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Naturally-derived injectable hydrogels for antitumor therapeutics

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As novel localized drug delivery platforms, injectable hydrogels demonstrate significant potential in precision tumor therapy. By enabling spatiotemporally controlled drug release at target sites, they not only reduce systemic toxicity but also facilitate synergistic codelivery of chemotherapeutic agents, immunomodulators and gene therapy carriers. However, synthetic polymer-based hydrogel scaffolds face major challenges in clinical translation due to complex fabrication processes, potential immunogenicity and metabolic toxicity. In recent years, natural biomaterials such as chitosan, gelatin, and hyaluronic acid have emerged as preferred matrices for constructing antitumor hydrogel carriers, owing to their inherent biocompatibility, tunable biodegradability and clinical feasibility. This review systematically summarizes the structural advantages of natural biomaterials and their design principles in developing injectable hydrogels for antitumor applications, with particular focus on their cargo-loading mechanisms for diverse therapeutic agents. Additionally, it provides an in-depth discussion of key challenges in the clinical translation of natural material-based injectable hydrogels, aiming to guide the development of novel antitumor hydrogel platforms.

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1. Introduction

Tumor constitutes a major public health threat to human populations,[1] with epidemiological projections forecasting over 35 million new tumor cases globally by 2050.[2] Among these malignancies, solid tumors such as lung, liver, gastric, and breast tumors persist as predominant causes of tumor-related mortality.[3] Conventional therapeutic approaches primarily encompass surgical resection, chemotherapy, and radiotherapy. Surgical intervention risks tumor recurrence, while chemotherapeutic agents indiscriminately damage metabolically active normal tissues due to their non-selective cytotoxicity. Although radiotherapy offers precise locoregional targeting, its therapeutic efficacy diminishes in anatomically complex tumor lesions. Current intratumoral immunotherapies, typified by toll-like receptor (TLR) agonists, are undergoing clinical evaluation, yet face persistent challenges in

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modulating the balance between localized drug retention and systemic dissemination.[4] Contemporary research on localized tumor treatment technologies seeks to transcend conventional therapeutic boundaries. For instance, the FDA-approved BCNU (carmustine)-loaded polymeric wafer Gliadel®, designed for post-resection implantation in glioblastoma, requires precise geometric matching with the excised cavity and exhibits constrained drug diffusion radii. Although yttrium-90 (Y-90) microspheres have gained global clinical adoption in hepatocellular carcinoma management,[5] single-dose [90Y]-loaded carbon microsphere administration remains dependent on combinatorial chemotherapy or immunotherapy rather than serving as a standalone therapeutic regimen. These unresolved limitations highlight the persistent challenges confronting emerging localized tumor therapies.

Hydrogels represent a promising locoregional therapeutic platform for oncology, integrating *in situ* gelation capacity with multifunctional therapeutic agent loading capabilities, thereby serving as an ideal biomaterial for tumor treatment.[6] Compared to alternative modalities, hydrogels exhibit five cardinal advantages: (1) precise targeting capability: direct lesion-specific delivery minimizes systemic toxicity; (2) morphological adaptability: *in situ* gelation enables dynamic volumetric adjustment to match resection cavities of varying dimensions;[7] (3) stimuli-responsive release: therapeutic agents encapsulated within hydrogel networks demonstrate controlled release mediated by pH, temperature, or enzymatic activity, thereby extending therapeutic exposure durations;[8,9] (4) combinatorial therapeutic potential: concurrent loading of chemotherapeutic agents and photothermal sensitizers is achievable;[10] (5) minimized invasiveness: hydrogel implantation minimizes surgical trauma and improves prognosis compared to conventional surgery.[11] Synthetic polymers such as poly(lactic-*co*-glycolic acid) (PLGA) and polyethylene glycol (PEG) have been employed as injectable hydrogel structural scaffolds. While these materials offer tunable chemical architectures and facile functionalization potential, they suffer from inherent bioinertness and potentially cytotoxic degradation byproducts. In contrast, naturally derived hydrogel matrices demonstrate superior biocompatibility and controlled degradability.[12] For instance, natural polymers such as silk fibroin and gelatin exhibit excellent cell proliferation and adhesion properties while demonstrating non-cytotoxic profiles. In contrast, synthetic polymers like polylactic acid (PLA) and polyvinyl alcohol (PVA) lack intrinsic binding motifs required for optimal cell adhesion. Current research strategies often employ composite scaffolds integrating natural and synthetic polymers to confer cytocompatibility while maintaining structural integrity.[13] Bioactive constituents in natural materials can potentiate antitumor efficacy, for instance, Pi *et al.* developed self-assembled glycyrrhizic acid-copper ion hydrogels that synergistically modulated tumor microenvironments through the anti-inflammatory action of glycyrrhizic acid combined with chemotherapeutic norcantharidin, significantly suppressing ovarian tumor cell proliferation.[14] The innate bioactivity, biosafety, and functional versatility of natural material-based injectable hydrogels confer distinct advantages over synthetic counterparts in antitumor applications.

In this review, we summarize emerging design strategies and recent advances in naturally derived injectable hydrogels, investigate the therapeutic potential of injectable hydrogels incorporating diverse therapeutic payloads for antitumor applications, and highlight persistent clinical translation challenges alongside future developmental trajectories. This review aims to consolidate existing research to provide a comprehensive understanding of the biomedical utility and clinical prospects of natural material-based injectable hydrogels in oncological therapies.

2. Naturally derived hydrogel matrices

Naturally derived materials, including polysaccharides, polypeptides and proteins, represent ideal substrates for antitumor injectable hydrogels due to their distinctive advantages: (1) high biocompatibility and low immunogenicity: naturally derived polymers (*e.g.*, chitosan, gelatin) sourced from plants,

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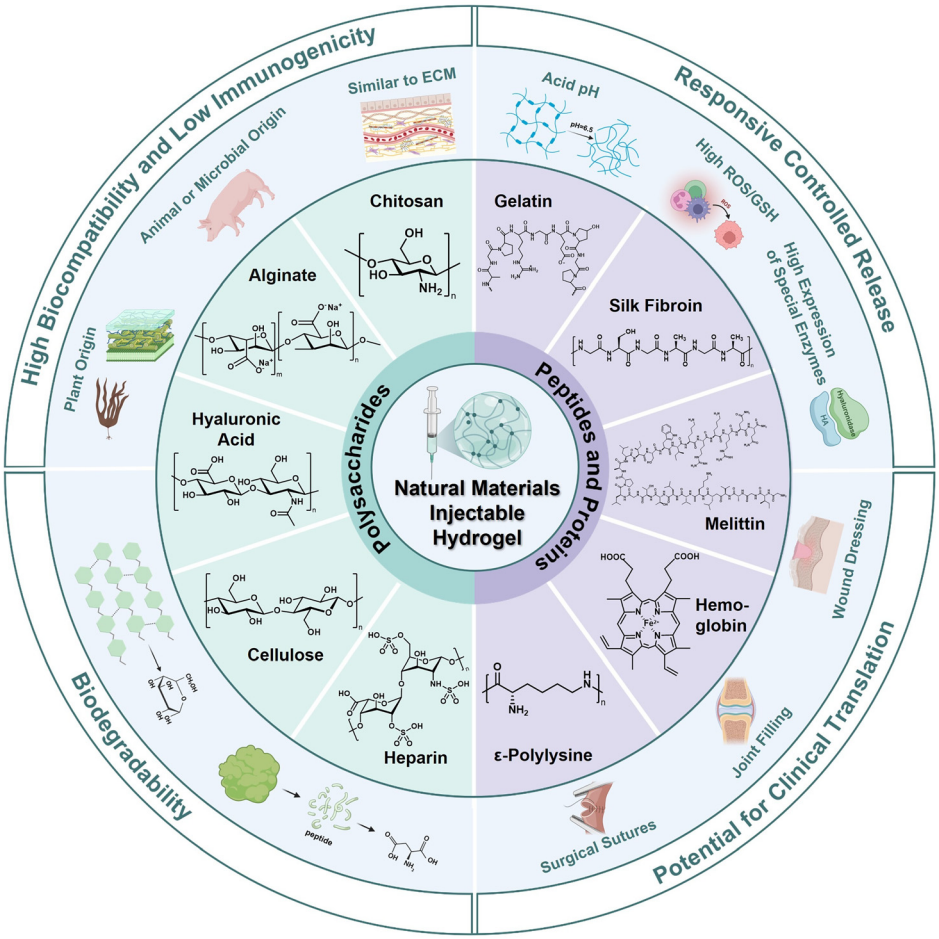

Fig. 1 Naturally derived hydrogel matrix materials and their advantages.

animals, or microorganisms exhibit chemical structures closely resembling human extracellular matrix (ECM) components, thereby reducing immune rejection.[15,16] (2) Biodegradability: chitosan and cellulose are degraded *in vivo* by lysozyme, while natural polypeptides and proteins undergo proteolytic cleavage into short peptides or amino acids for subsequent metabolic clearance.[17] (3) Responsive controlled release: the abundant reactive groups in naturally derived materials enable the construction of dynamically crosslinked hydrogels. These systems recognize tumor microenvironment (TME) features such as elevated ROS/GSH levels to achieve localized drug release. (4) Clinical translation potential: multiple naturally derived materials have been FDA-approved for clinical applications,[18,19] including alginate (approved as hemostatic materials and wound dressings)[25] and hyaluronic acid (utilized in joint lubrication[26] and skin regeneration). Naturally derived hydrogels, integrating inherent biomimetic properties, temporally controlled degradability, and modular multifunctionality, serve as precision-engineered platforms for localized combinatorial antitumor therapy (Fig. 1).

