity, has become a focal point in the development of exosome-based therapies.[71]

The porous structure and high porosity of hydrogels allow for substantial encapsulation of exosomes within the network, minimizing damage to exosome structures while facilitating their diffusion and release. The high water content and hydrophilicity of hydrogels provide an environment that simulates bodily fluids, which helps maintain the stability and bioactivity of exosomes. For example, Shi et al. produced a chitosan/silk hydrogel sponge that is both biodegradable and biocompatible to deliver exosomes secreted by human gingival mesenchymal stem cells (GMSCs), for treating wound tissues.[70] This exosome-loaded hydrogel accelerated wound healing by enhancing epithelial regeneration, collagen deposition, angiogenesis, and neuron growth. Besides, Yang et al. developed a thermosensitive PF-127 hydrogel to carry and sustain the release of human umbilical cord mesenchymal stem cell exosomes (hUCMSC-exos).[71] The results showed that the composite material not only preserved the bioactivity of the exosomes, promoting angiogenesis and cell proliferation in wound tissues, but also expedited the healing process of diabetic wounds.

4.3. Hormone Composite Hydrogels. As early as 1939, the U.S. Food and Drug Administration (FDA) approved the first commercial insulin preparation. Hormones have been widely used in clinical practice, highlighting the significance of hormone-based therapeutics in medicine and clinical treatment. Today, hormones find extensive applications in biomedical engineering including drug delivery systems, biosensors, and cancer therapy. However, the use of hormones in tissue repair still requires further in-depth research and resolution, due to nonspecific binding on healthy tissues, adverse side effects, tolerance issues, and difficulties in controlling localized therapeutic outcomes.

https://doi.org/10.1021/acsomega.4c08103
ACS Omega 2024, 9, 47964−47975

Hydrogels can serve as carriers to control hormone concentration and release rates at the treatment site as well as extend the stability and duration of hormone action in the body, thereby achieving effective local controlled release. Xie et al. designed a hydrogel barrier combining poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogel with estradiol-loaded mesoporous silica, which not only enhanced the mechanical properties and stability of the hydrogel but also enabled the sustained and stable release of estradiol.[72] This composite hydrogel shows great promise in applications, such as repairing damaged endometrial tissue and preventing postoperative adhesions. Hu et al. prepared a dynamic self-healing hydrogel incorporated with melatonin (Hydrogel@MT), demonstrating that melatonin effectively protected fibroblast matrix metabolism, energy production, and mitochondrial function, thereby promoting in situ regeneration of annulus fibrosus tissue and preventing intervertebral disc (IVD) degeneration.[73] Javanmardi et al. developed a cross-linked gelatin (Gela) hydrogel containing the proanthocyanidins (PAs) for delivering tyramine-substituted hyaluronic acid microparticles that are loaded with dexamethasone (Dex-HA-Tyr Mp).[74] These studies showed that the dexamethasone composite hydrogel exhibited excellent biocompatibility and could serve as an appropriate system for the sustained delivery of Dex, aimed at repairing damaged tissues surrounding the sciatic nerve.

5. STEM CELL COMPOSITE HYDROGELS

Stem-cell-based therapies have recently become a highly effective method for addressing both acute and chronic tissue defects. Stem cell transplantation has the potential to replenish damaged cells and enhance the functionality of surrounding tissues, providing an optimal treatment for a multitude of degenerative diseases and congenital defects. Nevertheless, this approach is not without inherent risks, including the potential for tumor formation and immune rejection, which require long-term monitoring. It is worth noting that using stem cells on their own exerts suboptimal effects, not only because the improper control of stem cell differentiation may result in abnormal proliferation but also because their constructs are prone to fragility; the survival rate and functional retention of transplanted cells are short-lived, requiring continuous replenishment. Furthermore, the microenvironment at the transplantation site can markedly impact the survival and differentiation of the cells; thus, it is crucial to use them in conjunction with carrier materials.

