Received: 1 April 2021 | Revised: 24 April 2021 | Accepted: 24 April 2021

DOI: 10.1002/nano.202100139

nano select Open Access WILEY

REVIEW

Multi-functional magnetic hydrogel: Design strategies and applications

Fangli Gang[1] | **Le Jiang**[2,3] | **Yi Xiao**[1] | **Jiwen Zhang**[4] | **Xiaodan Sun**[2,3]

[1] Department of Biology, Xinzhou Teachers University, Xinzhou, Shanxi 034000, China

[2] State Key Laboratory of New Ceramics and Fine Processing, School of Materials Science and Engineering, Tsinghua University, Beijing 100084, China

[3] Key Laboratory of Advanced Materials of Ministry of Education of China, School of Materials Science and Engineering, Tsinghua University, Beijing 100084, China

[4] State Key Laboratory of Crop Stress Biology for Arid Areas and College of Chemistry & Pharmacy, Northwest A&F University, Yangling, Shaanxi 712100, China

Correspondence
Fangli Gang, Department of Biology, Xinzhou Teachers University, Xinzhou, Shanxi 034000, China.
Email: gangfangli01@163.com
Xiaodan Sun, State Key Laboratory of New Ceramics and Fine Processing, School of Materials Science and Engineering, Tsinghua University, Beijing 100084, China.
Email: sunxiaodan@tsinghua.edu.cn

Funding information
Natural Sciences Foundation of China, Grant/Award Numbers: 21977083, 52072210; Tsinghua University-Peking Union Medical College Hospital Initiative Scientific Research Program, Grant/Award Number: 20191080871; Tsinghua University Initiative Scientific Research Program, Grant/Award Number: 2017THZWYX07

Abstract

Hydrogel is one of the hottest biomaterials in recent years. Especially, magnetic hydrogels (MHs) prepared by combining unique magnetic nanoparticles (MNPs) with hydrogels have attracted wide attention due to their excellent biocompatibility, mechanical properties, absorbability and rich magnetic properties (magnetocaloric, magnetic resonance imaging and intelligent response, etc.). However, the current literature mainly focuses on the application of MHs, without fully understanding the relationship between the design strategies and applications of each function in MHs. This review highlights six major functional properties of MHs, including mechanical properties, adsorption, magnetocaloric effect, magnetic resonance (MR) imaging, intelligent response and biocompatibility. Principles and design strategies of each performance are thoroughly analyzed. Furthermore, the latest applications of MHs in biomedicine, soft actuators, environmental protection, chemistry and engineering in recent 5 years are introduced from the perspective of each function. In the carefully selected representative cases, the design strategies and application principle of multi-functional MHs are detailed, respectively. The classical fabrication processing of MHs is summarized. At last, we discuss the unmet needs and potential future challenges in MHs development and highlight its emerging strategies.

KEYWORDS
adsorption, intelligent response, magnetic hydrogels, magnetic resonance imaging, magnetocaloric effect, multi-function

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
© 2021 The Authors. *Nano Select* published by Wiley-VCH GmbH

1 | INTRODUCTION

Hydrogels are a highly swollen three-dimensional (3D) polymer networks synthesized by hydrophilic monomers, which can be considered as polymer-reinforced water. Hydrogels with unique physicochemical properties, such as excellent softness, water content, biocompatibility, bioactivity, etc., provide a strong candidate material for many fields including biomedical and environmental engineering.[1] Various biomimetic hydrogels have been developed to mimic natural hydration microenvironments and successfully applied in tissue engineering and cancer treatment.[2] Hydrogels with specific microstructures (anisotropic, tubular, etc.) have also been developed to deliver drugs/cells and provide three-dimensional biochemical microenvironments for supporting cell growth.[3] Despite great progress has been made, conventional hydrogel systems still have some limitation. In particular, insufficient functionality severely limits its practical application potential in many fields. Therefore, it is a hot research topic to endow hydrogels with functionality.

With the rapid development of permanent magnet materials and electromagnetic technology, magnetic field as an important physical field is widely used in scientific research. The magnetic field can provide a feasible and flexible strategy for inducing the functionality of hydrogels. Thus, MHs composed of magnetic particles (γ-Fe_2O_3, Fe_3O_4, etc.) and hydrogel matrix have attracted more and more attention for their biocompatibility, controllable structure, high adsorption and rich magnetic properties (magnetocaloric, MR imaging and intelligent response, etc.).[4] For example, MNPs endow hydrogels with remotely controllable characteristics, which can be used in drug delivery,[5] local hyperthermia,[6] magnetic/thermal drive,[7] tissue image enhancement,[8] adsorption, separation and purification,[9] and so on. In addition, stimulus-responsive MHs have broad application prospects in soft robot.[10]

As everyone knows, the versatility of materials will enrich their potential in practical applications. In turn, different applications can also dictate the material desired properties. Therefore, in this paper, from the design concepts and application strategies of multi-functional MHs (Figure 1), we review the latest research progress on MHs. Six main functional properties of MHs are highlighted: mechanical properties, adsorption, magnetocaloric effects, MR imaging, intelligent response and biocompatibility. Focusing on its specific functions, the potential applications of MHs in biomedicine, environmental protection, soft actuators, chemical catalysis and engineering are further analyzed. Finally, the common preparation methods of multi-functional MHs are systematically reviewed.

2 | DESIGN STRATEGIES AND APPLICATIONS FOR MULTIPLE FUNCTIONALITIES OF MAGNETIC HYDROGELS

MHs are generally formed by the interaction between magnetic components (γ-Fe_2O_3, Fe_3O_4, etc.) and hydrogel matrix through non-covalent or covalent bonds. This combination simultaneously absorbs the advantages of hydrogel (high water content, flexibility, etc.) and magnetic particles (smart response, etc.). There are differences in raw material selection, design strategies and application fields of MHs with specific performance. For example, in most literatures, the composite MNPs in MHs are generally spherical nanoparticles with a diameter of 1~20 nm, and some MNPs with significant magnetocaloric effect have a ring shape.[11] Biomedical MHs focuses on biocompatible hydrogel matrix, while engineering application MHs uses cheap and readily available materials. Therefore, it is of great significance to study MHs from the six functions of mechanical properties, adsorption, magnetocaloric effect, magnetic resonance imaging, intelligent response and biocompatibility.

In general, the good dispersity of MNPs in the matrix is the fundamental factor in preparing high-performance composite gels. However, most MNPs have a high specific surface area and can easily agglomerate (Figure 2A). The MHs obtained by simply compounding MNPs and hydrogel matrix often exhibits uneven network structure and unstable properties. Notably, the introduction of functionalized MNPs or special hydrogels components can effectively solve these problems. Both of these aims to increase the dispersity and crosslinking degree of the MNPs in the hydrogels (Figure 2B,C). The difference is that the former focuses on the modification of MNPs (Fe_3O_4, $MnFe_2O_4$, etc.), mainly including increasing functional groups (e.g., carboxylic groups),[12] chemical loading,[13] coating (e.g., tannic acid),[14] etc. While the latter usually selects specific hydrogel components with a large number of active functional groups (carboxyl, hydroxyl, etc.), which can coordinate with Fe ions and easily gelled. Polyacrylamide,[15] polyvinyl alcohol,[16] hyaluronic acid,[17] fibrin,[18] and nano-cellulose are commonly used MHs with high coordination activity. The MHs obtained by these two methods have uniform structure, stable performance and enhanced mechanical properties. Under the action of long-range magnetic field, functional MNPs exhibit remarkable intelligent response (mobility), magnetocaloric effect and MR imageability. The hydrogel matrix, as a structural and mechanical support, is also affected by MNPs to produce corresponding behaviors, including deformation, movement, thermogenesis and MR imaging. By regulating the

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

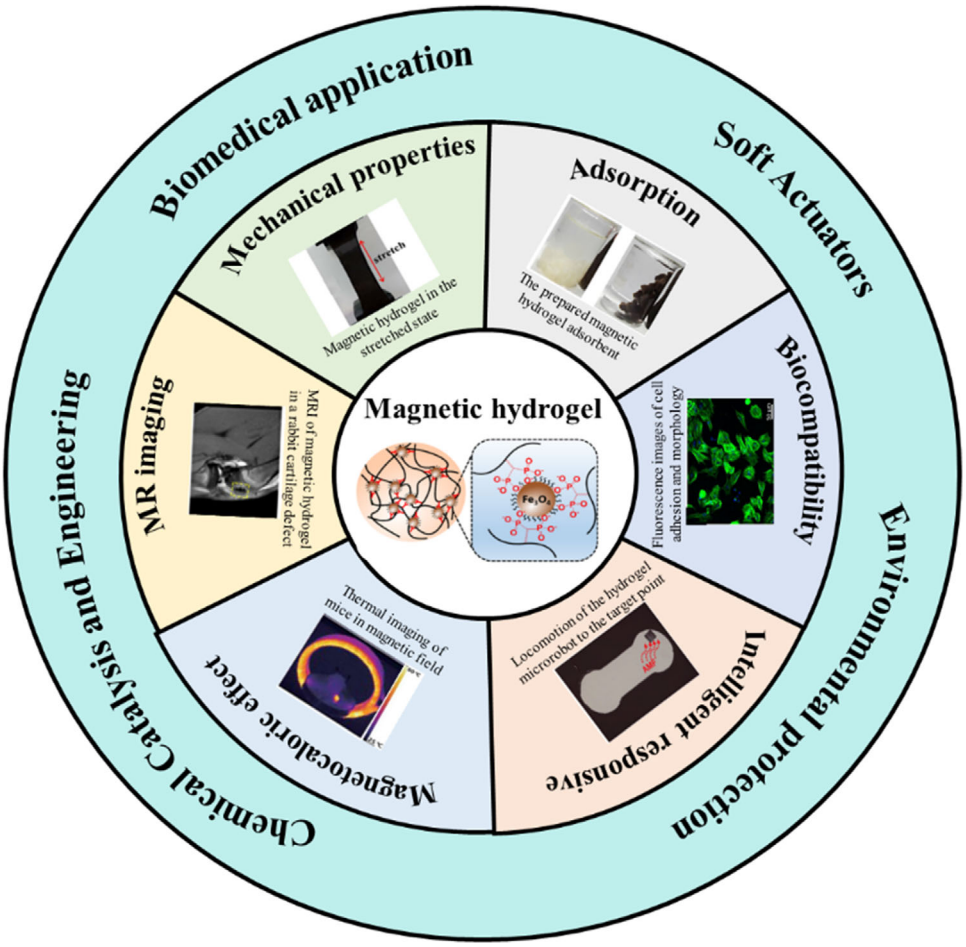

FIGURE 1 Schematic illustration of multifunctional MHs and their applications

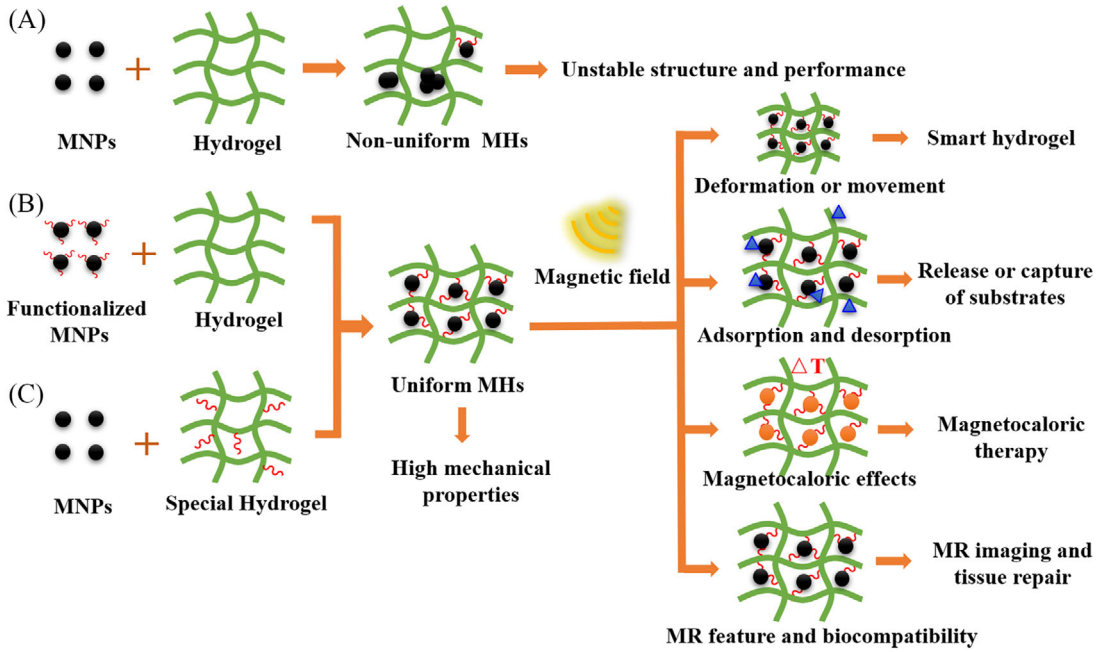

FIGURE 2 Design strategies of MHs. Structure and properties of MHs prepared by A, MNPs + hydrogel, B, functionalized MNPs + hydrogel and C, MNPs + special hydrogel