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2.1 Natural polysaccharides

Current studies identify chitosan, hyaluronic acid, sodium alginate and cellulose as predominant naturally derived polysaccharides serving as injectable hydrogel scaffolds for antitu-

mor therapy. Their respective advantages and application potentials are critically evaluated in this section.

2.1.1 Chitosan. Chitosan (CS), a naturally derived cationic polysaccharide obtained from chitin through deacetylation involving acetyl group removal,[27] demonstrates enzymatic biodegradability *via* lysozyme-mediated degradation into nontoxic glucosamine *in vivo*. Chitosan exhibits functionalization potential due to abundant amino/hydroxyl groups along its polysaccharide backbone, enabling facile chemical modification and conjugation with diverse targeting ligands, stimuli-responsive moieties or nanoparticles to form gel networks *via* covalent crosslinking[20] or electrostatic interactions.[28]

Injectable chitosan-based hydrogels exhibit tunable mechanical properties, as their molecular weight governs the adjustment of gel mechanical strength and porosity, thereby modulating drug release kinetics to achieve localized drug retention and sustained release. Chen *et al.* developed an oxygen/ROS-responsive chitosan hydrogel (CS-FTP-gel) capable of effectively encapsulating hypoxia-activated prodrugs (AQ4N). By employing low-molecular-weight chitosan (150 kDa) as the gel matrix, they optimized scaffold integrity while minimizing cellular membrane disruption, achieving an optimal balance between gel performance and biosafety.[29] Chitosan, with its inherent positive charge, enables electrostatic interactions with negatively charged chemotherapeutic agents, nanoparticles or tumor cells, thereby enhancing drug loading efficiency. Su *et al.* developed a chitosan-based protein composite hydrogel (E72-chitosan-Ag_3AuS_2) where cationic chitosan interacts with surface anions of Ag_3AuS_2 NPs through electrostatic forces, effectively neutralizing nanoparticle surface charges to mitigate cytotoxicity for *in situ* photothermal therapy (PTT) of tongue carcinoma.[30]

The amino groups undergo Schiff base formation with aldehyde/ketone-containing compounds,[21,31] where acidic tumor TME-triggered cleavage of Schiff bonds induces hydrogel network disintegration and payload release (Fig. 2a and b). Furthermore, pH sensitivity of chitosan facilitates drug release *via* pH-responsive swelling under acidic TME conditions. Chung *et al.* engineered an injectable chitosan-based hydrogel where covalent crosslinking between chitosan amino groups and genipin (Gp) ester groups enables protonation-induced swelling under acidic TME conditions. This pH-responsive behavior accelerated the release of the ferroptosis inducer ML210, demonstrating antitumor efficacy in a 4T1 breast tumor murine model (Fig. 2c).[22] The synergistic interplay between the amino reactivity and pH-responsive behavior of

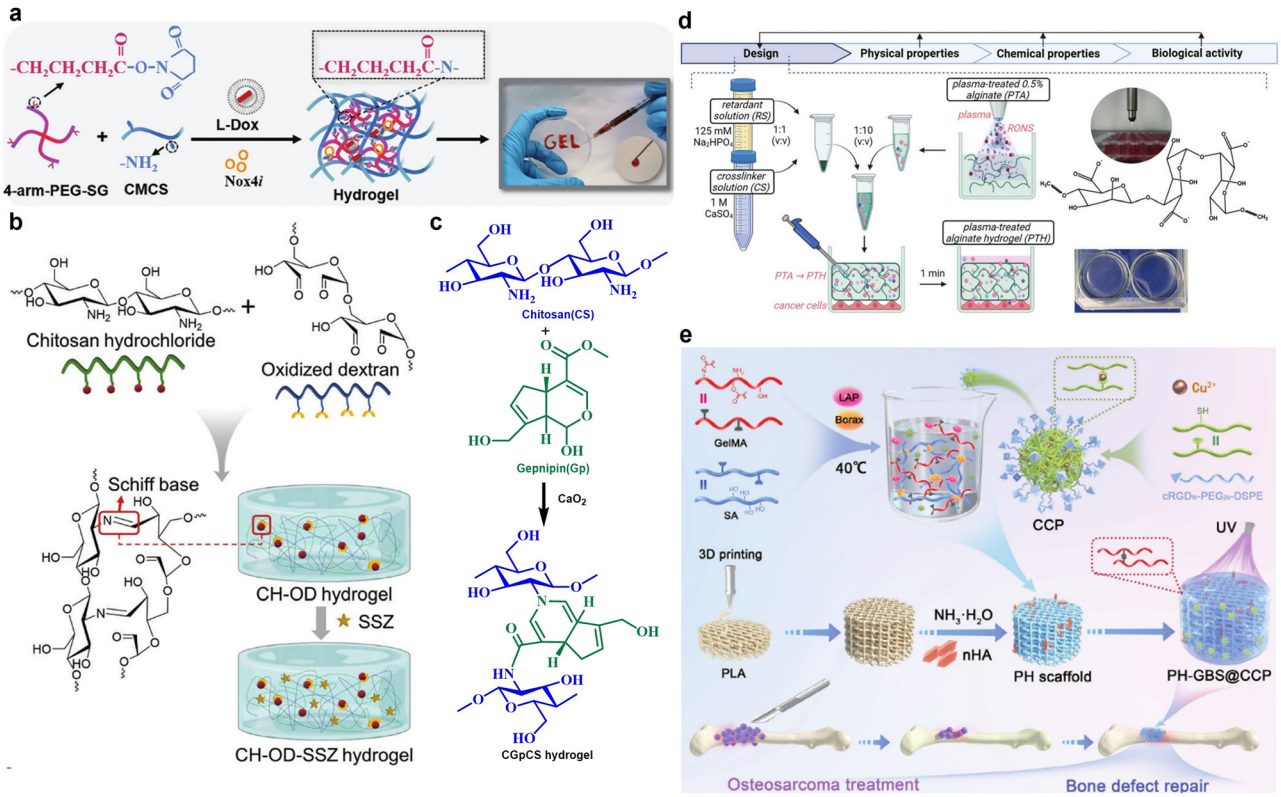

Fig. 2 Injectable chitosan/alginate hydrogels. (a) Schematic illustration of hydrogel formation through Schiff base reaction-mediated crosslinking between 4-arm-PEG-SG and CMCS.[20] Copyright (2023), Wiley–VCH GmbH. (b) Diagrammatic representation of chitosan hydrochloride and oxidized dextran (CH-OD) hydrogel formation.[21] Copyright (2023), The Authors. *Adv. Sci.* published by Wiley–VCH GmbH. (c) Reaction mechanism underlying CGpCS hydrogel formation;[22] Copyright (2024), Elsevier B.V. (d) Controlled alginate crosslinking *via* mixing of $CaSO_4$ crosslinker solution (CS) and salt retarding solution (RS).[23] Copyright (2023), The Authors. *Adv. Funct. Mater.* published by Wiley–VCH GmbH. (e) GelMA-SA hydrogel loaded with copper-Cys-PEG nanoparticles.[24] Copyright (2024), Wiley–VCH GmbH.

chitosan achieves dual drug loading and tumor-targeted release.

Chitosan exhibits pH-responsive *in situ* gelation; however, its solubility is restricted to acidic aqueous solutions, which may limit its applicability. This limitation can be addressed through chemical modifications such as quaternization to modulate solubility.

2.1.2 Alginate. Alginate, a natural anionic polysaccharide extracted from brown algae, is classified as a GRAS (generally recognized as safe)-certified material under U.S. FDA regulations. This polysaccharide has been extensively investigated for injectable hydrogel applications due to its superior biocompatibility and controlled biodegradability, undergoing hydrolysis or enzymatic degradation *in vivo* to prevent long-term retention risks. The abundant carboxyl and hydroxyl groups on its molecular chain constitute the key functional moieties enabling its utility as injectable hydrogel scaffolds. The abundant carboxyl and hydroxyl groups on alginate surfaces serve as core functional moieties for injectable hydrogel scaffolds. Carboxyl groups physically crosslink with divalent cations (*e.g.*, Ca^{2+}) *via* ionic bonds, enabling *in situ* gelation for minimally invasive delivery and precise filling of complex tumor cavities, while hydroxyl groups establish hydrogen bonds with water molecules, constructing a hydrophilic 3D network.