For the past few years, hydrogel materials have been increasingly applied in tissue engineering because of their excellent biocompatibility and biodegradability. Stem cell composite hydrogels combine specific types of stem cells with hydrogel materials, which represent a promising approach. By adjusting the physical and chemical properties of hydrogels, it is possible to control cell behavior, thereby facilitating cell attachment, proliferation, and survival.[75,76] This approach enables the localized delivery of exogenous stem cells and offers significant advantages in tissue repair. Consequently, stem cell composite hydrogels possess immense potential for application, advancing personalized and precision medicine, and hold broad value in the field of regenerative medicine (Figure 4).

5.1. Bone Marrow Mesenchymal Stem Cells. Bone marrow mesenchymal stem cells (BMSCs) demonstrate multilineage differentiation capacity, enabling them to differentiate into osteoblasts, chondrocytes, and adipocytes. This capability makes them valuable for bone tissue engineering and fracture repair. Among various novel biomaterials, injectable hydrogels loaded with BMSCs are particularly advantageous due to their injectability and gel-like consistency, allowing them to flow across complex and irregular vertebral surfaces and increase the contact area. Moreover, these hydrogels provide excellent mechanical stability when combined with BMSCs, creating an optimal biomechanical environment for joint cartilage repair and other bone tissue regeneration therapies.

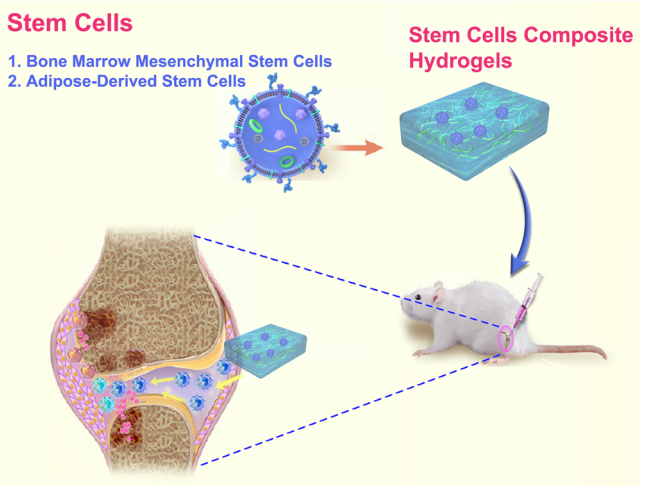

Figure 4. Schematic diagram of the synthesis of stem cell composite hydrogels and their roles in regenerative medicine.

Hydrogels offer scaffold structures and growth environments that enhance BMSC attachment, proliferation, and differentiation, thereby facilitating bone tissue regeneration and repair. Zhang et al. designed an injectable composite hydrogel loaded with BMSCs, which optimizes the stem cell microenvironment to promote bone formation and angiogenesis, contributing to new bone development and the formation of more mature tissue structures.[77] Li et al. developed a novel porous poly(vinyl alcohol) (PVA)/chitosan (CS) hydrogel that, when combined with BMSCs, supports cartilage regeneration and repair in joint applications.[78] Additionally, Pei et al. incorporated BMSCs into hydrogel/nanofiber composite scaffolds, finding that BMSCs within these composite scaffolds exhibited superior survival rates and migration capabilities.[79] Thus, BMSC composite hydrogels represent promising synthetic materials for cartilage repair, with broad applications in fracture healing, cartilage regeneration, and cardiovascular repair, offering new pathways for advancing tissue regeneration.[80]

5.2. Adipose-Derived Stem Cells. Adipose-derived stem cells (ADSCs) can differentiate into a multitude of cell types including adipocytes, chondrocytes, and endothelial cells. ADSCs also secrete numerous growth factors and cytokines and possess self-renewal and immunomodulatory abilities. Compared to other stem cells, ADSCs are easier to obtain and cause less donor injury, and their yield is approximately 500 times higher than that from bone marrow.[81] Despite these advantages, the use of ADSCs alone often leads to poor outcomes in tissue engineering due to their tendency to degrade.[82]