26834011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

types or proportions of MNPs and hydrogel matrix to control multiple functions of MHs, so as to promote its fascinating application prospects in different fields.

2.1 | Mechanical properties

Mechanical property is a set of commonly used indexes, which is the resistance to failure of materials under load (such as tension, compression, torsion, impact, cyclic load, etc.). Generally, the mechanical properties of hydrogels mainly include strength, stiffness, toughness and fatigue strength. For hydrogels, their mechanical properties determine their usage and service life.

At present, there are mainly four ways to improve the mechanical properties of hydrogels: (1) the "sacrifice bond" is introduced to dissipate energy effectively, thereby enhancing the mechanical properties of hydrogels. A variety of non-covalent interactions such as hydrogen bonding, complexation, supramolecular recognition and hydrophobic association have been applied to prepare high-strength hydrogel.[19] The most representative example is double network hydrogels. (2) The "pulley effect" is used to reduce the internal stress in the crosslinking network and greatly enhance the mechanical properties of the hydrogels. Topological hydrogel is a kind of material with high strength by using O-shaped crosslinking ring which can slide freely on the polymer chain as a controllable crosslinking point.[20] (3) the fracture and reconstruction of some reversible non-covalent bonds will also give hydrogels high-strength,[21] while providing certain recoverability and self-healing properties. (4) The introduction of nanoparticles has been shown to significantly alter hydrogel mechanical properties.[22] This paper focuses on MNPs composite hydrogel materials. On the one hand, the rigid MNPs can not only improve the compression modulus, storage modulus and thermal stability of the composite hydrogel, but also adjust the water absorption, retention, saturation magnetization and pore size of the MHs by changing its content. On the other hand, the reversible interaction between MNPs and hydrogel components can endow MHs with good self-healing, thermal stability, shear-thinning, and mechanical properties (rigidity and viscoelasticity). Therefore, the design and application of high-performance MHs with intrinsic magnetism have received much attention from scientists.

High-strength MHs, as an important branch of nanocomposite hydrogels, have important applications in biomedical and soft actuators.[23] Biomaterials are a promising strategy for repairing damaged or diseased tissue. In general, in order to ensure the clinical safety of biomaterials, rigorous in vitro biological evaluation must be carried out in advance. In vitro simulation, hydrogels can be used as mechanical support for cell growth and differentiation. Unlike most in vitro cell culture 2D substrates (petri dishes, porous plates), hydrogels provide a 3D microenvironmental cell experience,[24] better mimicking the in vivo biological environment. Up to now, a variety of MHs have been used as multi-functional in vitro culture platform to explore the effects of different conditions (e.g., magnetic field and hyperthermia) on cell function and morphology.[25] Gu et al. reported a magnetic polyacrylamide hydrogel with cell adhesion microarray interface,[25] which can effectively promote the formation of multicellular spheroids. It is considered as a prevailing tool to study the microenvironmental regulation of therapeutic problems and tumor cell physiology. In addition, as a polymer material most similar to biological tissue, hydrogels can be used as scaffolds for tissue engineering to repair or replace damaged tissues. As one of the three key elements of tissue engineering, it is very important for scaffolds to have excellent mechanical properties. In particular, for osteochondral repair materials, excellent compressive and anti-fatigue properties ensure that they can withstand repeated mechanical stress without being damaged, so as to steadily continue to exercise their biological functions. However, it is still a great challenge to develop MHs that match the mechanical properties of normal tissues for repairing osteochondral defects in situ.

2.2 | Adsorption

As a highly absorbent and high water-retaining material, 3D network hydrogels have been widely applied in many fields, such as food preservation, drought resistance in arid areas. Moreover, hydrogels have a broad application prospect in wastewater treatment by virtue of their high adsorption capacity.[26] Heavy metals (Pb, Cu, Cs, etc.), organic compounds (pesticides, etc.) and dyes are all water pollutants causing worldwide environmental problems. These pollutants are non-biodegradable, carcinogenic and highly toxic and should be removed from wastewater prior to disposal. Compared with traditional hydrogels, MHs, as an environment-friendly 3D nanomaterial with high physical strength, high adsorption rate and renewability, has attracted increasing attention in wastewater treatment.[27] As shown in Table 1, the combination of magnetic additives (such as magnetite) and hydrogel matrix can simultaneously adsorb contaminants such as heavy metal ions and dyes. Some MHs have a removal rate of more than 99.5%. Moreover, the optimized MHs has high-sensitivity, high-selectivity, fast-adsorption and reusability.

The adsorption principle of MHs is shown in Figure 3A. Porous hydrogels containing active functional groups such as carboxyl, hydroxyl and amino groups can act as

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Typical examples of magnetic hydrogels successfully applied in the removal of heavy metals, organic compounds, inorganic salts and dyes

Magnetic additive	Hydrogel matrix	Contaminant	Remarks[a]	Ref.
Fe_3O_4	Modified gum tragacanth	Pb^{II}, Cu^{II}, dyes (crystal violet and congo red)	q_{max} values: 94.0 mg g^{-1} Pb^{II}, 101.74 mg g^{-1} Cu^{II}, 81.78 mg g^{-1} crystal violet, 69.67 mg g^{-1} congo red	[28]
Iron oxide nanoparticles	Prussian blue/polyvinyl alcohol	^{137}Cs	Excellent selectivity, high removal efficiency (>99.5%)	[29]
γ-Fe_2O_3	(3-acrylamiddopropyl) trimethylammonium chloride/lanthanum nitrate	Fluoride	$q_{max} = 136.78 \pm 2.19$ mg g^{-1}, the adsorption capacity reaches 93% in 10 minutes, better fluoride adsorption at low pH (2.8-4.0)	[30]
Graphene oxide/magnetite	Ascorbic acid	$Au(CN)^{2-}$	$q_{max} = 309$ mg g^{-1}, the spent hydrogel could be easily collected using a magnetic separator	[31]
Fe_3O_4 nanoparticles	Xylan/poly(acrylic acid)	Methylene blue	$q_{max} = 438.60$ mg g^{-1}, porous structure, paramagnetism, reusability	[32]
Fe_3O_4 nanoparticles	Polycyclodextrin-modified cationic hydrogel	Brilliant red X-3B	$q_{max} = 2792.3$ mg g^{-1}, five cycles, pH stability, adsorption kinetics could be well-described by the Weber–Morris model and the homoge neous surface diffusion model	[33]
Fe_3O_4	Modified lignin	Organic dyes and inorganic ions (Pb^{II}, Hg^{II} and Ni^{II})	Low-cost, suitable adsorption capacities for removal dyes and heavy metal ions, regenerating from acid condition, reusability	[34]
Magnetite nanoparticles	Alginate/metal-organic framework	Chlorophenoxy acid herbicides	high hydrophilicity, large adsorption capacity, enrichment factors range between 27 and 107	[35]
Fe_3O_4 nanoparticles	Reduced graphene oxide/polypyrrole nanotube	Multi-residue insecticides	simultaneous enrichment of different types of insecticides, no matrix effect, high sensitivity, ease of operation	[36]
Nano γ-Fe_2O_3	Cationic hydrogel	Aromatic pollutants	rapid sorption rate (99% dye removal within 5 minutes), 30 cycles, wide pH adsorption range	[37]
γ-Fe_2O_3	$La^{3+}/La(OH)_3$ loaded cationic hydrogel	Phosphate	$q_{max} = 90.2 \pm 2.9$ mg P/g, wide pH adsorption range, easily regenerated, five cycles	[38]
γ-Fe_2O_3	Alginate	Heat stable salts	3.0 g of composites giving the highest removal of 29.24% in 240 minutes, eight cycles	[39]
Fe_3O_4 nanoparticles	Gluten/pectin	Lake Urmia sediments	62% of the total heavy metal removal rate, 42% of the total organic matter removal rate	[40]
Iron oxide nanoparticles	Alginate	Sulfide	$q_{max} = 136.9$ mg g^{-1}, 98% removal, easily regenerated with calcium chloride solution, five cycles	[41]

[a](n cycle refers to the adsorption/desorption cycle n times, and qmax refers to the maximum adsorption capacity).