Current alginate-based systems predominantly utilize Ca^{2+}-mediated crosslinking to form 3D networks. By incorporating retardants (*e.g.*, sodium phosphate[23]), crosslinking kinetics can be modulated to tailor hydrogel mechanical properties to tumor microenvironmental requirements (Fig. 2d). The Ca^{2+}-crosslinked alginate network further serves as a structural platform for dual-network architectures. For instance, Zhou *et al.* developed an injectable interpenetrating network (IPN) hydrogel combining alginate and fibrin.[32] The rigid alginate-Ca^{2+} network interpenetrates with thrombin-triggered flexible fibrin network, enabling co-encapsulation of NETs inhibitor (DNase I) and propranolol within PLGA NPs. Sustained drug release occurs upon *in situ* hydrogel degradation. Wu *et al.* developed an injectable dual-network hydrogel (GPA) using NIR-initiated PEGDA photopolymerization (primary network) combined with Ca^{2+}-chelated alginate (secondary network), which stabilized 125I-GNR-RGDY for sustained photothermal-radiotherapy synergy.[33] Cao *et al.* designed an alginate-based injectable hydrogel (RA-gel) whose porous architecture and ionic-rich composition enhance microwave absorption.[34] When loaded with R837 immunoadjuvant, it synergizes with percutaneous microwave ablation (MWA) for combined primary/metastatic tumor therapy. Additionally, the carboxyl/hydroxyl groups of alginate enable chemical conjugation or electrostatic interactions[35] with therapeutic payloads or functional modules. Xie *et al.* created a tumor microenvironment-responsive sodium alginate hydrogel (GBS@CCP) *via* dynamic borate ester crosslinking (Fig. 2e).[24] This system achieves on-demand CCP nanoparticle release during early degradation phases, followed by sequential liberation of copper-based nanoparticles and nanohydroxyapatite (nHA), enabling concurrent post-surgical osteosarcoma treatment and bone regeneration.

Alginate rapidly crosslinks with divalent metal ions such as Ca^{2+}, undergoing instantaneous gelation under physiological conditions and making it suitable for minimally invasive injection. However, the resulting hydrogel network exhibits high porosity, which may lead to rapid drug release kinetics. Incorporation of redox-responsive moieties enables stimuli-responsive drug release.

2.1.3 Hyaluronic acid. Hyaluronic acid (HA), an endogenous polysaccharide with remarkable hydrophilicity (capable of binding water 1000 times its weight), has received FDA approval for clinical applications. Its degradation into non-toxic products through enzymatic/oxidative/acidic pathways, combined with hyaluronidase overexpression in tumor tissues that accelerates HA degradation, enables precise drug release control.[36] These superior biocompatibility and tunable degradation properties establish HA as a clinically translatable injectable hydrogel scaffold. The abundant surface carboxyl and hydroxyl groups of HA enable functional versatility through covalent crosslinking[37,38] or physical interactions.[39] Contemporary approaches typically employ chemical functionalization strategies involving double bond or thiol group introduction to modify HA for establishing versatile crosslinking interfaces with polymeric counterparts. Li *et al.* developed an injectable hydrogel (TRM-1-EH) *via* thiol–ene click chemistry between acrylate-modified HA and α,ω-dithiol polyethylene glycol (PEG-SH) for delivering *in vitro*-expanded tissue-resident memory T cells (TRM-like cells).[40] Xu *et al.* developed a disulfide-crosslinked thiolated HA hydrogel (HA-SS-HA) for localized antitumor drug delivery (Fig. 3a).[41]

The hydroxyl-formed hydrophilic network and negatively charged carboxylates (physiological pH) cooperatively enable dual binding: hydrogen bonds with water and electrostatic attraction of cationic drugs/metal ions. Esterification of HA carboxyl groups with hydrophobic drugs produces amphiphilic carriers that significantly enhance hydrophobic drug solubility. Simultaneously, HA-CD44 receptor binding on tumor cells improves drug bioavailability while reducing off-target toxicity.[37,42] Mathiyalagan *et al.* developed an injectable HA hydrogel co-conjugated with β-cyclodextrin and triterpenoid saponins (HG-Gel).[42] Its hydrophobic network synergizes with HA hydrophilicity to enhance drug dissolution, while CD44 targeting and pH-responsive degradation collectively enable tumor-specific drug accumulation for precision melanoma therapy (Fig. 3b).

HA enables active tumor targeting *via* specific binding to the CD44 receptor overexpressed on tumor cell surfaces. However, its degradation relies on endogenous hyaluronidases (HYAL1/HYAL2) and oxidative radicals, which exhibit heterogeneous distribution and significant inter-individual variability. This may result in uncontrolled degradation and drug release kinetics. Strategies such as incorporation of biocompatible materials or chemical modification can optimize its pharmacokinetic profile.

2.1.4 Cellulose and its derivatives. Natural cellulose, primarily derived from plant cell walls and certain microorganisms, demonstrates facile chemical modifiability to yield

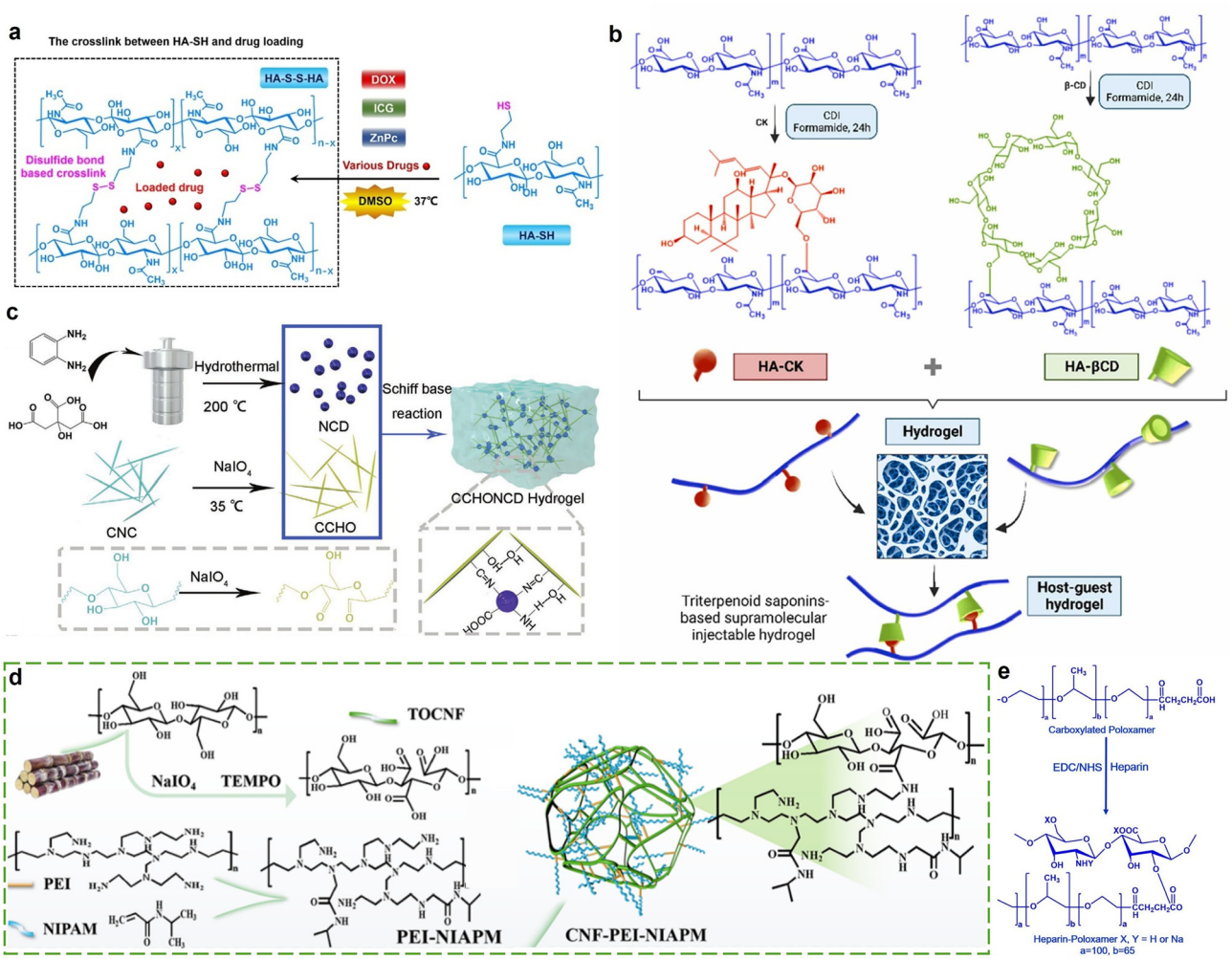

Fig. 3 Injectable hyaluronic acid/cellulose/heparin hydrogels. (a) Synthesis mechanism of drug-loaded HA-SS-HA hydrogel.[41] Copyright (2020), Elsevier Ltd. (b) Fabrication of injectable supramolecular hydrogels through HA-βCD and HA-CK conjugates.[42] Copyright (2024), The Author(s). Published by Elsevier B.V. (c) Schiff base reaction-mediated formation of CCHONCD hydrogel.[43] Copyright (2021), Wiley–VCH GmbH. (d) Synthetic route for CNF-PEI-NIPAM.[44] Copyright (2021) Elsevier B.V. (e) Synthesis of Heparin-poloxamer conjugate.[45] Copyright (2019), Elsevier B.V.

derivatives such as carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC) and methyl cellulose (MC) that exhibit enhanced aqueous solubility or thermosensitive properties. Furthermore, cellulose-based nanomaterials including cellulose nanocrystals and nanofibrils demonstrate exceptional biocompatibility and low toxicity, showing considerable potential for various *in vivo* therapeutic applications.

