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Editorial

Advanced Materials for High Biocompatible Hydrogel System

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Hydrogels are gels with water as the dispersion medium and three-dimensional porous polymer networks cross-linked chemically or physically. Due to their inherent hydrophilic property and network structure, hydrogels can accommodate water and tissue fluids and swell but not dissolve in a physiological environment. The high-water retention three-dimensional (3D) porous polymer networks of hydrogels are very close to the natural extracellular matrix and can simulate the microenvironment of cell growth. Owing to their hydrophilic, biocompatible, highly tunable nature and human soft tissue similarity, hydrogels have broad biomedical application prospects in wound dressing [1], tissue repair [2], drug delivery [3], biosensing monitoring [4,5], biomaterial coating [6], situ transplantation [7] and other fields.

Hydrogels are formed from various natural or synthetic polymers by cross-linking. Natural polymers are materials that widely occur in nature or are extracted from plants or animals, including sodium alginate, chitosan, gelatin and silk fibroin. Synthetic polymers are human-made polymers, including Polyacrylamide (PAM), polyvinyl alcohol (PVA) and Polyethylene glycol (PEG). The physicochemical properties of hydrogels can be designed to meet the specific application demands by adjusting the proportion of hydrophilic and hydrophobic chain segments in the polymer or adding an active recognition motif.

Silk fibroin (SF) is a natural protein material produced by silkworms. Hydrogels made from SF have been widely used in tissue engineering due to their biocompatibility, adjustable secondary structure, hydrophilicity and good processability and modifiability. Hong et al. used digital light processing (DLP) 3D printing to prepare glycidyl methacrylate (GMA)-modified SF hydrogels containing rabbit-derived chondrocytes, transplanted into the defective tracheal part of a rabbit model. The results showed that GMA-modified SF hydrogels can replace the defective tracheal part and guide tracheal regeneration [8].

Polyvinyl alcohol (PVA) is a synthetic water-soluble polymer with good mechanical properties, biocompatibility and high hydrophilicity, making it widely used in biomedical materials. Darabi et al. induced crystallization by adding a high concentration of sodium hydroxide to a high-density PVA polymer, resulting in a PVA physically cross-linked hydrogel with high mechanical properties, low water content, and resistance to damage. Polyvinyl alcohol-hydroxy-vinyl acid hydrogels (PVA-hs) prepared by this method also have shape memory properties, are capable of retracting 90% of plastic deformation and have a contraction force sufficient to lift objects 1100 times their weight, so that they can be used in actuators, artificial catheters, articular cartilage and artificial muscle applications [9].

According to the different crosslinking methods, hydrogels can be divided into chemical and physical crosslinking hydrogels. Different crosslinking methods determine the performance of the hydrogels. Physical crosslinks are formed through supramolecular structures, such as van der Waals forces, hydrogen bonding, ionic bonding and hydrophobic interactions. Physical crosslinking is usually weak and reversible but is more susceptible to environmental changes. Di et al. prepared hydrogels with high tensile (680%) and elastic (92.53%) properties by incorporating modified bases as "rigid" cross-linked nanostructures into a "soft" pure hydrogen-bonded crosslinked hydrophobic bonded non-homogeneous

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network. This purely physical crosslinked "soft-hard" structure allows for tunable electromechanical behavior. The hydrogels applied to pressure and strain sensors can not only distinguish between macroscopic mechanical tension and compression but also monitor subtle physiological signals of human motion [10].

Unlike physical crosslinking, chemical crosslinking is usually non-spontaneous, formed by forming covalent bonds between molecules, and is generally not reversible. Chemical crosslinking is usually initiated by the reaction of a polymer with a small molecule crosslinker (e.g., aldehyde) or by radiation (e.g., electron beam, γ-rays or UV light). Sun et al. combined the transglutaminase (TGase) reaction with the Schiff base reaction to produce two crosslinking networks within the hydrogel that can be used to tune the mechanical properties. The aldehyde groups in the polymer chain segments can react with amine groups in the skin tissue to prepare hydrogels with mucoadhesive properties, thus, enabling in situ polymerization of hydrogels adhering to wet biological tissue surfaces. Its high adhesion, low cytotoxicity and good hemocompatibility allow it to be used as good hemostatic material, showing good hemostatic behavior in rat arterial hemorrhage and liver injury models [11].