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

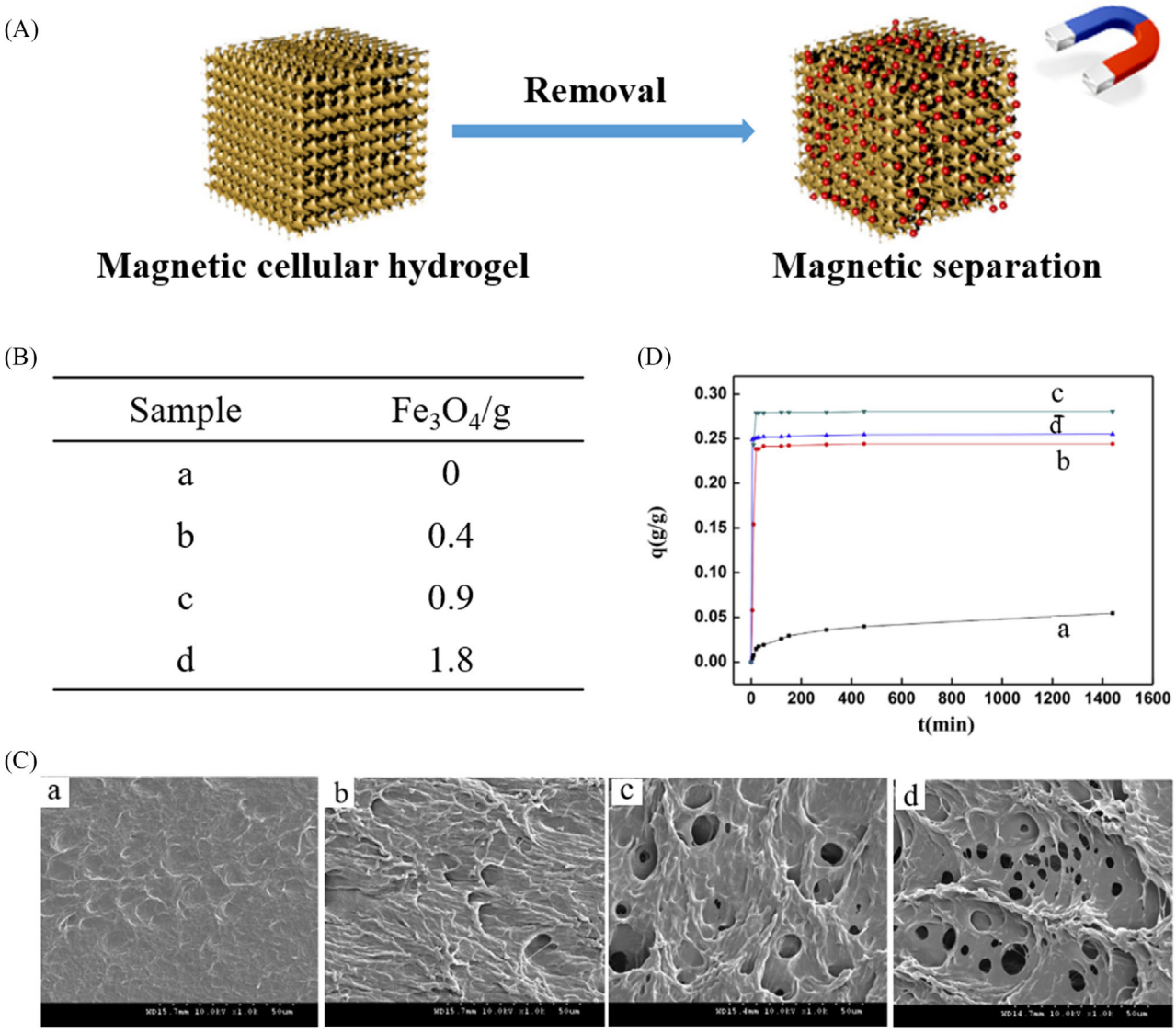

FIGURE 3 A, Schematic diagram of removing contaminants from wastewater using MHs. B, MHs with different Fe_3O_4 contents. C, SEM images of different MHs. D, Adsorption kinetics of Cr^{VI}on the MHs adsorbent. Reprinted with permission.[44] Copyright 2018, Elsevier

adsorbents to remove contaminants through electrostatic, ionic exchange or complexation with contaminants such as heavy metal ions. More importantly, the incorporation of MNPs can promote the separation, collection and reuse of hydrogel adsorbents,[42] and also have a positive effect on the adsorption of MHs (Figure 3B-D).[43] The main results are as follows: (1) MNPs embedded in MHs can increase the cross-linking degree and porosity of the system, providing a channel for the entry, exit and adsorption of some substances. (2) When the amount of MNPs is in a certain range, the adsorption amount of MHs is positively correlated with the amount of MNPs. The reason is that with the increase of MNPs addition, the surface of the hydrogel becomes rougher, which can increase the surface area and adsorption capacity of MHs. However, once the amount of MNPs exceeds a certain value, the saturation absorptivity of MHs will decrease unexpectedly. This may be attributed to the excessive coordination of the active groups in the hydrogel system with MNPs, resulting in a decrease in the number of free active groups and insufficient binding to pollutants.[44]

The complete adsorption process of MHs is described in Figure 4. First, the prepared MHs were added to the treated wastewater, and the complete adsorption was guaranteed by shaken in an end-over-end manner. Then, under the assistance of magnets, magnetic separation is carried out on contaminants-loaded hydrogel. In this way, treated water and renewable hydrogels are obtained. The reutilization of MHs requires regeneration solution to desorb the contaminants on the hydrogel, and then magnetic separation to obtain reusable adsorption materials. The realization of this process is attributed to the large surface

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

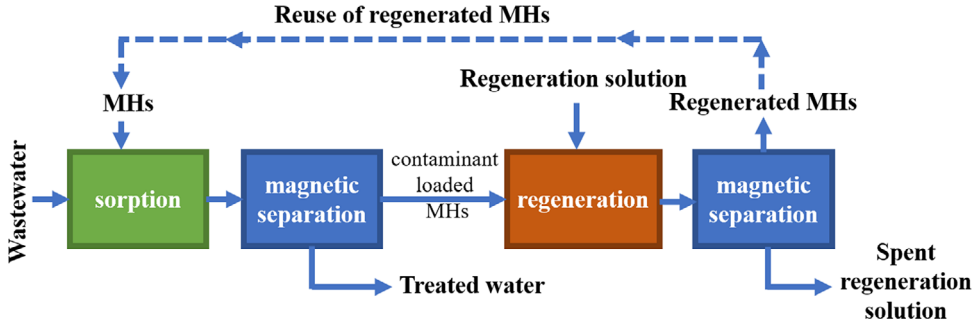

FIGURE 4 The process flow chart of removing contaminants from wastewater using MHs

area, multiple adsorption (hydrogen bond, hydrophobic interaction, etc.), suitable pore size distribution and paramagnetism of MHs. Therefore, MHs can be considered as a low-cost, efficient and recyclable adsorbent, and have great attraction and broadly applicable in wastewater treatment.

Because magnetic separation methods can selectively recover the desired proteins from biological fluids, MHs materials have been extensively studied in protein separation.[45] For biomedical applications, especially tissue engineering, the tendency of hydrogel to adsorb protein in biological media should be considered as an important characteristic. It has been demonstrated that magnetic apatite nanoparticles introduced into poly(vinyl alcohol) (PVA)/sodium alginate hydrogel could generate magnetic response and enhance hydrogels.[46] When pH = 4.5, the maximum adsorption capacity of nano-beads for bovine serum albumin was the highest, reaching 127.3 $mg \cdot g^{-1}$. In addition to the above applications, the absorbability of MHs could also be used for enzyme immobilization,[47] dehydrators,[48] data storage,[49] moisture transport,[50] and so on.

2.3 | Magnetocaloric effects

Magnetocaloric effect refers to the phenomenon that the magnetic energy is transferred to the particles in the form of heat when the ferromagnet or paramagnetism is placed in the alternating magnetic field (AMF) and the magnetic direction is randomly transformed between parallel and anti-parallel. This phenomenon can be used to destroy morbid cells in organisms and control drug release. As a common magnetocaloric agent, superparamagnetic iron oxide (SPIOs) nanoparticles have obtained considerable development in tumor ablation. However, SPIOs have shortcomings such as short residence time in vivo, limited timeliness, and many injections. Notably, the magnetic particles were incorporated into hydrogels will greatly prolong the residence time in vivo. Not only that, hydrogel matrix with a 3D internal network microstructure, high water content and biocompatibility, which are analogous with those of the natural tissue, plays a key role in the application of MHs. On the one hand, hydrogel matrix provides a microenvironment for magnetocaloric therapy,[51] effectively avoiding heat damage to normal tissues, and provides adjustable 3D scaffolds for cell adhesion, migration and differentiation.[52] On the other hand, injectable hydrogels with pores or microchannels are one of the best candidates for local drug delivery.[53] The magnetocaloric effect of MHs can be designed to sustain and control the release of one or more combined therapeutic drugs. Studies demonstrated that the anisotropic magnetic coupling inside the gel is the main reason for the thermogenesis of MHs. Moreover, compared with the disordered MHs, the self-assembled oriented MHs has stronger thermogenesis.[54]

The practical application of MHs magnetocaloric effect is mainly reflected in biomedicine, including tumor treatment and tissue repair. Surgery is currently one of the most common methods for solid tumor treatment. However, wound infection and postoperative recurrence are major challenges facing the surgical treatment of solid tumors. Neoadjuvant and postoperative adjuvant therapies play an important role in improving the prognosis of patients. MHs have been applied to target tumors by remote heating with an external magnetic field and controlled release of anticancer drugs from hydrogels for cancer therapy.[55] Compared with photothermal therapy, magnetocaloric therapy has unlimited tissue penetration depth and is effective for deep-seated tumors such as liver cancer and glioma. Moreover, an AMF-triggered delivery system enables on-demand drug delivery with more effective anticancer chemotherapy effects. However, increasing the efficacy of 42°C therapeutic temperature without resistance to induced thermal stress has been a challenge. Therefore, Zhang et al. designed an injectable magnetic hydrogel nano-enzyme (MHZ) utilizing the inclusion interaction between α-cyclodextrin and PEGylated nanoparticles.[56] Employing this hydrogel could

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

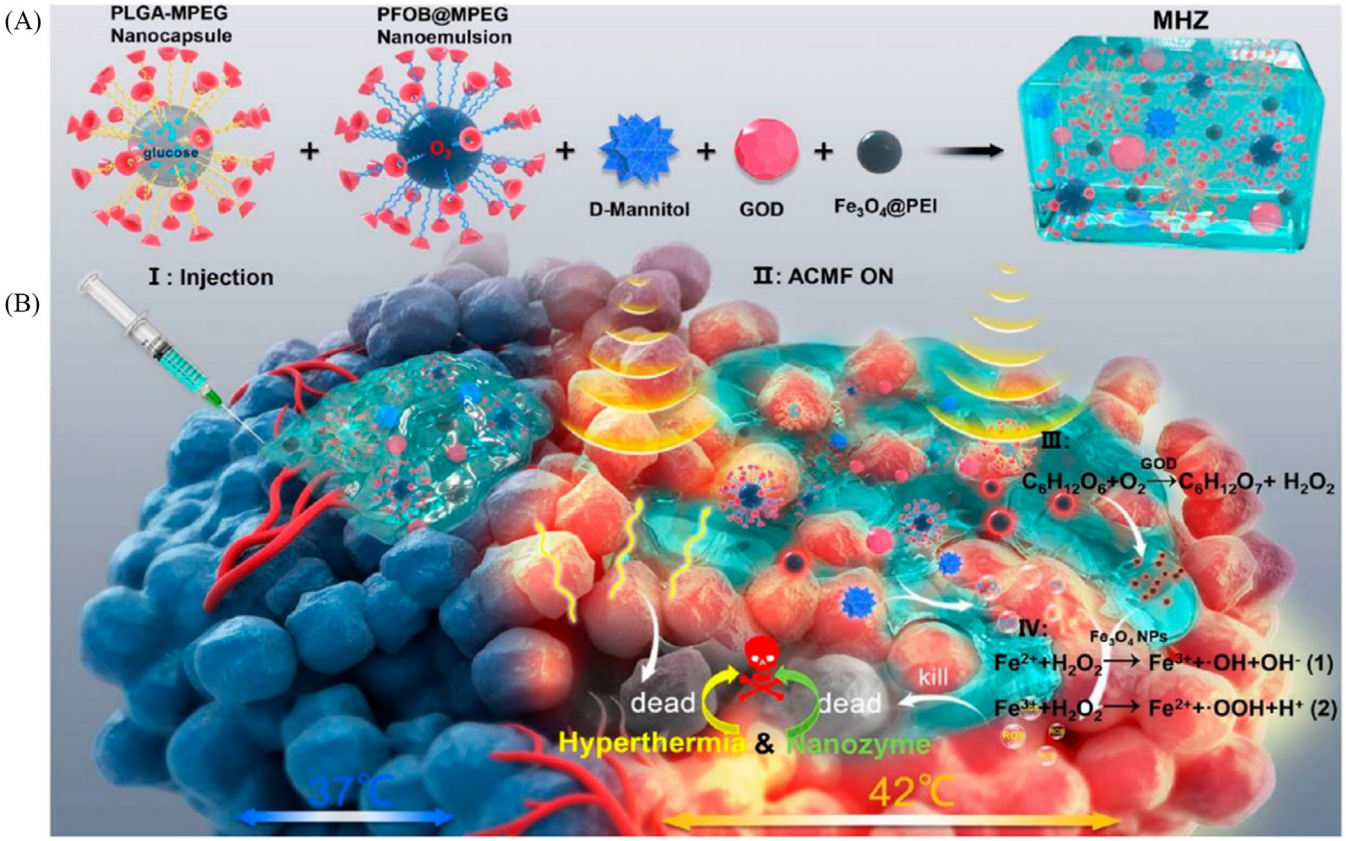

FIGURE 5 Schematic diagram of enhanced tumor synergistic therapy by injectable MHZ.[42] A, Synthetic procedure for MHZ. B, The synergistic mechanism of MHZ on the generation of hyperthermia and ROS for cancer therapy. Reprinted with permission.[42] Copyright 2019, American Chemical Society

improve the tumor oxidative stress level by generating reactive oxygen species via nanozyme catalyzed reaction based on hyperthermia (Figure 5). Magnetic Fe_3O_4 nanoparticles play a dual role of nanozymes and magnetic heating simultaneously in the hydrogel system. On the one hand, the magneto-heat generated after MHZ injection into tumor tissue promoted Fe_3O_4 nanozymes to produce more ·OH. On the other hand, ·OH further damages the highly expressed protective heat shock protein 70 in hyperthermia, thereby improving the efficacy of hyperthermia. As such, this MHs exerts dual functions of catalytic therapy and hyperthermia to synergistically treat tumors and overcome the resistance of tumor cells to induced thermal stress. This developed system offers a universal platform for safer and precise synergistic therapy of solid tumors.