Cellulose surfaces possess abundant hydroxyl groups capable of forming gel networks through hydrogen bonding, while also exhibiting chemical modifiability *via* oxidation[43] (Fig. 3c), grafting and other approaches. Andrade *et al.* developed a thermosensitive chemically crosslinked hydrogel through ceric ammonium nitrate (CAN)-initiated graft copolymerization of cellulose with N-isopropylacrylamide (NIPAM), enabling dual loading of niclosamide (NCS) and doxorubicin (DOX).[46] Chen *et al.* engineered pH/temperature dual-responsive materials by oxidizing hydroxymethyl groups on TEMPO-oxidized cellulose nanofibers (TOCNF) to carboxyl groups, followed by PEI-NIPAM polymer grafting (Fig. 3d).[44] Zhou *et al.* designed an oxidized hydroxypropyl cellulose (Ox-HPC) and carboxymethyl chitosan (CMCS) hydrogel system, where gelation occurs through Schiff base formation between the components for drug delivery applications.[47]

Furthermore, the high specific surface area of cellulose nanocrystals/nanofibrils enhances drug loading capacity. Belyaeva *et al.* developed an injectable hydrogel based on PNIPAM-grafted cellulose nanocrystals (CNC-g-PNIPAM), achieving sustained paclitaxel (PTX) release *via* synergistic sulfate group electrostatic adsorption and hydrophobic collapse.[48] Notably, cellulose nanointerfaces enable component segregation to prevent mutual interference between therapeutic agents. Sun *et al.* engineered a multifunctional cellulose nanocrystal-based hydrogel (MTCH) by grafting polyethyleneimine (PEI) with protocatechualdehyde (PA), while integrating Prussian blue nanoparticles (PBNPs), upconversion nanoparticles (UCNPs) and detection micelles (DM). This system

ensures molecular isolation through chelation, electrostatic attraction and hydrogen bonding crosslinking, effectively preventing performance interference between fluorescent probes and photothermal agents.[49]

Cellulose derivatives, such as cellulose nanofibers, exhibit tumor microenvironment compatibility by matching the dimensions of collagen fibrils in the tumor stroma. However, the absence of endogenous cellulases in humans results in degradation primarily through non-specific hydrolysis or microbial metabolism, complicating precise drug release kinetics. Tailoring degradation kinetics *via* chemical modification enables synchronization of scaffold breakdown with on-demand drug release.

2.1.5 Heparin. Heparin, a strongly anionic glycosaminoglycan (GAG) comprising sulfated glucosamine and uronic acid repeats, demonstrates potent anticoagulant activity through its abundant sulfate/carboxylic acid groups. This inherent bioactivity has enabled its widespread clinical application in thrombotic disorder management.[50] As an endogenous, low-immunogenicity glycosaminoglycan, heparin exerts antitumor effects *via* dual anticoagulant and antiangiogenic mechanisms, while its drug-delivery capability for chemotherapeutics or immunotherapeutics mitigates metastasis risks, thereby demonstrating ideal compatibility with injectable hydrogel platforms for *in vivo* applications.[51]

The sulfate and carboxylic acid groups in heparin allow photo-crosslink or temperature/pH-responsive gelation through diverse chemical modifications, achieving minimally invasive injection requirements. For instance, Li *et al.* developed an injectable thermosensitive hydrogel using low-molecular weight heparin (LMWH), where amidation between carboxylated Poloxamer 407 and LMWH generated HP copolymer, exhibiting enhanced biocompatibility with reduced anticoagulant side effects (Fig. 3e).[45] Heparin exhibits antitumor efficacy by suppressing proliferation, angiogenesis and metastasis, while demonstrating synergistic therapeutic coordination with composite material systems.

Heparin leverages its strong anionic properties to electrostatically conjugate bioactive molecules, while its functionalization modifications enable high-efficiency cell encapsulation, demonstrating unique advantages in constructing biomimetic hydrogel scaffolds that recapitulate tumor/lymph node microenvironments. Pérez Del Río *et al.* developed a three-dimensional (3D) PEG-heparin hydrogel where LMWH retains chemokine CCL21 *via* electrostatic anchoring, significantly enhancing T-cell chemotaxis and proliferation.[52] This system overcomes the scalability limitations of T-cell expansion in adoptive cell therapy (ACT), serving as an optimized carrier for T-cell amplification and differentiation. Furthermore, Aliperta *et al.* engineered a heparin-PEG hydrogel scaffold with RGD peptide modification to reinforce mesenchymal stem cell (MSC) adhesion, creating transplantable "stem cell factories" for sustained bispecific antibody release against acute myeloid leukemia (AML).[53] As a versatile carrier for drugs, biomolecules, and cells, the potential of heparin in injectable antitumor hydrogel systems warrants deeper exploration.

Although heparin sulfate ester bonds can hydrolyze under acidic conditions, their responsiveness remains limited in the tumor acidic microenvironment. Incorporating additional pH-responsive crosslinking groups enables environment-responsive gel degradation to reconcile its unique functionalities with practical applicability.

2.2 Natural peptides and proteins

Current research identifies gelatin, silk fibroin and melittin as predominant natural polypeptides/proteins for injectable antitumor hydrogel scaffolds. This section systematically evaluates their distinct therapeutic advantages and application potentials.

2.2.1 Gelatin. Gelatin, a natural protein derived from animal collagen primarily sourced from porcine skin, bovine hide, and cattle bones, possesses a low-immunogenic collagenous structure containing the RGD (arginine-glycine-aspartic acid) sequence.[54] This property enhances cell adhesion and maintains biocompatibility through non-toxic degradation products, with FDA recognition as a safe *in vivo* biomaterial.

Gelatin surfaces feature abundant amino groups that enable conjugation with targeting molecules or functional materials *via* chemical bonds or electrostatic interactions.[55] Methacryloyl-modified gelatin (Gel-MA) forms three-dimensional networks with tunable mechanical properties and porosity through photoinitiated crosslinking, making it suitable for precisely tailored injectable hydrogel applications (Fig. 4a).[56] For instance, Huang *et al.* developed a photo-crosslinked GMNG hydrogel integrating gadolinium complexes (Gd-TCPP) and molybdenum disulfide (MoS_2) nanomaterials, achieving synergistic photothermal therapy, osteogenic induction and imaging monitoring (Fig. 4b).[57] Furthermore, Gel-MA can encapsulate hydrophobic drugs through hydrophobic interactions[58] while its hydrophilic matrix enables sustained drug release *via* gradual degradation to mitigate burst release and prolong therapeutic efficacy. Gelatin also permits controlled cargo release through enzymatic degradation. Kim *et al.* created an F127-g-Gelatin hydrogel demonstrating MMP9-responsive degradation for sustained release of nitric oxide donor (GSNO) and anti-CTLA-4 antibody (aCTLA-4) in melanoma combination therapy.[59]

Collagen is a key component of the natural ECM, forming fibrillar architectures that provide structural integrity and modulate cellular activities. Gelatin derived from denaturation of the collagen triple helix retains inherent RGD motifs that mediate superior cell adhesion, effectively mimicking native ECM functions.[6,60] Barough *et al.* engineered an injectable gelatin-LAPONITE® (gel-Lap) hydrogel that leverages RGD-mediated immune cell infiltration and gemcitabine (GEM) loading to achieve chemo-immunotherapeutic synergy against tumors.[61]

Gelatin degradation depends on matrix metalloproteinases (MMPs) and collagenases, however, tumor heterogeneity and inter-individual variability cause unpredictable kinetics. Chemical engineering enables tunable degradation profiles.

2.2.2 Silk fibroin. As an FDA-approved natural biomaterial, silk fibroin (SF) demonstrates excellent biocompatibility, con-