The similarity of hydrogels to human soft tissues allows hydrogels to be used for skin wounds, nerve and cartilage repair. Qi et al. grew silver nanocrystals in situ on the surface of polydopamine (PDA) nanoparticles, then encapsulated uniformly in a cationic guar gum (CG) hydrogel matrix by a one-pot bending method. The hydrogels prepared exhibited high photothermal conversion efficiency in vitro and in vivo, resulting in excellent bactericidal activity. which has significant advantages in skin wound repair [12].

When the hydrogel is applied to the joint wound, the movement of the interface usually affects the healing, which requires the self-healing hydrogel to prolong the dressing use. In small activities, the flexibility of the hydrogel can maintain the integrity of the dressing; in large movements, the self-healing ability of the hydrogel can achieve rapid self-healing, extending its service life, thus effectively ensuring wound closure, preventing wound infection and further promoting tissue repair. Mo et al. used tannic-acid-enabled dynamic interactions (TEDI) as a complete alternative to conventional covalent crosslinking to prepare a self-healing hydrogel with super stretchability and high adhesion. TA-mediated multiple dynamic interactions, including hydrogen bonding, ligand bonding, and borate ester bonding, can provide stretchability and excellent self-healing ability and control the hydrogel's interfacial properties with good adhesion [13].

Wound healing often involves infection by bacteria, but misuse of antibiotics can lead to drug resistance, so hydrogels with antimicrobial properties have attracted much attention for soft tissue repair and regeneration. Liu et al. prepared a naturally antimicrobial, bioresorbable hydrogel by spontaneous self-aggregation of oxadiazole group-modified amphiphilic quaternary ammonium salts (QAS) conjugated poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCEC-QAS) micelle nanoparticles. PCEC-QAS nanoparticles serving as nanoantimicrobials endow the hydrogel with broad antibacterial efficiency against gram-positive and -negative bacteria, promote skin regeneration and prevent bacterial infections without additional drugs, cells, light or delivery systems [14].

When hydrogels are used for subcutaneous implantation, conventional prefabricated hydrogels can cause more significant damage during implantation. To address this issue, injectable hydrogels undergo in situ gelation when applied to the target environment, allowing the filling of irregular cavities. This makes implantation minimally invasive and enables the co-injection of drugs and biologics, which is significant for tissue engineering and drug delivery applications. Vashahi et al. studied the synthesis of thermosensitive polyethylene glycol bottlebrush blocks and poly(N-isopropylacrylamide) linear blocks as hydrophilic thermosensitive linear-bottlebrush-linear (LBL) triblock copolymer. In this copolymer, the compact conformation of the bottlebrush block leads to reduced solution viscosity. At the same time, the thermally responsive linear fragment allows rapid gelation at 37 °C and can contribute to improved material injectability [15].

Implant-associated bacterial infections impair integration between implants and soft tissues, disrupt natural tissue structure and interfere with cellular function. Combining implants with hydrogel coatings can enhance the biocompatibility of implants to meet different clinical needs. He et al. introduced a catechol motif in methacrylate gelatin (G elMA) to enhance adhesion on metallic materials. The resulting coating adhered tightly to the titanium surface and improved stability due to the encapsulated mesoporous polydopamine nanoparticles (MPDA NPs). Photobiological modulation (PBM) was then combined with photodynamic therapy (PDT) to enable the hydrogel coating to have fibroblast activation and antibacterial ability [16].