In the past decade, the combination of hyperthermia-based physical therapy and biomaterials has exhibited significant potential in tissue repair. In vitro cell experiments have proved that mild thermal stimulation could effectively promote osteochondral repair.[57] Further in vivo experiments are yet to be studied. In addition, hyperthermia plays an important role in inhibiting local inflammatory response, relieving pain and protecting joint function.[58] Therefore, hydrogels with magnetothermal effect can be expected to have great application prospects in the treatment of rheumatoid arthritis and osteoarthritis.

It is worth mentioning that the superior magnetocaloric effect of MHs is conducive to develop discoloration hydrogel,[59] which may provide a new platform for color display. This remarkable magnetochromatic property is attributed to the superior magnetocaloric effect of 1D magnetic chain immobilized in a thermosensitive hydrogel. Under an AMF, the magnetocaloric effect of aggregated magnetic chains leads to hydrophilic–hydrophobic transition of the hydrogel, which reduces the inter-particle distance of the 1D magnetic chains and results in a blueshift of the diffraction wavelength. Thus, the MHs also shows the potential to monitor magnetic hyperthermia with significant changes in its color and appearance.

2.4 | MR imaging

Non-invasive imaging is a powerful tool that can provide effective feedback for clinical diagnosis. MR imaging has

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

become one of the most powerful detection methods in contemporary clinical diagnosis due to its characteristics such as safety, functional sequence diversity, good soft tissue contrast and penetration depth. However, in practical application, the relaxation time of different tissues or tumors overlaps with each other, which leads to the diagnosis difficult. Therefore, the contrast agent began to be studied in order to enhance the signal contrast and improve the image resolution. Due to its biocompatibility and superparamagnetism, Fe_3O_4-based superparamagnetic contrast agents are widely used in cancer detection, drug delivery monitoring and stent implantation labeling. Significantly, the incorporation of magnetic particles with MR imaging into the hydrogel system will endow the gels a good imaging capability.[60] This non-invasive imaging of materials could provide effective feedback for the real-time degradation of biomaterials and the remodeling of new tissues in vivo.[61] Moreover, non-invasive monitoring methods help to reduce the number of experimental subjects. The reason is that the experimental data can be obtained repeatedly to avoid unnecessary sacrifice in histological analysis at different time points. In addition, non-invasive continuous observation will provide more effective information, reduce individual differences, and contribute to the clinical transformation of tissue engineering.

For the first time, Chen developed a functional, visualizable superparamagnetic iron oxide (USPIO)-labeled natural hydrogel system for semi-quantitative monitoring the cartilage degradation process and elucidated the regeneration of hyaline cartilage by multiparametric MRI.[62] USPIO particles with diameter of ~15.7 ± 2.0 nm and a concentration less than 25 μg Fe/mL had no effect on chondrogenesis and cell proliferation of human bone marrow mesenchymal stem cells (hBMSCs).[63] In this experiment, cellulose nanocrystal (CNC)/silk fibroin (SF) blend hydrogel was selected as scaffold for tissue engineering to promote cartilage regeneration. It has a moderate degradation rate to coincide with cartilage regeneration, which is essential to maintain the structural integrity and mechanical properties of the joint. As shown in Figure 6A, the USPIO-labeled CNC/SF hydrogel has an interconnected network structure and uniform porosity. Prussian blue staining exhibited that USPIO was evenly distributed in the hydrogel matrix, and the material showed no obvious cytotoxicity. This biocompatible hydrogel with pore sizes ranging from 70 to 250 μm, are effective in promoting cartilage formation.[64] Next, MRI characterization of the composite hydrogel was performed with T2-weighted imaging (T2WI) sequence, indicating that the signal contrast of the prepared hydrogel increased with USPIO content. In vivo MR imaging further demonstrated that the USPIO-labeled hydrogel had sufficient MR contrast to monitor the degradation process (Figure 6D). Therefore, this system may provide meaningful insights for non-invasive monitoring and therapeutic efficacy of implanted hydrogels in tissue engineering.

2.5 | Intelligent response

Smart hydrogel is a kind of material that can perceive small physical/chemical stimuli (such as temperature, light, magnetism, pH) and make significant response behaviors.[65] Because of this intelligence, hydrogel has a fascinating application prospect in tissue engineering, drug-controlled release and soft actuators. Especially, as an external stimulus of stimulus-responsive materials, magnetic field has the advantages of instant action, contactless control and easy integration into electronic devices. Therefore, the research and development of smart MHs has been very active in recent years.[66]

Over the past few decades, tissue engineering has been successfully applied to the repair of various tissues (retinas, ligaments, fats, blood vessels, etc.). With the potential of hydrogel to construct microenvironment, the scaffolds based on multi-functional MHs have attracted much attention due to their intelligence. On the one hand, under the guidance of magnetic field, MHs can move directionally or be induced into specific tissue-like microstructure,[67] providing a suitable growth environment for tissue reconstruction. Schmidt proposed a novel magnetic templating technology which can induce highly aligned 3D tubular microstructures in naturally derived hydrogel scaffolds.[68] The scaffold was constructed by adding soluble magnetic alginate particles (MAM) containing nano-iron oxide to the hydrogel precursor solution. The diameter of MAM is 100 nm~20 μm, and a concentration of 5 mg mL^{-1} of MAM is the upper-limit allowing for optimal chain length on the millimeter scale. Under an external magnetic field, the gel forms an aligned columnar structure (Figure 7A). The removal of MAM results in scaffolds with aligned tubular microarchitectures that can facilitate cell remodeling in various applications. Moreover, the hydrogels with electromagnetic effects can realize the above functions, while constructing electric microenvironment under external electrical stimulation to simulate directional tissue, guide cell proliferation and tissue regeneration.[69] On the other hand, magnetic scaffolds can control the biological behavior of cells through the magnetic response between MNPs and magnetic field[70]; thus, promoting revascularization, cartilage/bone regeneration,[71] neuroregulation,[72] and wound repair.[67] Carlo et al. described a 3D magnetic hyaluronic hydrogel that provides non-invasive neuromodulation by magneto-mechanically stimulating primary dorsal root ganglion (DRG) neurons (Figure 7B).[73] Mechanosensitive PIEZO2 channel is

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

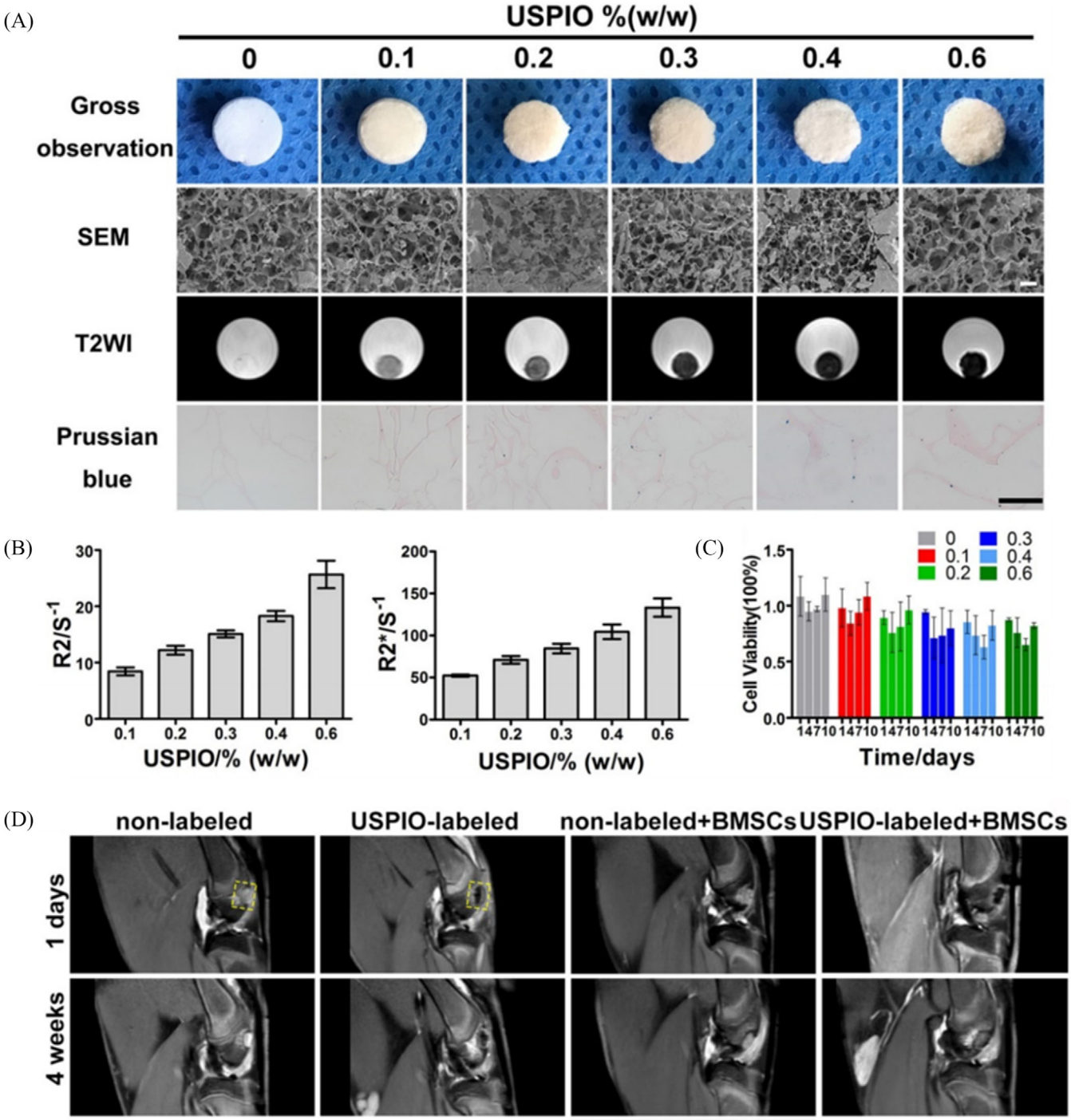

FIGURE 6 Non-invasive monitoring of hydrogel degradation by multiparametric MR imaging.[62] A, In vitro SEM observation, MRI characterization and Prussian blue staining of CNC/SF hydrogels incorporated USPIO. B, R2 and R2* relaxometry rates and (C) cytotoxicity of USPIO-labeled hydrogel. D, MRI analysis of the in vivo degradation of non-labeled and USPIO-labeled CNC/SF hydrogels in a rabbit cartilage defect model. Reproduced with permission.[62] Copyright 2018, Ivyspring International Publisher

activated by magnetic particles embedded in the system through membrane stretching. Mechanosensitive TRPV4 channel is activated by magnetically induced deformation of HA hydrogel. Under acute magneto-mechanical stimulation, calcium influx in DRG neurons is induced through TRPV4 and piezo2 channels, avoiding the step of exogenous ion channel transfection.[74] Under chronic magneto-mechanical stimulation, is able to reduce piezo2 channel expression, playing a role in chronic pain modulation. This general strategy offers a way to achieve remote magnetic modulation of different types of excitable cells through 3D magnetic biomaterials.