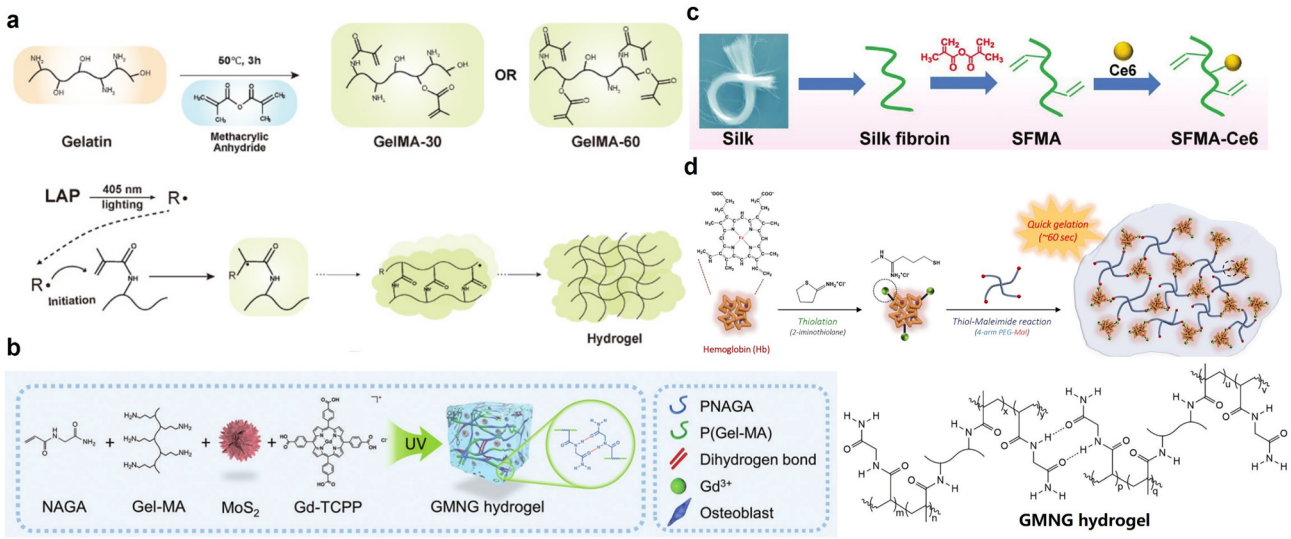

Fig. 4 Natural protein-based injectable hydrogels. (a) Chemical modification synthesis and photo-crosslinking process of GelMA hydrogel.[56] Copyright (2022), Elsevier Ltd. (b) Gadolinium (Gd) complex and molybdenum disulfide (MoS_2) co-doped *N*-acryloyl glycinamide (NAGA)/gelatin methacryloyl (GelMA) hydrogel (GMNG).[57] Copyright (2023), Wiley–VCH GmbH. (c) Photo-crosslinkable gel network formed between methacrylated silk fibroin (SFMA) and photosensitizer chlorin e6 (Ce6).[62] Copyright (2021), Wiley–VCH GmbH. (d) PEG-crosslinked hemoglobin hydrogel.[63] Copyright (2018), Elsevier B.V.

trollable biodegradability and low immunogenicity, rendering it suitable for long-term *in vivo* implantation.[64] Furthermore, this protein functions as a natural immunomodulator capable of recruiting macrophages to the tumor microenvironment while serving as a building block for gel-based scaffolds, thereby exhibiting substantial development potential in localized antitumor therapy.

SF contains β-sheet crystalline domains formed by repetitive amino acid sequences and modifiable active groups. Under acidic conditions, adjusting SF solution pH to neutral reduces protein solubility, thereby promoting β-sheet alignment through enhanced hydrophobic interactions (Fig. 4c).[65] Its unique structure enables the construction of robust drug delivery systems for targeted/sustained release.[62,64] Guo *et al.* developed an injectable hydrophilic silk fibroin (HSF)-based hydrogel that encapsulates DOX and Cy7 *via* β-sheet/hydrogen-bond mediated 3D network self-assembly.[66] This system achieves pH/ROS/GSH triple-responsive DOX release while synergistically enhancing antitumor efficacy through Cy7-mediated photothermal effects. Furthermore, Guo *et al.* created an injectable supramolecular hydrogel utilizing SF, sericin (SS) and Fe(II) ions, which achieves intelligent CD47 antibody delivery *via* H_2O_2-responsive dityrosine crosslinking.[67]

As a natural protein, SF synergizes with diverse biomaterials to achieve localized tumor therapy. Zhang *et al.* developed a multifunctional hydrogel based on SF, poly(lipoic acid) (PolyLA) and arginine (Arg) that enhances rigidity through β-sheet formation and hydrogen bonding while sustaining LA/Arg release, enabling prolonged post-operative breast tumor treatment.[68]

Similar to gelatin, SF degradation may exhibit enzymatic heterogeneity across anatomical sites and individuals, compromising spatiotemporal control over drug release. Conjugation of pH/ROS-responsive groups enables tumor microenvironment-triggered drug release, overcoming limitations caused by enzymatic heterogeneity in SF degradation.

2.2.3 Melittin. Melittin, the primary bioactive component of honeybee venom, is a cationic amphipathic peptide characterized by distinct hydrophilic and hydrophobic domains within its molecular structure.[69] This structural duality underpins its unique bioactivities, which have been extensively explored in the context of anti-inflammatory, antimicrobial, and antitumor applications according to current research.

Melittin cooperates with RADA self-assembling peptides through α-helical interactions to construct hydrogels, leveraging its inherent cytotoxicity combined with drug-loading capacity for antitumor therapy.[70,71] Hydrogel encapsulation significantly reduces the hemolytic side effects of melittin while enabling controlled release to minimize systemic toxicity. The peptide exerts dual antitumor immune effects by inducing cell apoptosis/necrosis through tumor cell membrane disruption, while stimulating IL-2/IFN-γ secretion to enhance T/NK cell activity. In hydrogel systems, melittin serves dual roles as both structural and functional components, constituting the core element of multifunctional antitumor platforms. Jin *et al.* developed a hybrid peptide hydrogel through solid-phase synthesis, stably conjugating melittin to the RADA32 backbone and encapsulating ICG photothermal agents.[72] This system achieves controlled melittin release, markedly reducing systemic toxicity and minimizing damage to healthy tissues.

Melittin demonstrates favorable biosafety through protease-directed degradation *in vivo*, which however results in an abbreviated plasma half-life—an inherent pharmacokinetic constraint compromising clinical translatability.[73] Injectable hydrogel delivery systems based on melittin effectively balance degradation kinetics with therapeutic maintenance, thus enhancing advantages for localized antitumor applications.

2.2.4 Other peptides and proteins. Hemoglobin, an iron-containing protein predominantly found within vertebrate erythrocytes, is composed of four subunits (two α-chains and two β-chains), it can be efficiently extracted from human or animal blood through well-established blood separation protocols. As an endogenous protein in humans, hemoglobin exhibits low immunogenicity, conferring intrinsic advantages for *in vivo* applications. Lee *et al.* developed an injectable hydrogel system *via* click cross-linking between thiolated hemoglobin and four-armed maleimide PEG, capitalizing on the Fe(II) present in hemoglobin to achieve near-infrared photothermal conversion for localized photothermal therapy (Fig. 4d).[63] This hydrogel platform demonstrates complete dependence on hemoglobin-mediated photothermal therapy (PTT) mechanisms for antitumor efficacy, wherein hemoglobin serves a dual role as both the photothermal functional element and structural matrix component.

Polylysine, a naturally occurring polypeptide formed through amide-bonded linkage of lysine monomers, primarily exists as ε-polylysine with favorable metabolic properties including non-toxic degradation products. Recognized by the FDA as generally recognized as safe (GRAS),[74] ε-polylysine demonstrates potential for biomedical applications beyond its established use as a food preservative. Yang *et al.* engineered an injectable hydrogel (PR-gel) *via* cross-linking between polylysine (PLL) and aldehyde-modified polyethylene glycol (CHO-PEG-CHO), capable of co-loading immunomodulators PP2 and R848 for localized gastric tumor immunotherapy.[75] The inherent cationic nature of polylysine enables not only efficient encapsulation of negatively charged chemotherapeutics, nucleic acids or immunomodulators for controlled release, but also bacterial/tumor cell membrane disruption *via* electrostatic interactions, conferring antimicrobial and antitumor functionality.

3. Injectable hydrogels incorporating diverse cargos for antitumor therapy

Hydrogels derived from naturally sourced materials serve as versatile carriers for delivering chemotherapeutic drugs, cytokines, and immunotherapeutic agents. These systems enable tumor-targeted delivery while mitigating systemic toxicity, achieving sustained and stable release of encapsulated therapeutics (Fig. 5).

3.1 Chemotherapeutic drug

In tumor therapeutics, chemotherapy delivers chemotherapeutic agents systemically *via* intravenous injection to target lesions, yet its cytotoxic effects may cause irreversible damage to healthy tissues. Natural-derived injectable hydrogels enable localized and sustained delivery of chemotherapeutic agents, reducing single-dose requirements and significantly lowering

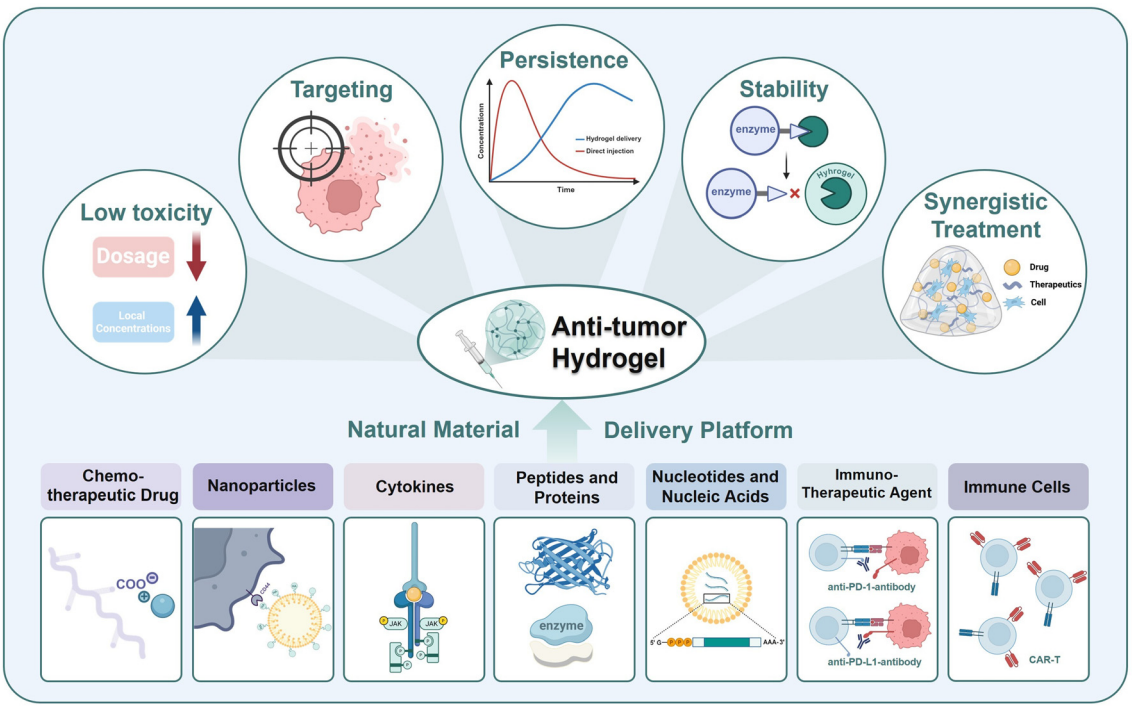

Fig. 5 Injectable hydrogels loaded with different cargos for anti-tumor therapy.