Hydrogels are very sensitive to their surroundings and can sense small external changes, which allows them to be used for sensing biological signals, including mechanical, pH, light, heat and electromagnetic signals. Hydrogels can convert external stimuli into electrical signals and mimic the human skin's flexibility and sensory properties to prepare electronic skins (E-skins). Ge et al. prepared highly stretchable and transparent PVA-polyacrylamide (PAM) hydrogels by a sol-gel process. These self-patterned hydrogels have layered wrinkled microstructures and interconnected ridges on their surfaces that improve the skin compliance and signal-to-noise ratio (SNR) of hydrogels, which allows hydrogel-based pressure sensors with high sensitivity and accurate sensing of dynamic pressure [17].

The high water content and suitable material exchange capacity properties of hydrogels also give them significant advantages for loading biological probes; for example, although gold nanoclusters (AuNCs) have a high intrinsic peroxidase-like activity and can detect the presence of H_2O_2 well, their aqueous solutions are unstable and not convenient for direct application in physiological environments, such as certain specific tissues in vivo. Wang et al. used hydrogels as carriers to load AuNCs to prepare solid-state biosensors that can detect H_2O_2, providing a valuable method for visual detection of H_2O_2 with a limit of detection (LOD) of 0.072 mM H_2O_2 [18]. Further, the use of self-healing carboxymethyl chitosan (CMCS)/oxidized carboxymethyl cellulose (OCMC) hydrogels with their own Schiff base bond stabilization exhibits a catalytic effect on Glucose Oxidase (GOx), and using AuNCs and Gox as fluorescent biosensors enables fluorescence visualization for quantitative detection of H_2O_2 and glucose [19].

The three hydrophilic networks of hydrogels are well suited as carriers for drugs, and the addition of a tunable drug delivery mechanism can modulate their release. The main modes of drug delivery include encapsulation and physical or chemical adsorption methods. The combination of drug-carrying nanoparticles with hydrogel-based delivery systems can achieve high targeting through hydrogels and prolong the duration of drug release by employing nanoparticles. Yu et al. used silk fibroin (SF)/hyaluronic acid esterified by methacrylate (HAMA) (CCNPs-SF/HAMA) hydrogels encapsulated with chitosan nanoparticles (CCNP) loaded with curcumin and CCNPs-SF/HAMA hydrogels, which exhibited a dose-dependent inhibition of MG-63 cell growth and significantly promoted CCNPs-SF/HAMA hydrogels with a more sustained drug release, which is beneficial for the long-term treatment of osteosarcoma [20].

Adding fillers to hydrogels can impart different properties to hydrogels. Compared to other conventional stimuli, magnetic fields are contactless, simple to operate, and easy to achieve precise control of stimulation sources. Adding inorganic magnetic particles, such as Fe_3O_4 and $CoFe_2O_4$, to impart magnetic response properties makes the magnetically responsive hydrogels more suitable for drug release, biomedical devices, etc. Chen et al. used polymethacrylic acid to modify the surface of MOS_2 and grew magnetic nanoparticles in situ, allowing the nanosheets to modulate the orientation direction under a magnetic field. The modified nanosheets spontaneously assemble into a fibrous structure in solution, which can interpenetrate with poly(N-isopropyl acrylamide) (PNIPAm) molecular chains to form hydrogels. Modulating the magnetic field direction at different parts of the gel surface can change the orientation of the nanosheets to achieve controlled release of the drug [21].

In summary, as a biocompatible material with high similarity to human soft tissues, hydrogels play an important role in the field of biomedical applications and biosensing. However, there are still some challenges to overcome. First, hydrogels need match the mechanical strength and stiffness of different tissues and organs to ensure successful transplantation. Second, the functionalization of hydrogels can affect the mechanical properties, biocompatibility and biodegradability. In addition, conventional hydrogels are usually designed for treatment only. In the future, the development of the diagnostic and therapeutic hydrogels with multi-stimuli responsiveness can be more intelligent and applicable.

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