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

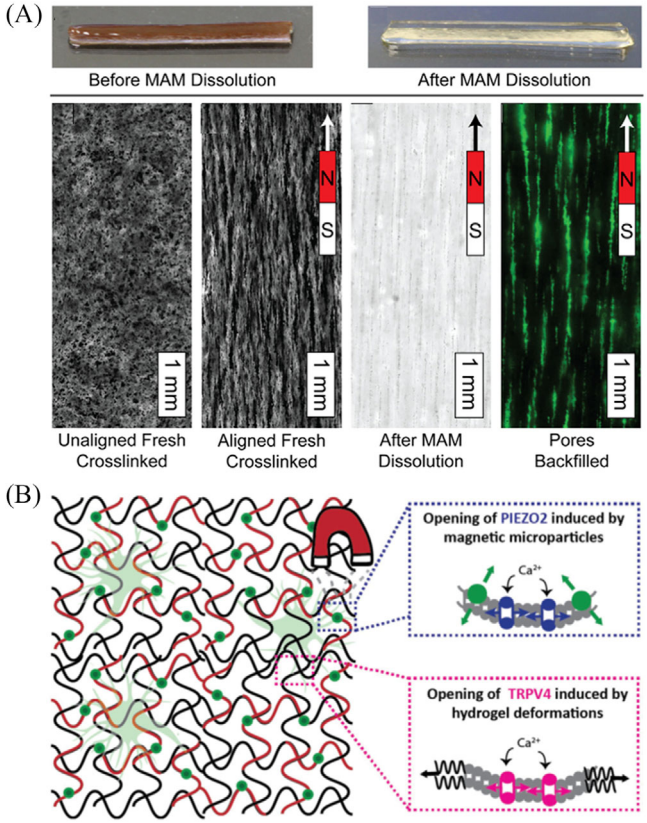

FIGURE 7 A, Macroscopic view of crosslinked hydrogel, and porous microarchitecture after removal of MAM.[68] Copyright 2020, IOP Publishing Ltd. B, Mechanism of magneto-mechanical stimulation of dorsal root ganglion neurons by magnetic hyaluronic acid (HA) hydrogels.[73] Copyright 2018, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Another important application of smart soft material is soft robot. The advent of soft robots has made great strides in robotics, wearable devices and other areas by using complete software systems that can safely interact with any random surface while provide excellent mechanical flexibility. The latest development in soft robotics have benefited from advances in soft actuators and sensors that enable robots to work mechanically unimpeded; thus, expanding the range of robotic applications.[75] Soft actuator generally refers to a soft body that can reliably adapt to any surface and cause various motions of the robot. Up to now, many attempts have been made to fabricate soft actuators sensitive to external stimuli.[76] Especially, MHs with flexibility and sensitivity to external magnetic fields are expected to form a new research focus in the coming era of soft robots.[77] What is more, taking advantage of the minimal invasions and the drive ability to use magnetic fields of magnetic microrobots, therapeutic drugs can be delivered to target areas.[78] This controlled release method can significantly reduce the dosage and minimize the side effects on normal cells. Sukho park presented a

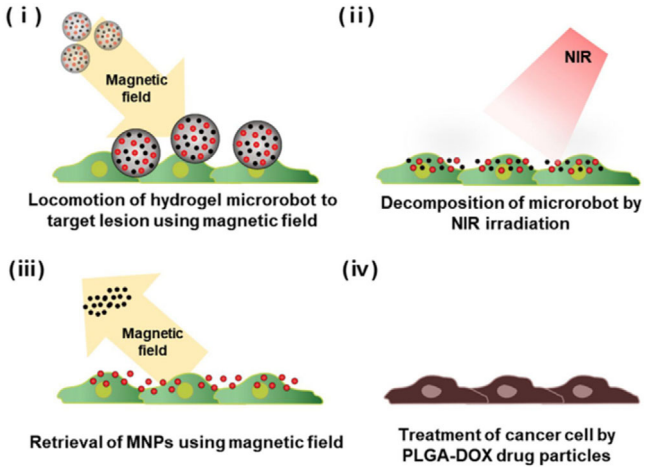

FIGURE 8 Schematic diagram of the treatment process using retrievable biodegradable hydrogel microrobot for drug delivery. Reproduced with permission.[79] Copyright 2019, Elsevier

novel hydrogel actuator (Figure 8),[79] which can deliver anticancer drugs to cancer targets through a customized near-infrared (NIR) and electromagnetic actuation (EMA) integrated system, then retrieve problematic MNPs. First, the microrobot reaches the predetermined lesion target through the magnetic field of EMA. Next, after the NIR irradiation, the hydrogel matrix was decomposed, drug particles and MNPs were left in the target tissue. Finally, with the assistance of EMA magnetic field, the disassembled MNPs were recovered from the target region, and the remaining anticancer drugs are continuously released to generate therapeutic effects. This hydrogel actuator can compensate for the inherent disadvantages of MNPs (toxicity) by retrieval of MNPs, thereby maintaining the advantages of electromagnetic drive (target characteristics and drug delivery). In the future, developing a practical drug delivery hydrogel robot is an attractive topic.

2.6 | Biocompatibility

Biocompatibility refers to the degree of compatibility of materials with human body after implantation, that is, whether they will cause toxic effects on human tissues. It mainly includes blood compatibility and histocompatibility. Blood compatibility refers to the ability of materials to interact with blood directly without causing coagulation, thrombosis, damaging blood composition and function. Hydrogel directly contacting blood requires good blood compatibility, such as hemostatic dressing.[80] Histocompatibility is the affinity between materials and tissues without being eroded by tissues when they come into contact with organs. Tissue engineering and regenerative medicine research put more emphasis on the

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

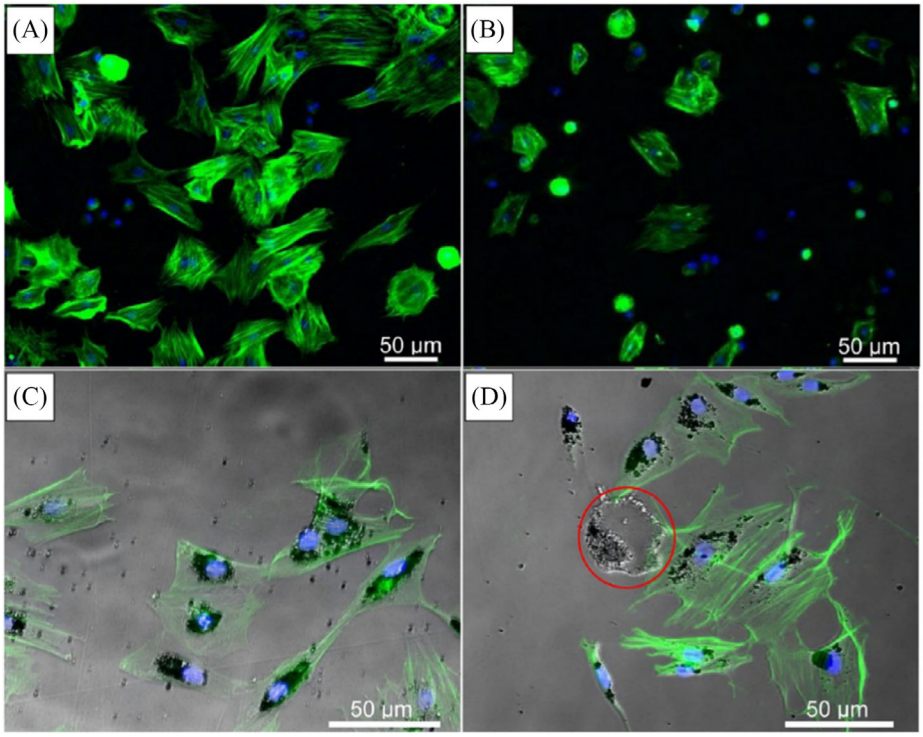

FIGURE 9 Cytocompatibility of magnetic nanocomposite hydrogels (MagGel).[86] Fluorescence images of BMSCs adhesion and morphology cultured on (a) MagGel and (b) gel. c-d, The endocytosis of magnetic nanoparticles by BMSCs. Black: magnetic nanoparticles; Blue: nucleus; Green: F-actin; Red circle: magnetic nanoparticles outside of the BMSCs. Reproduced with permission.[86] Copyright 2015, American Chemical Society

histocompatibility and cytocompatibility of hydrogels.[81] Generally, strict biocompatibility evaluation is required first to ensure the clinical safety of biomaterials. At present, the biocompatibility evaluation of hydrogels is mainly from the following aspects: cytotoxicity, hemolysis test, acute systemic toxicity, subacute toxicity test, implant test evaluation and so on.

In recent years, MHs find widespread applications in biomedical fields due to their similar structure to native extracellular matrix, hydrated environment, tunable properties (mechanical, biocompatibility) and unique active response characteristics. Fibrin, chitosan, hyaluronic acid, collagen and other natural biomaterials are the preferred raw materials for preparing medical MHs hydrogel matrix.[82] The reason is that they have excellent biocompatibility, low toxicity, enzyme degradation and degradation products are not easy to trigger immune response. Some compounds are decomposed into small molecules (water, carbon dioxide, etc.) that can be metabolized by human body, such as polyglycolic acid. Therefore, these compounds can also be widely used in the synthesis of biocompatible MHs. In addition, the concentration of MNPs in most MHs is generally less than 1 wt.%, but it has a positive effect on cells. Huang has proposed that the existence of magnetic Fe_3O_4 nanoparticles can promote the growth of stem cells and accelerate the cell cycle process.[83] When MNPs are incorporated into the scaffold, their magnetic field effect may affect ion channels on cell membrane and initiate changes in cytoskeleton structure.[84] However, the biosafety issues related to MNPs is the impact of MNPs released from the degradation of implanted MHs. In general, MNPs (1~20 nm in diameter) selected for preparing MHs can be absorbed by the interaction with proteins and cells. They can then distribute to different organs, where they may stay in the same nanostructure or be metabolized.[85]

Liu and his colleagues created a magnetic hydrogel (MagGel) containing type II collagen, hyaluronic acid and polyethylene glycol to provide a biomimetic, bioactive and biodegradable platform for cartilage tissue engineering.[86] In cell experiments, MagGel has the highest average cell adhesion density, indicating its excellent cytocompatibility. This is attributed to the synergistic effect of hydrogel matrix and magnetic nanoparticles to improve cytocompatibility,[87] including adhesion and growth. First, hydrogel mimics the extracellular matrix, providing a favorable environment for cells. Second, the interaction between magnetic nanoparticles and BMSCs might promotes cell adhesion and growth. In addition, BMSCs were observed to phagocytize magnetic nanoparticles in cell culture without any effect on cell adhesion or morphology (Figure 9).[88] The authors suggest that the