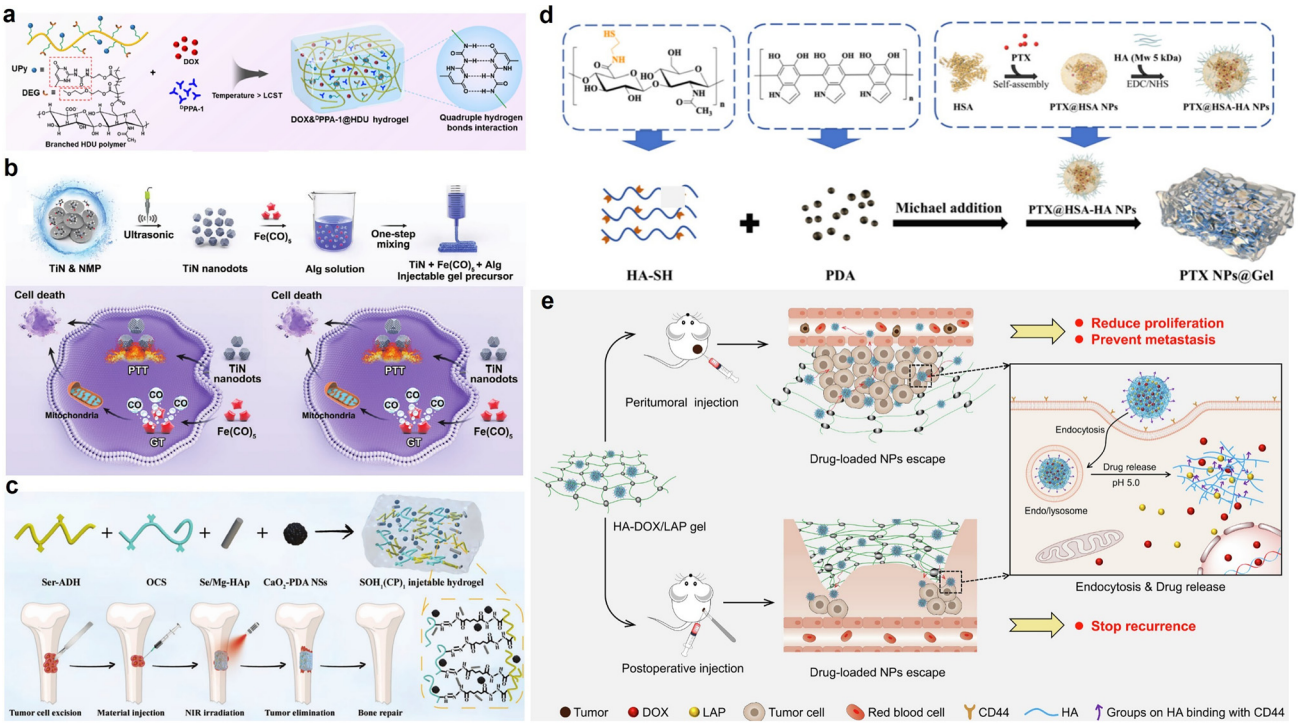

Fig. 6 Injectable hydrogels loaded with chemotherapeutic agents/nanoparticles. (a) Thermoresponsive hyaluronic acid-based hydrogel incorporating DPPA-1 and DOX.[79] Copyright (2021), American Chemical Society. (b) Preparation of TiN/Fe(CO)5/ALG hydrogel and its *in vivo* antitumor mechanism.[80] Copyright (2024), Wiley–VCH GmbH. (c) Sericin-based injectable hydrogel co-loaded with Se/Mg co-doped hydroxyapatite nanorods and polydopamine-coated calcium oxide nanospheres.[81] Copyright (2024), Wiley–VCH GmbH. (d) Injectable hydrogel synthesis *via* Michael addition reaction using thiol-modified hyaluronic acid (HA-SH) and polydopamine (PDA) backbones.[82] Copyright (2024), Elsevier Ltd. (e) HA-DOX/LAP gel treating uveal melanoma (UM) *via* synchronous cascade drug release.[83] Copyright (2024), Elsevier B.V.

systemic toxicity compared to conventional chemotherapy. Doxorubicin (Dox) is a common chemotherapeutic agent, acts as an immunogenic cell death (ICD) inducer by upregulating the expression of calreticulin (CRT) and high-mobility group box 1 (HMGB1) on tumor cell surfaces. This triggers release of damage-associated molecular patterns (DAMPs) and tumor-associated antigens (TAAs), activating antigen-presenting cells such as dendritic cells (DCs).[76] Activated DCs stimulate $CD8^+$ T cells to initiate antigen-specific antitumor immunity, suppressing both primary tumors and metastatic lesions. Natural materials can encapsulate Dox through physical entrapment[77] or electrostatic interactions. For example, negatively charged carboxyl groups in alginate[77,78] and hyaluronic acid[79] (Fig. 6b) under physiological conditions bind electrostatically with positively charged Dox, enabling controlled drug release. Celecoxib (CXB) inhibits the COX-2/PGE2 pathway in tumor cells, lowering intra-tumoral PGE2 levels and suppressing secretion of pro-inflammatory cytokines including IL-1β and IL-6.[84] CXB also exhibits anti-angiogenic effects by reducing tumor vascular density while upregulating CXCL9/CXCL10 chemokines. Li *et al.* engineered an alginate hydrogel incorporating CXB *via* physical entrapment and hydrophobic interactions within the gel network.[85] This hydrogel-mediated delivery addresses challenges associated with low aqueous solubility and poor oral bioavailability of CXB, enhancing localized drug concentration and therapeutic efficacy. Hydrogel-mediated co-delivery of celecoxib and anti-PD-1 monoclonal antibodies (mAb) significantly reduced metastatic lung nodule counts and primary tumor volume while enhancing survival rates in murine models compared to direct administration.

Injectable hydrogels enable multimodal combination of chemotherapy, photothermal therapy and other modalities. Cisplatin is a common chemotherapeutic agent, exerts antitumor effects by crosslinking tumor cell DNA to block replication. Mirrahimi *et al.* co-loaded cisplatin and gold nanoparticles (AuNPs) into alginate hydrogels, combining chemotherapy with photothermal therapy for localized synergistic antitumor effects.[86] Similarly, Zhang *et al.* incorporated ROS-responsive tegafur (TF)-protoporphyrin IX heterodimer (TTP) into chitosan (CS)-silk sericin (SS) hydrogels *via* hydrogen bonding and van der Waals forces.[87] Enzymatic conversion of TF in the tumor microenvironment synergizes with laser-induced ROS generation from protoporphyrin IX to achieve antitumor efficacy.

3.2 Nanoparticles

The three-dimensional network structure of hydrogels enables sustained nanoparticle release, mitigating systemic toxicity caused by burst drug release. Current studies demonstrate that injectable hydrogel scaffolds can effectively incorporate photo-

thermal components such as polydopamine nanoparticles to synergistically enhance antitumor efficacy.[80,88] For instance, Yao *et al.* physically embedded polydopamine-coated CaO_2 nanospheres (CaO_2-PDA NSs) within silk fibroin hydrogels (Fig. 6e).[81] These CaO_2 NSs release oxygen under NIR irradiation to alleviate tumor hypoxia and amplify photothermal therapeutic outcomes. Similarly, magnetothermal nanoparticles have been successfully integrated into hydrogel systems. Qian *et al.* developed an injectable ferromagnetic silk hydrogel (FSH) incorporating PEG-modified iron oxide nanocubes (IONCs) through hydrogen-bonded networks.[89] This system achieves deep tumor ablation *via* magnetothermal effects under alternating magnetic fields, overcoming the depth limitations of conventional photothermal therapy while enabling ultrasound-guided precision in treating hepatocellular carcinoma. Photothermal nanoparticles further synergize with thermosensitive natural materials for controlled drug release. Wang *et al.* engineered an injectable thermosensitive hydrogel combining agarose with Ti_3C_2 MXene nanosheets.[96] The hydrogen bonding between MXene's oxygen-containing groups and agarose hydroxyl groups facilitates both physical adsorption and photothermal functionality. Hyaluronic acid conjugated to nanoparticles enables targeted delivery.[82] Guo *et al.* developed a targeted injectable hydrogel system (HA-DOX/LAP gel) comprising hyaluronic acid-conjugated pH-responsive drug-loaded nanoparticles (HA-DOX/LAP NPs) and alginate-dopamine (ALG-DPA), achieving precise chemotherapy for uveal melanoma through HA-mediated CD44 receptor-targeted delivery and pH-triggered drug release mechanisms.[83] Compared to the free DOX + LAP gel group without HA conjugation, the HA-DOX/LAP gel group exhibited significantly higher apoptotic cell counts in tumor regions than other groups, demonstrating enhanced tumor-targeting capability.