ADSC composite hydrogels can enhance tissue regeneration, wound healing, and bone and cartilage repair and regulate stem cell differentiation. ADSC-loaded hydrogels help form new

https://doi.org/10.1021/acsomega.4c08103
ACS Omega 2024, 9, 47964−47975

blood vessels, which is particularly beneficial for promoting vascularization in engineered organs and tissues, thereby facilitating wound healing and skin regeneration in cases of ischemic diseases.[83] Ni et al. demonstrated that alginate/branch starch/hyaluronic acid hydrogel scaffolds loaded with adipose-derived mesenchymal stem cells (ADSCs) improved the healing process and accelerated wound closure.[84] Liu et al. prepared ADSC-loaded β-chitin nanofiber (β-ChNF) hydrogels. Their research indicated that the β-ChNF hydrogels effectively regulated the expression of VEGFR, α-SMA, collagen I, and collagen III, activated TGFβ/Smad signaling, reduced Smad phosphorylation, and decreased TIMP1, VEGFR, as well as α-SMA expression, significantly enhancing wound healing efficiency.[85] Li et al. developed an injectable decellularized matrix hydrogel (DAM-gel) loaded with rat ADSCs, which improved peripheral nerve regeneration in rats and accelerated sciatic nerve defect healing.[86] It can be reasonably deduced that ADSC composite hydrogels demonstrate considerable potential for the promotion of angiogenesis, the optimization of nerve function, and the acceleration of wound healing, thus advancing tissue regeneration and repair.

6. CONCLUSION AND FUTURE PERSPECTIVE

Multifunctional composite hydrogels offer a number of significant advantages, including ease of preparation, favorable mechanical properties, enhanced responsiveness, and functionality through the synergistic effects of various drugs, nanoparticles, bioactive substances, and stem cells.[87,88] These characteristics have resulted in the extensive utilization of the multifunctional composite hydrogels in tissue repair applications.[89−91] This review classifies multifunctional composite hydrogels according to loaded materials and provides an overview of the latest developments in hydrogels for tissue repair. Nevertheless, obstacles persist in the clinical implementation of multifunctional composite hydrogels. For example, although the incorporation of nanoparticles of metals and metal oxides into hydrogels effectively enhances their mechanical properties, it is also essential to evaluate the influence of these nanoparticles on the diffusion of bioactive factors and cellular metabolites within the hydrogel. Furthermore, degradation rates are crucial aspects to consider in the evaluation of composite hydrogels for tissue repair. The degradation time should be optimized to achieve an equilibrium between the need for hydrogel support during the physical and biochemical microenvironments of tissue healing and the necessity for its degradation to minimize any adverse effects associated with prolonged material retention on tissue healing.

The majority of multifunctional composite hydrogels have been demonstrated to possess favorable biocompatibility and nontoxicity. However, these studies typically involve limited in vitro and in vivo testing periods and primarily use cells or animal models.[92,93] Therefore, the long-term biological safety of multifunctional composite hydrogels in biomedical applications has not been systematically evaluated. Prior to clinical application, it is imperative to validate the long-term effects of these drug delivery systems, including chronic toxicity, biocompatibility, immunogenicity, pharmacokinetics, and pharmacodynamics, in both small animal models (e.g., mice and rats) and large animal models (e.g., monkeys, pigs). Moreover, it is essential to prioritize the refinement of their preparation techniques to guarantee the long-term biological safety of hydrogel delivery systems. This entails the development of environmentally friendly solvents, green synthesis methods, and nontoxic cross-linkers. Additionally, further development of intelligent, responsive multifunctional composite hydrogels that can react to changes in the microenvironment of damaged tissues (such as pH, temperature, humidity, and infection) and trigger the release of loaded substances in response to these stimuli holds significant promise for future clinical applications.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (82460368, 82160352), Science and Technology Plan Project of Guizhou Province, China (qiankehejichu-ZK[2022]yiban590), Young Talent Development Program in Education Department of Guizhou Province, China (KY[2022]282), and Innovative Projects for University Students of China (ZHCX2023006).

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