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

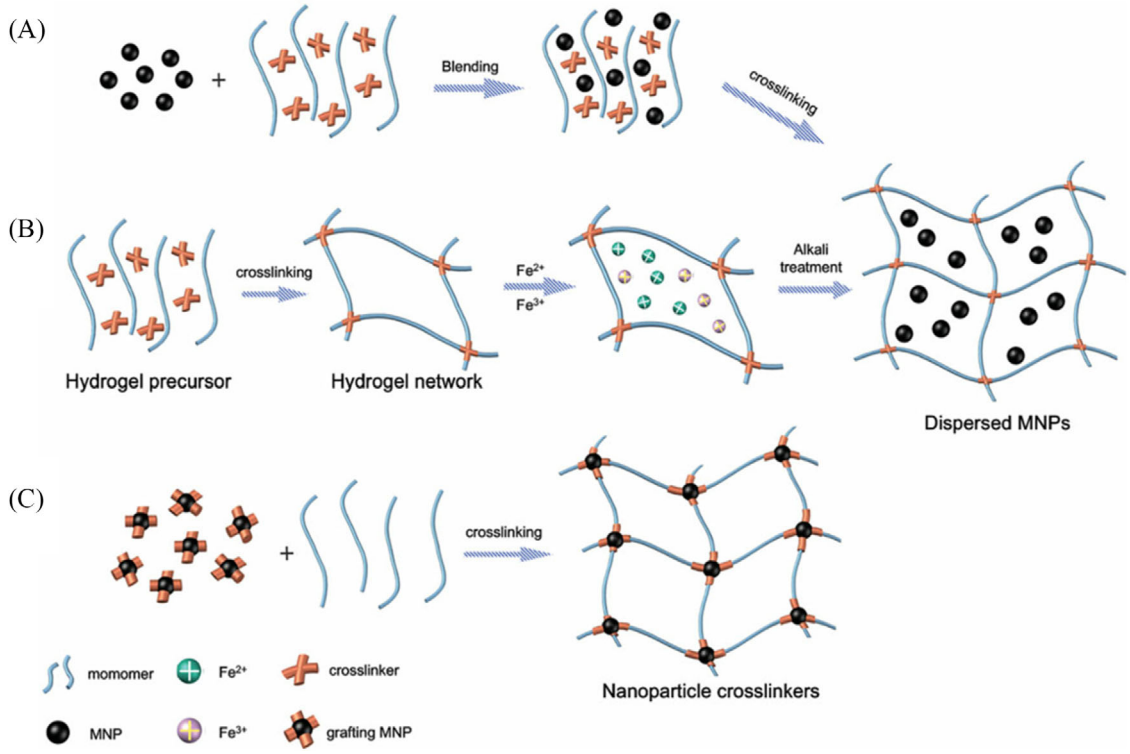

FIGURE 10 Preparation technology of MHs. a, The blending method:[89] the prepared MNPs was mixed with a hydrogel precursor solution and crosslink hydrogels to embed the MNPs. b, In-situ precipitation method:[91] MNPs was prepared by in-situ precipitation reaction in polymer hydrogel network after cross-linking reaction. c, The grafting-onto method:[93] MNPs and hydrogel systems are connected by covalent or coordination bonds. Reprinted with permission.[94] Copyright 2012, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

ingested nanoparticles may eventually be decomposed by lysosomes and excreted by exocytosis.

3 | FABRICATION PROCESSING OF MHs

MHs are generally composed of polymer matrix and magnetic components embedded in the matrix (such as γ-Fe_2O_3, Fe_3O_4). Up to now, various methods have been developed to prepare MHs, including blending method, in-situ precipitation method and grafting-onto method.

The blending method refers to simply mixing the pre-prepared MNPs with hydrogel precursor solution, so that MNPs is covered in hydrogels (Figure 10A).[89] This is the simplest and most commonly method for fabricating MHs. However, the hydrogel obtained by simple blending method usually has the defects of uneven distribution of magnetic particles in colloids. This may result in unstable properties (mechanical, magnetocaloric, MR imaging) of the prepared MHs.

In the in-situ precipitation method,[90] the hydrogel network work as a chemical reactor, within which metal ions react with precipitating agents (NaOH, $NH_3 \cdot H_2O$, etc.) to generate MNPs (Figure 10B). For example, Ye and Shen prepared a novel magnetic chitosan/polyvinyl alcohol hydrogel beads (MCPHBs) by freeze-thaw method combined with in-situ precipitation method.[91] First, the prepared PVA solution was mixed with CS solution, and then Fe^{3+} and Fe^{2+} solutions were added. Then, the mixed solution was added to the beaker containing ammonium hydroxide to form MNPs. Finally, MHs beads were obtained by repeated freezing and thawing. However, the preparation of MHs by in-situ precipitation is often limited by alkali-resistant hydrogel matrix.

Apparently, for both blending method and in-situ precipitation, there are no bonding interactions between MNPs and hydrogel networks. Therefore, the stability of MNPs dispersed in hydrogels cannot be guaranteed. The generalized grafting-onto method,[92] including modifying or changing the structure and properties of MNPs, can connect MNPs and hydrogel systems through covalent or coordination bonds (Figure 10C). This direct coupling allows MNPs to be stably and uniformly embedded in the hydrogel. Recently, our group fabricated a magnetic nano-Fe_3O_4 composite polyolefin-chitosan (AAD-CS-Fe) double network hydrogel by grafting-onto method.[93] A large amount of Fe ions is exposed on the surface of nano-Fe_3O_4 pre-etched by HCl, which can be cross-linked with the active groups (carboxyl and hydroxyl) in the hydrogel

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

system. In this way, magnetic AAD-CS-Fe hydrogel with uniform structure and stable properties can be obtained.

4 | CONCLUSION REMARKS

MHs are composed of magnetic components (such as γ-Fe_2O_3) and hydrogel matrix. The incorporation of MNPs can enhance the initial performances (mechanical properties, adsorption, etc.) of the hydrogel, while providing further magnetic properties (magnetocaloric, MR imaging and intelligent response, etc.). In recent years, MHs have attracted worldwide attention as a potential multifunctional intelligent soft platform. This paper focuses on six major functions of MHs, including mechanical properties, adsorption, magnetocaloric effects, MR imaging, intelligent response and biocompatibility. The design strategies of various functions, as well as its application prospects in biomedicine, soft actuators, environmental protection, chemical catalysis and engineering in recent 5 years are reviewed. In addition, the classical fabrication processing of MHs was introduced.

To further promote the development and practical application of MHs, its future research focuses include the following aspects:

1. At present, the magnetic component in MHs is mainly confined to iron-containing nanoparticles. Further exploration of other MNPs to enhance thermotherapy, MRI contrast and intelligent response is of great significance for promoting the practical application of multifunctional MHs.
2. MHs have important application prospects in biomedical fields, mainly including tissue engineering, because of their unparalleled advantages such as in situ magnetocaloric therapy, magnetocaloric drive and MR imaging. However, a lot of work remains to be done on the long-term fate of implanting MHs to truly achieve clinical application, such as metabolism and biodegradability evaluation.[95]
3. The development of MHs in the future depends largely on the synthesis of novel multi-functional hydrogels. Combining magnetic stimulation with other stimuli, such as light,[96] electricity,[97] temperature,[98] pH,[99] and redox,[100] MHs will become more intelligent and versatile.

ACKNOWLEDGMENTS

This work was supported by the Natural Sciences Foundation of China (21977083); Natural Sciences Foundation of China (No. 52072210); Tsinghua University-Peking Union Medical College Hospital Initiative Scientific Research Program (grant number 20191080871); Tsinghua University Initiative Scientific Research Program [grant number 2017THZWYX07].

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Fangli Gang https://orcid.org/0000-0002-1507-2539

REFERENCES

1. a) Y. S. Zhang, A. Khademhosseini, *Science* **2017**, *356*, eaaf3627;. b) T. Nonoyama, J. P. Gong, *Proc. Inst. Mech. Eng. H* **2015**, *229*, 853; c) N. A. Jalili, M. Muscarello, A. K. Gaharwar, *Bioeng. Transl. Med.* **2016**, *1*, 2975.
2. a) Z. Gu, K. Huang, Y. Luo, L. Zhang, T. Kuang, Z. Chen, G. Liao, *WIREs Nanomed Nanobiotechnol.* **2018**, *10*, e1520; b) Y. Wu, H. Wang, F. Gao, Z. Xu, F. Dai, W. Liu, *Adv. Funct. Mater.* **2018**, *28*, 1801000.
3. a) N. Rodkate, M. Rutnakornpituk, *Carbohydr. Polym.* **2016**, *151*, 251; b) M. Karzar Jeddi, M. Mahkam, *Int. J. Biol. Macromol.* **2019**, *135*, 829.
4. a) N. S. Satarkar, D. Biswal, J. Z. Hilt, *Soft Matter* **2010**, *6*, 2364; b) J. Zhang, Q. Huang, J. Du, *Polym. Int.* **2016**, *65*, 1365.
5. a) X. Chen, M. Fan, H. Tan, B. Ren, G. Yuan, Y. Jia, J. Li, D. Xiong, X. Xing, X. Niu, X. Hu, *Mater. Sci. Eng. C Mater. Biol. Appl.* **2019**, *101*, 619; b) X. Hu, Y. Wang, L. Zhang, M. Xu, J. Zhang, W. Dong, *Int. J. Biol. Macromol.* **2018**, *107*, 1811.
6. Y. P. Jia, K. Shi, F. Yang, J. F. Liao, R. X. Han, L. P. Yuan, Y. Hao, M. Pan, Y. Xiao, Z. Y. Qian, X. W. Wei, *Adv. Funct. Mater.* **2020**, *30*, 2001059.
7. R. Patwa, N. Saha, P. Sáha, *AIP Conference Proceedings* **2020**, *2205*, 020027.
8. a) T. Jin, F. J. Nicholls, W. R. Crum, H. Ghuman, S. F. Badylak, M. Modo, *Biomaterials* **2017**, *113*, 176; b) X. Yang, Y. Sun, S. Kootala, J. Hilborn, A. Heerschap, D. Ossipov, *Carbohydr. Polym.* **2014**, *110*, 95.
9. Y. Guo, J. Bae, Z. Fang, P. Li, F. Zhao, G. Yu, *Chem. Rev.* **2020**, *120*, 7642.
10. a) J. Yeom, A. Choe, S. Lim, Y. Lee, S. Na, H. Ko, *Sci. Adv.* **2020**, *6*, eaba5785; b) Y. Ye, Y. Zhang, Y. Chen, X. Han, F. Jiang, *Adv. Funct. Mater.* **2020**, *30*, 2003430; c) K. Liu, Y. Zhang, H. Cao, H. Liu, Y. Geng, W. Yuan, J. Zhou, Z. L. Wu, G. Shan, Y. Bao, Q. Zhao, T. Xie, P. Pan, *Adv. Mater.* **2020**, *32*, e2001693.
11. F. Gao, W. Xie, Y. Miao, D. Wang, Z. Guo, A. Ghosal, Y. Li, Y. Wei, S. Feng, L. Zhao, H. Fan, *Adv. Healthcare Mater.* **2019**, *8*, e1900203.
12. H. Liu, J. Yang, Y. Yin, H. Qi, *Chin. J. Chem.* **2020**, *38*, 1263.
13. K. Liu, X. Pan, L. Chen, L. Huang, Y. Ni, J. Liu, S. Cao, H. Wang, *ACS Sustain. Chem. Eng.* **2018**, *6*, 6395.
14. X. Hu, Y. Wang, M. Xu, L. Zhang, J. Zhang, W. Dong, *Polymer Testing* **2018**, *71*, 344.
15. Y. Wang, J. Zhang, C. Qiu, J. Li, Z. Cao, C. Ma, J. Zheng, G. Huang, *Carbohydr. Polym.* **2018**, *196*, 82.
16. M. Chen, G. Gong, L. Zhou, F. Zhang, *RSC Adv.* **2017**, *7*, 21476.
17. L. Shi, Y. Zeng, Y. Zhao, B. Yang, D. Ossipov, C.W. Tai, J. Dai, C. Xu, *ACS Appl. Mater. Interfaces* **2019**, *11*, 46233.
18. A. B. Bonhome-Espinosa, F. Campos, I. A. Rodriguez, V. Carriel, J. A. Marins, A. Zubarev, J. D. G. Duran, M. T. Lopez-Lopez, *Soft Matter* **2017**, *13*, 2928.