3.3 Cytokines

Cytokines demonstrate antitumor potential through immunomodulation within the tumor microenvironment (TME). Interleukin-2 (IL-2) enhances TH1-type immune responses by promoting the proliferation of T cells and natural killer (NK) cells.[97] Antagonizing protumoral cytokines such as TGF-β and IL-6 reduces the infiltration of immunosuppressive cells like regulatory T cells. However, clinical translation of cytokine-based therapies faces multiple challenges: (1) short half-lives (*e.g.*, 85 minutes for IL-2) necessitate frequent administration, compromising patient compliance;[98] (2) high systemic toxicity due to narrow therapeutic windows limits clinical applicability;[98,99] (3) poor targeting specificity allows cytokines to act on immune cells in non-tumor regions, intensifying toxicity; (4) immunosuppressive signals (*e.g.*, TGF-β, PD-L1) and stromal barriers within the TME hinder effective cytokine delivery. Natural material-based injectable hydrogels overcome these challenges through localized and sustained cytokine delivery. They encapsulate cytokines (*e.g.*, IL-2,[90] XCL-1,[100] IFN-α2b[101]) and localize them intratumorally, reducing systemic exposure while maintaining sustained efficacy (Fig. 7a). Xiong *et al.* developed Ni^{2+}-alginate injectable hydrogel microspheres (Ni-ALGMS) that achieve high-efficiency loading and controlled release of recombinant IL-2 through histidine tag (His-tag)-Ni^{2+} coordination (Fig. 7b).[91] Similarly, Hu *et al.* developed an injectable methacrylated hyaluronic acid (HA-MA) hydrogel to encapsulate IL-15 in PLGA nanoparticles, achieving 94.6% loading efficiency with sustained release of over 60% IL-15 within 120 hours, which maintained CAR-T cell viability and proliferative capacity.[102] Such natural material-based hydrogels significantly enhance the therapeutic efficacy and safety profiles of cytokines through localized sustained release and targeted delivery.

3.4 Peptides and proteins

When delivering protein-based therapeutics *in vivo*, challenges such as enzymatic degradation or denaturation-induced inactivation frequently arise. Injectable hydrogels have emerged as a promising platform for protein delivery, where their three-dimensional network structures effectively encapsulate proteins and protect them from enzymatic degradation or denaturation, thereby preserving their bioactivity. In the context of antitumor therapy, injectable hydrogels fabricated from naturally derived materials have been increasingly explored as protein delivery systems, enabling localized and targeted tumor treatment through sustained therapeutic agent release.

Certain natural materials contain functional groups such as carboxyl and amino groups, which can enhance protein loading efficiency *via* electrostatic interactions,[106] hydrogen bonding, or covalent crosslinking. For instance, He and Li *et al.* developed a methacrylated hyaluronic acid-based injectable hydrogel (HA-JM2) that achieved covalent grafting and sustained release of JM2 peptides *via* Michael addition, effectively suppressing postoperative tumor recurrence while promoting wound healing (Fig. 7c).[92] Similarly, Gu *et al.* engineered an oxidized pectin/TCS-IL2 fusion protein hydrogel (TL-pectin Gel) crosslinked through Schiff base reactions, enabling dynamic loading and sustained release of the fusion protein. This system significantly prolonged survival rates in triple-negative breast tumor murine models and suppressed tumor metastasis.[107] Wei *et al.* designed a peptide/chitosan-derivative (GCF) injectable hydrogel that co-embedded GOx and CPO to construct an enzymatic cascade system, generating tumor-localized singlet oxygen ($^1O_2$) for apoptosis induction while circumventing systemic toxicity (Fig. 7d).[93] As versatile protein carriers, hydrogels have been extensively investigated in tissue engineering and regenerative medicine. In antitumor therapy, their applications warrant further exploration to fully realize their therapeutic potential.

3.5 Nucleotides and nucleic acids

Similar to proteins, nucleic acids as biomacromolecules face the challenge of nuclease degradation *in vivo*. Naturally derived injectable hydrogels have emerged as robust delivery vehicles for biomacromolecules including proteins and nucleic acids, owing to their inherent biocompatibility and controlled release properties. These hydrogels enable prolonged retention

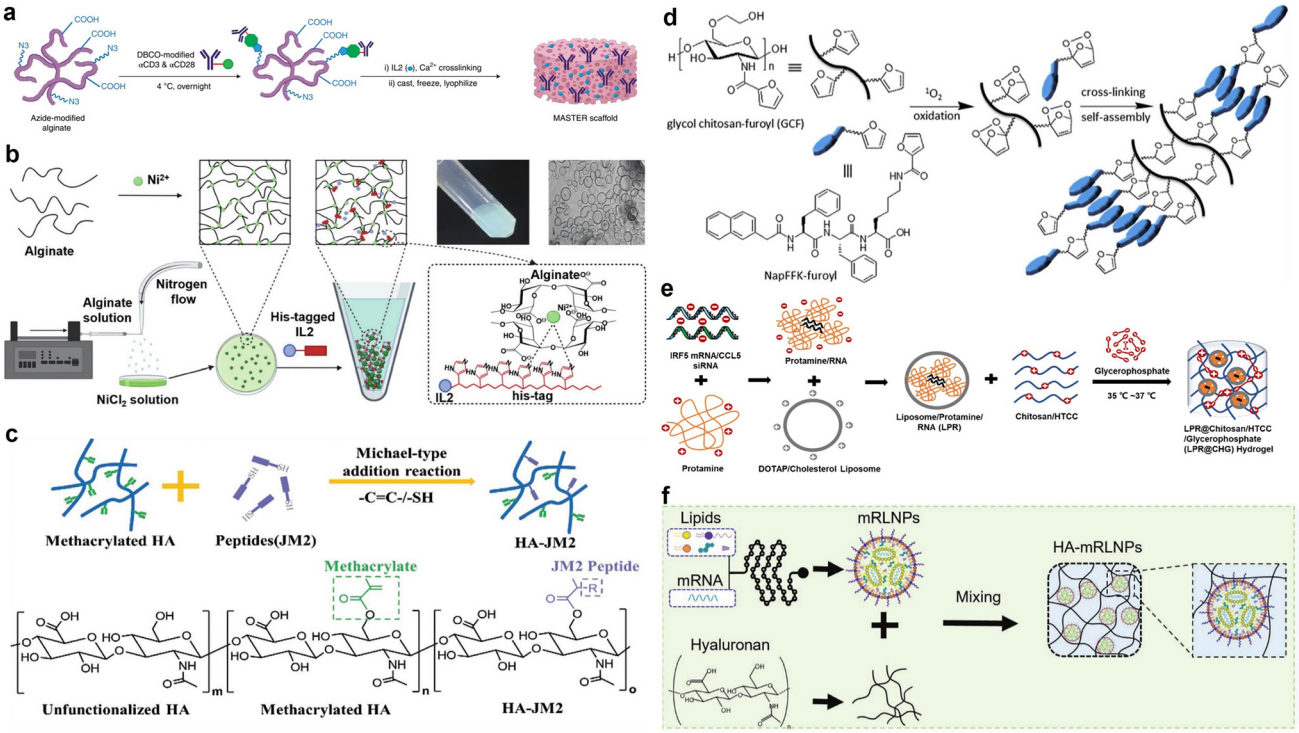

Fig. 7 Injectable hydrogels loaded with cytokines/peptides/proteins/nucleic acids. (a) Synthesis of implantable multifunctional alginate scaffold (MASTER) for T-cell engineering and release.[90] Copyright (2022), The Author(s), under exclusive licence to Springer Nature America, Inc. (b) Ni-ALGMS hydrogel microspheres with His-tagged IL-2 recombinant protein-specific loading.[91] Copyright (2022), Wiley–VCH GmbH. (c) Grafting reaction process of JM2 peptide onto HA molecules.[92] Copyright (2020), Wiley–VCH GmbH. (d) Hybrid hydrogel preparation *via* dual-enzyme (GOx and CPO)-Initiated singlet oxygen cross-linking of NapFFK-furoyland GCF.[93] Copyright (2019), The Authors. (e) Chitosan-based hydrogel incorporating LPR nanoparticles embedded with anionic IRF5 mRNA/CCL5 siRNA.[94] Copyright (2022), American Chemical Society. (f) Dynamic hyaluronic acid hydrogel physically encapsulating mRLNP.[95] Copyright (2022), Wiley–VCH GmbH.