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

19. a) S. Liu, A. K. Bastola, L. Li, *ACS Appl. Mater. Interfaces* **2017**, *9*, 41473; b) F. Chen, Q. Chen, L. Zhu, Z. Tang, Q. Li, G. Qin, J. Yang, Y. Zhang, B. Ren, J. Zheng, *Chem. Mat.* **2018**, *30*, 1743; c) S. Azevedo, A. M. S. Costa, A. Andersen, I. S. Choi, H. Birkedal, J. F. Mano, *Adv. Mater.* **2017**, *29*, 1700759.
20. A. Bin Imran, K. Esaki, H. Gotoh, T. Seki, K. Ito, Y. Sakai, Y. Takeoka, *Nat. Commun.* **2014**, *5*, 5124.
21. a) X. H. Wang, F. Song, D. Qian, Y. D. He, W. C. Nie, X. L. Wang, Y. Z. Wang, *Chem. Eng. J.* **2018**, *349*, 588; b) H. Wang, H. Zhu, W. Fu, Y. Zhang, B. Xu, F. Gao, Z. Cao, W. Liu, *Macromol. Rapid Commun.* **2017**, *38*, 1600695.
22. a) P. Zhu, M. Hu, Y. Deng, C. Wang, *Adv. Eng. Mater.* **2016**, *18*, 1799; b) Y. Zhai, H. Duan, X. Meng, K. Cai, Y. Liu, L. Lucia, *Macromol. Mater. Eng.* **2015**, *300*, 1290.
23. a) Z. Liu, J. Liu, X. Cui, X. Wang, L. Zhang, P. Tang, *Pharmaceutics* **2018**, *10*, 145; b) S. Veloso, P. Ferreira, J. Martins, P. Coutinho, E. Castanheira, *Smart Mater. Struct.* **2016**, *25*, 027001; c) H. Li, G. Go, S.Y. Ko, J. O. Park, S. Park, *Smart Mater. Struct.* **2016**, *25*, 027001; d) D. I. Kim, S. Song, S. Jang, G. Kim, J. Lee, Y. Lee, S. Park, *Smart Mater. Struct.* **2020**, *29*, 085024.
24. a) Q. Liu, H. Li, K.Y. Lam, *Bioelectrochemistry* **2019**, *129*, 90; b) R. Singh, A. Wieser, S. Reakasame, R. Detsch, B. Dietel, C. Alexiou, A. R. Boccaccini, I. Cicha, *J. Biomed. Mater. Res. A* **2017**, *105*, 2948; c) M. Santhosh, J. H. Choi, J. W. Choi, *Nanomaterials (Basel)* **2019**, *9*, 1293.
25. a) J. Huang, P. Zhang, M. Li, P. Zhang, L. Ding, *Biochem. Eng. J.* **2016**, *114*, 262; b) S. Tang, K. Hu, J. Sun, Y. Li, Z. Guo, M. Liu, Q. Liu, F. Zhang, N. Gu, *ACS Appl. Mater. Interfaces* **2017**, *9*, 10446; c) X. Shi, Z. Shi, D. Wang, M. W. Ullah, G. Yang, *Macromol. Biosci.* **2016**, *16*, 1506.
26. a) J. Li, S. Dong, Y. Wang, X. Dou, H. Hao, *J. Environ. Sci. (China)* **2020**, *91*, 177; b) G.M. Ispas, S. Porav, D. Gligor, R. Turcu, I. Crăciunescu, *Water Environ. J.* **2020**, *34*, 916.
27. a) N. Malatji, E. Makhado, K. E. Ramohlola, K. D. Modibane, T. C. Maponya, G. R. Monama, M. J. Hato, *Environ. Sci. Pollut. Res.* **2020**, *27*, 44089; b) N. Sarkar, G. Sahoo, S. K. Swain, *Journal of Molecular Liquids* **2020**, *302*, 112591.
28. R. Sahraei, Z. Sekhavat Pour, M. Ghaemy, *J. Clean. Prod.* **2017**, *142*, 2973.
29. H. M. Yang, J. R. Hwang, D. Y. Lee, K. B. Kim, C. W. Park, H. R. Kim, K. W. Lee, *Sci. Rep.* **2018**, *8*, 11476.
30. S. Dong, Y. Wang, *Water. Res.* **2016**, *88*, 852.
31. K. Sun, W. Peng, H. Li, S. Song, *Hydrometallurgy* **2018**, *176*, 208.
32. X. F. Sun, B. Liu, Z. Jing, H. Wang, *Carbohyd. Polym.* **2015**, *118*, 16.
33. J. Li, Y. Wang, X. Dou, H. Hao, S. Dong, X. Shao, Y. Deng, *J. Environ. Sci. (China)* **2020**, *89*, 264.
34. Y. Meng, C. Li, X. Liu, J. Lu, Y. Cheng, L. P. Xiao, H. Wang, *Sci. Total Environ.* **2019**, *685*, 847.
35. S. C. Tan, H. K. Lee, *Microchim. Acta* **2019**, *186*, 545.
36. S. Wang, X. Li, M. Li, X. Li, X. Li, S. Li, Q. Zhang, H. Li, *Appl. Sci.* **2020**, *10*, 5665.
37. M. Khan, I. M. C. Lo, *J. Hazard. Mater.* **2017**, *322*, 195.
38. S. Dong, Y. Wang, Y. Zhao, X. Zhou, H. Zheng, *Water Res.* **2017**, *126*, 433.
39. A. A. Edathil, E. Alhseinat, F. Banat, *International Journal of Greenhouse Gas Control* **2019**, *83*, 117.
40. S. Pirsa, F. Asadzadeh, I. Karimi Sani, *J. Inorg. Organomet. Polym. Mater.* **2020**, *30*, 3188.
41. P. Pal, A. A. Edathil, L. Chaurasia, K. Rambabu, F. Banat, *J. Inorg. Organomet. Polym. Mater.* **2020**, *30*, 3188.
42. D. P. Facch, A. L. Cazetta, E. A. Canesin, V. C. Almeida, E. G. Bonafé, M. J. Kipper, A. F. Martins, *Chem. Eng. J.* **2018**, *337*, 595.
43. G. Yao, W. Bi, H. Liu, *Colloids and Surfaces A* **2020**, *588*, 124393.
44. E. Yan, M. Cao, X. Ren, J. Jiang, Q. An, Z. Zhang, J. Gao, X. Yang, D. Zhang, *J.Phys. Chem. Solids* **2018**, *121*, 102.
45. a) K. Rajar, E. Alveroglu, *Journal of Molecular Structure* **2017**, *1146*, 592; b) M. Soleymani, A. Akbari, G. R. Mahdavinia, *Polymer Bulletin* **2018**, *76*, 2321; c) G. R. Mahdavinia, M. Soleymani, H. Etemadi, M. Sabzi, Z. Atlasi, *Int. J. Biol. Macromol.* **2018**, *107*, 719.
46. G. R. Mahdavinia, S. Mousanezhad, H. Hosseinzadeh, F. Darvishi, M. Sabzi, *Carbohydr. Polym.* **2016**, *147*, 379.
47. J. Song, W. He, H. Shen, Z. Zhou, M. Li, P. Su, Y. Yang, *Chem. Commun. (Camb)* **2019**, *55*, 2449.
48. S. Li, Z. Zhu, Z. Hu, H. Sun, P. Mu, C. Xiao, W. Liang, L. Chen, A. Li, *J. Appl. Polym. Sci.* **2018**, *135*, 46869.
49. Q. Gui, Y. Zhou, S. Liao, Y. He, Y. Tang, Y. Wang, *Soft Matter* **2019**, *15*, 393.
50. M. K. Lima-Tenório, E. T. Tenório-Neto, M. R. Guilherme, F. P. Garcia, C. V. Nakamura, E. A. G. Pineda, A. F. Rubira, *Chem. Eng. J.* **2015**, *259*, 620.
51. X. Zhou, L. Wang, Y. Xu, W. Du, X. Cai, F. Wang, Y. Ling, H. Chen, Z. Wang, B. Hu, Y. Zheng, *RSC Adv*. **2018**, *8*, 9812.
52. Y. Zhang, Y. Cheng, C. Chen, Q. Liu, X. Bi, L. Duan, J. Liu, M. Wan, L. Huang, K. Hu, *J. Biomed. Nanotechnol.* **2018**, *14*, 594.
53. B. Chen, J. Xing, M. Li, Y. Liu, M. Ji, *Colloids Surf. B Biointerfaces* **2020**, *190*, 110896.
54. K. Hu, J. Sun, Z. Guo, P. Wang, Q. Chen, M. Ma, N. Gu, *Adv. Mater.* **2015**, *27*, 2507.
55. a) H. Wu, L. Song, L. Chen, Y. Huang, Y. Wu, F. Zang, Y. An, H. Lyu, M. Ma, J. Chen, N. Gu, Y. Zhang, *Nanoscale* **2017**, *9*, 16175; b) H. Wu, L. Song, L. Chen, W. Zhang, Y. Chen, F. Zang, H. Chen, M. Ma, N. Gu, Y. Zhang, *Acta Biomater*. **2018**, *74*, 302; c) R. Jahanban-Esfahlan, H. Derakhshankhah, B. Haghshenas, B. Massoumi, M. Abbasian, M. Jaymand, *Int. J. Biol. Macromol.* **2020**, *156*, 438.
56. H. Wu, L. Liu, L. Song, M. Ma, N. Gu, Y. Zhang, *ACS Nano* **2019**, *13*, 14013.
57. a) J. Huang, Z. Jia, Y. Liang, Z. Huang, Z. Rong, J. Xiong, D. Wang, *RSC Adv*. **2020**, *10*, 541; b) A. B. Bonhome-Espinosa, F. Campos, D. Durand-Herrera, J. D. Sanchez-Lopez, S. Schaub, J. D. G. Duran, M. T. Lopez-Lopez, V. Carriel, *J. Mech. Behav. Biomed. Mater.* **2020**, *104*, 103619.
58. a) S. Zhang, L. Wu, J. Cao, K. Wang, Y. Ge, W. Ma, X. Qi, S. Shen, *Colloids Surf. B Biointerfaces* **2018**, *170*, 224; b) S. M. Lee, H. J. Kim, Y. J. Ha, Y. N. Park, S. K. Lee, Y. B. Park, K. H. Yoo, *ACS Nano* **2013**, *7*, 50; c) S. Wang, J. Lv, S. Meng, J. Tang, L. Nie, *Adv. Healthcare Mater.* **2020**, *9*, e1901541.
59. W. Wang, X. Fan, F. Li, J. Qiu, M.M. Umair, W. Ren, B. Ju, S. Zhang, B. Tang, *Adv. Optical Mater.* **2018**, *6*, 1701093.
60. a) T. Cheng, M. Mishkovsky, M. J. Junk, K. Munnemann, A. Comment, *Macromol. Rapid Commun.* **2016**, *37*, 1074; b) R. Bakalova, B. Nikolova, S. Murayama, S. Atanasova, Z. Zhelev, I. Aoki, M. Kato, I. Tsoneva, T. Saga, *Anal. Bioanal. Chem.* **2016**, *408*, 905.
61. a) Q. Li, Z. Feng, H. Song, J. Zhang, A. Dong, D. Kong, W. Wang, P. Huang, *Biomater. Sci.* **2020**, *8*, 3301; b) V. Nandwana, S.-R.

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Ryoo, T. Zheng, M. M. You, V. P. Dravid, *ACS Biomater. Sci. Eng.* **2019**, *5*, 3049.
62. Z. Chen, C. Yan, S. Yan, Q. Liu, M. Hou, Y. Xu, R. Guo, *Theranostics* **2018**, *8*, 1146.
63. E. Roeder, C. Henrionnet, J. C. Goebel, N. Gambier, O. Beuf, D. Grenier, B. Chen, P. Vuissoz, P. Gillet, A. Pinzano, *PLoS One* **2014**, *9*, e98451.
64. Q. Zhang, H. Lu, N. Kawazoe, G. Chen, *Acta Biomater.* **2014**, *10*, 2005.
65. Q. Liu, M. Liu, H. Li, K. Y. Lam, *International Journal of Solids and Structures* **2020**, *190*, 76.
66. a) B. Rashidzadeh, E. Shokri, G. R. Mahdavinia, R. Moradi, S. Mohamadi-Aghdam, S. Abdi, *Int. J. Biol. Macromol.* **2020**, *154*, 134; b) W. Shi, J. Huang, R. Fang, M. Liu, *ACS Appl. Mater. Interfaces* **2020**, *12*, 5177; c) O. Goncharuk, Y. Samchenko, D. Sternik, L. Kernosenko, T. Poltorats'ka, N. Pasmurtseva, M. Abramov, E. Pakhlov, A. Derylo-Marczewska, *Applied Nanoscience* **2020**, *10*, 4559; d) M. R. Nematollahi, M. Montazer, *J. Appl. Polym. Sci.* **2020**, *137*, 48961.
67. M. Noh, Y. H. Choi, Y.-H. An, D. Tahk, S. Cho, J. W. Yoon, N. L. Jeon, T. H. Park, J. Kim, N. S. Hwang, *ACS Biomater. Sci. Eng.* **2019**, *5*, 3909.
68. C. S. Lacko, I. Singh, M. A. Wall, A. R. Garcia, S. L. Porvasnik, C. Rinaldi, C. E. Schmidt, *J. Neural. Eng.* **2020**, *17*, 016057.
69. K. Liu, L. Han, P. Tang, K. Yang, D. Gang, X. Wang, K. Wang, F. Ren, L. Fang, Y. Xu, Z. Lu, X. Lu, *Nano Lett.* **2019**, *19*, 8343.
70. M. Namdari, A. Eatemadi, *Artif. Cells Nanomed. Biotechnol.* **2017**, *45*, 731.
71. H. Y. Lin, H. Y. Huang, S. J. Shiue, J. K. Cheng, *J. Magn. Magn. Mater.* **2020**, *504*, 166680.
72. J. J. Pavon, J. P. Allain, D. Verma, M. Echeverry-Rendon, C. L. Cooper, L. M. Reece, A. R. Shetty, V. Tomar, *Macromol. Biosci.* **2019**, *19*, e1800225.
73. A. Tay, A. Sohrabi, K. Poole, S. Seidlits, D. Di Carlo, *Adv. Mater.* **2018**, *30*, 1800927.
74. A. Tay, F. E. Schweizer, D. Di Carlo, *Lab. Chip.* **2016**, *16*, 1962.
75. a) Y. Lin, Y. Sun, Y. Dai, W. Sun, X. Zhu, H. Liu, R. Han, D. Gao, C. Luo, X. Wang, *Talanta* **2020**, *207*, 120300; b) J. Y. Wang, Q. Y. Guo, Z. Y. Yao, N. Yin, S. Y. Ren, Y. Li, S. Li, Y. Peng, J. L. Bai, B. A. Ning, J. Liang, Z. X. Gao, *Mikrochim. Acta* **2020**, *187*, 333.
76. L. Vikingsson, A. Vinals-Guitart, A. Valera-Martínez, J. Riera, A. Vidaurre, G. Gallego Ferrer, J. L. Gómez Ribelles, *J. Mater. Sci.* **2016**, *51*, 9979.
77. a) X. Ma, Z. Yang, Y. Wang, G. Zhang, Y. Shao, H. Jia, T. Cao, R. Wang, D. Liu, *ACS Appl. Mater. Interfaces* **2017**, *9*, 1995; b) J. Li, F. Ji, D. H. L. Ng, J. Liu, X. Bing, P. Wang, *Chemical Engineering Journal* **2019**, *369*, 611.
78. a) G. Babaladimath, V. Badalamoole, *Polymer International* **2018**, *67*, 983; b) J. Supramaniam, R. Adnan, N. H. Mohd Kaus, R. Bushra, *Int. J. Biol. Macromol.* **2018**, *118*, 640; c) M. P. Kesavan, S. Ayyanaar, N. Lenin, M. Sankarganesh, J. Dhaveethu Raja, J. Rajesh, *J. Biomed. Mater. Res. A* **2018**, *106*, 543.
79. a) D. I. Kim, H. Lee, S. H. Kwon, Y. J. Sung, W. K. Song, S. Park, *Adv. Healthcare Mater.* **2020**, *9*, e2000118; b) D. I. Kim, H. Lee, S. H. Kwon, H. Choi, S. Park, *Sensors and Actuators B: Chemical* **2019**, *289*, 65.
80. a) Y. Hong, F. Zhou, Y. Hua, X. Zhang, C. Ni, D. Pan, Y. Zhang, D. Jiang, L. Yang, Q. Lin, Y. Zou, D. Yu, D. N. Arnot, X. Zou, L. Zhu, S. Zhang, H. Ouyang, *Nat. Commun.* **2019**, *10*, 2060; b) Y. Huang, X. Zhao, Z. Zhang, Y. Liang, Z. Yin, B. Chen, Y. Han, B. Guo, *Chem. Mat.* **2020**, *32*, 6595.
81. S. Khorshidi, A. Karkhaneh, *J. Tissue Eng. Regen. Med.* **2018**, *12*, 1974.
82. a) M. S. Amini-Fazl, R. Mohammadi, K. Kheiri, *International Journal of Biological Macromolecules* **2019**, *132*, 506; b) W. Xie, Q. Gao, Z. Guo, D. Wang, F. Gao, X. Wang, Y. Wei, L. Zhao, *ACS Appl. Mater. Interfaces* **2017**, *9*, 33660.
83. D. Huang, J. Hsiao, Y. Chen, L. Chien, M. Yao, Y. Chen, B. Ko, S. Hsu, L. Tai, H. Cheng, S. Wang, C. Yang, Y. Chen, *Biomaterials* **2009**, *30*, 3645.
84. S. Hughes, A. El Haj, J. Dobson, *Med. Eng. Phys.* **2005**, *27*, 754.
85. G. Liu, J. Gao, H. Ai, X. Chen, *small* **2013**, *9*, 1533.
86. N. Zhang, J. Lock, A. Sallee, H. Liu, *ACS Appl. Mater. Interfaces* **2015**, *7*, 20987.
87. a) S. Hughes, A. J. El Haj, J. Dobson, *Med. Eng. Phys.* **2005**, *27*, 754; b) J. F. Shen, Y. L. Chao, L. Du, *Neurosci. Lett.* **2007**, *415*, 164.
88. S. Park, H. S. Kim, W. J. Kim, H. S. Yoo, *Int. J. Pharm.* **2012**, *424*, 107.
89. a) J. Liang, B. He, P. Li, J. Yu, X. Zhao, H. Wu, J. Li, Y. Sun, Q. Fan, *Chem. Eng. J.* **2019**, *358*, 552; b) F. Fan, J. Sun, B. Chen, Y. Li, K. Hu, P. Wang, M. Ma, N. Gu, *Science China Materials* **2018**, *61*, 1112.
90. A. A. Mohamed, G. A. Mahmoud, M. R. E. ElDin, E. A. Saad, *Polymer-Plastics Technology and Materials* **2019**, *59*, 357.
91. W. Wang, H. Zhang, J. Shen, M. Ye, *Colloids and Surfaces A: Physicochemical and Engineering Aspects* **2018**, *553*, 672.
92. M. Hayati, G. R. Bardajee, M. Ramezani, S. S. Hosseini, F. Mizani, *Polym. Int.* **2020**, *69*, 156.
93. F. Gang, H. Yan, C. Ma, L. Jiang, Y. Gu, Z. Liu, L. Zhao, X. Wang, J. Zhang, X. Sun, *Chem. Commun.* **2019**, *55*, 9801.
94. Y. Li, G. Huang, X. Zhang, B. Li, Y. Chen, T. Lu, T. J. Lu, F. Xu, *Adv. Funct. Mater.* **2013**, *23*, 660.
95. Z. Liu, J. Liu, X. Cui, X. Wang, L. Zhang, P. Tang, *Front. Chem.* **2020**, *8*, 124.
96. S. Cho, A. Kim, W. Shin, M. B. Heo, H. J. Noh, K. S. Hong, J. Cho, Y. T. Lim, *Int. J. Nanomedicine* **2017**, *12*, 2607.
97. K. H. Didehban, L. Mohammadi, J. Azimvand, *Materials Chemistry and Physics* **2017**, *195*, 162.
98. H. Qiao, J. Jia, W. Chen, B. Di, O. A. Scherman, C. Hu, *Adv. Healthcare Mater.* **2019**, *8*, e1801458.
99. S. Rittikulsittichai, A. G. Kolhatkar, S. Sarangi, M. A. Vorontsova, P. G. Vekilov, A. Brazdeikis, T. R. Lee, *Nanoscale* **2016**, *8*, 11851.
100. J. T. Auletta, G. J. LeDonne, K. C. Gronborg, C. D. Ladd, H. T. Liu, W. W. Clark, T. Y. Meyer, *Macromolecules* **2015**, *48*, 1736.

AUTHOR BIOGRAPHIES

Fangli Gang received her PhD degree in chemical biology from Northwest A&F University in 2020. Currently, she joined the Biology department of Xinzhou Teachers University. Her research interests are mainly focused on functional hydrogel materials and their biomedical applications.

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Xiaodan Sun received her PhD degree in engineering from Tsinghua University under the supervision of Prof. Hengde Li. At present, she is an associate researcher in the School of Materials of Tsinghua University. Her current research is on the nano biomaterials, osteochondral tissue engineering, nerve tissue engineering, tumor diagnosis and treatment.

How to cite this article: F. Gang, L. Jiang, Y. Xiao, J. Zhang, X. Sun, *Nano Select* **2021**, *2,* 2291. https://doi.org/10.1002/nano.202100139

26884011, 2021, 12, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nano.202100139 by CAPES, Wiley Online Library on [23/12/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License