at injection sites while sustaining the release of nucleic acid-loaded nanoparticles, significantly extending immune activation or gene silencing effects while reducing hepatic toxicity and immunogenicity associated with conventional lipid nanoparticles (LNPs). The porous gel architecture can partially restrict nanoparticle migration or aggregation. Current strategies typically involve complexing nucleic acids (*e.g.*, siRNA) with LNPs or nanoparticles through electrostatic/hydrophobic interactions, followed by physical encapsulation within hydrogel networks (Fig. 7e).[94,108] Fu *et al.* developed an alginate-based hydrogel (SOG) incorporating cationic multilamellar liposomes (MSLs), achieving sustained STAT3 siRNA release *via* electrostatic interactions to effectively downregulate STAT3 expression and induce lung tumor cell apoptosis.[109] The natural polymer matrices of hydrogels can also stabilize nucleic acid nanoparticles through electrostatic interactions, as exemplified by positively-charged chitosan stabilizing RNA complexes for postoperative pancreatic tumor recurrence suppression.[94] Hyaluronic acid hydrogels not only possess intrinsic targeting capability and environmentally responsive degradability, but their crosslinked networks can maintain a weakly acidic pH to restrict nucleic acid degradation (Fig. 7f).[95]

3.6 Other immunotherapeutic agents

In tumor immunotherapy, immunotherapeutic agents and adjuvants enhance antitumor immune responses by activating and modulating the immune system. Representative agents include PD-1 antibodies such as pembrolizumab, which block PD-1 receptors on T cells to disrupt PD-1/PD-L1 or PD-1/PD-L2 interactions in the tumor microenvironment, thereby reinstating T cell-mediated tumoricidal activity. PD-L1 antibodies such as atezolizumab directly target PD-L1 on tumor cells or immune cells, thereby blocking its interaction with PD-1 to abrogate immunosuppressive signaling and restore T cell functionality. TLR agonists that convert cold tumors to hot tumors engage pathogen-associated molecular patterns PAMPs or damage-associated molecular patterns DAMPs to activate innate immunity and amplify adaptive antitumor responses. Despite their therapeutic advantages, current systemic administration routes (intravenous or subcutaneous injection) for these immunomodulators face challenges including potential systemic toxicity and suboptimal delivery efficiency. Naturally derived hydrogels offer a promising solution through physical encapsulation of immunotherapeutic agents such as the TLR7 agonist R848, enabling efficient localized delivery.[103,110] These

hydrogel platforms can co-deliver chemotherapeutic agents, antibodies and immunetherapeutics to synergistically reprogram the immunosuppressive tumor microenvironment.[111]

Injectable hydrogels as combinatorial delivery systems enable temporally controlled release of multiple therapeutics based on molecular weight or charge disparities. For instance, Zhang *et al.* developed a fibrin-based hydrogel platform that achieves rapid cyclophosphamide (CTX) release to suppress Treg cells, coupled with sustained anti-PD-L1 antibody (aPDL1) delivery for immune checkpoint blockade, demonstrating enhanced synergistic antitumor efficacy.[112] Similarly, Chen *et al.* developed an injectable thiolated chitosan/pullulan disulfide-crosslinked hydrogel that synchronizes rapid cyclopamine liposome release with glutathione-responsive sustained anti-CD47 antibody delivery, synergistically blocking CD47-SIRPα signaling and activating macrophage function.[113]

3.7 Immune cells

Current cell-based therapies for tumor treatment rely on engineering or activating patients' own immune cells to specifically recognize and eliminate malignant cells, as exemplified by advanced modalities like CAR-T therapy and TCR-T therapy. CAR-T therapy involves genetically modifying T cells to express tumor antigen-targeting chimeric receptors, thereby enhancing their specific cytotoxic potential. This approach has gained clinical approval for treating hematological malignancies such as B-cell lymphomas. In such therapeutic strategies, the delivery methodology critically determines both therapeutic efficacy and safety profiles. Current delivery approaches face inherent limitations: intravenous infusion depends on passive cellular migration to tumor sites, resulting in low targeting efficiency and potential systemic toxicity (*e.g.*, off-target toxicity against normal B cells in CD19 CAR-T therapy), while intra-tumoral injection remains applicable only for superficial tumors like melanoma and often requires repeated administration for large neoplasms. To address these challenges in overcoming solid tumor delivery barriers and improving safety, emerging research demonstrates that injectable natural hydrogels could serve as promising cell delivery systems.[114,115] By physically encapsulating T cells or CAR-T cells within three-dimensional gel networks, this strategy potentially resolves key limitations of conventional adoptive cell therapy (ACT), including high

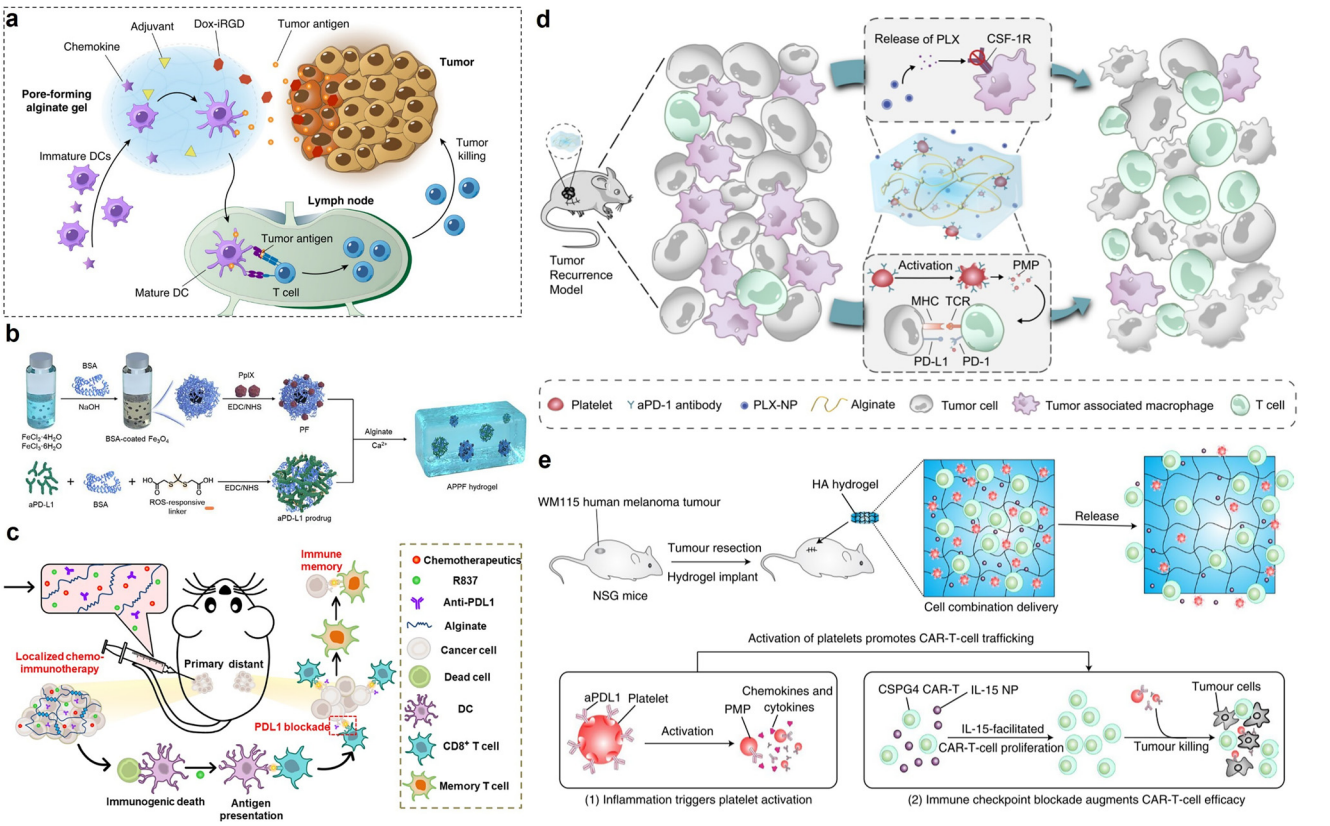

Fig. 8 Injectable hydrogels with multifunctional co-loading systems. (a) Alginate scaffold co-encapsulating chemokines, adjuvants and chemotherapeutic agents (Dox-iRGD) for constructing *in situ* tumor vaccines.[77] Copyright (2020), The Author(s). (b) Alginate hydrogel loaded with PLX-NP and P-aPD-1 for modulation of tumor immunosuppressive microenvironment in recurrence models.[102] Copyright (2021), The Author(s), under exclusive licence to Springer Nature Limited. (c) Grafting reaction process of JM2 peptide onto HA molecules.[103] Copyright (2022), The Author(s). (d) Alginate hydrogel containing protoporphyrin IX (PpIX)-modified Fe_3O_4 nanoparticles and aPD-L1 prodrug nanoparticles.[104] Copyright (2022), Acta Materialia Inc. Published by Elsevier Ltd. (e) Alginate (ALG) hydrogel combining immunogenic cell death (ICD)-inducing chemotherapeutic agents with immune adjuvants for local chemoimmunotherapy.[105] Copyright (2020), The American Association for the Advancement of Science.

cell dosage requirements, systemic toxicity, and inefficient cellular homing. Tsao *et al.* developed an injectable polyethylene glycol-grafted chitosan hydrogel (PC gel) as a sustained-release carrier for therapeutic T lymphocytes in glioblastoma immunotherapy.[116] Compared to conventional Matrigel (a commercial biomaterial derived from basement membrane matrices secreted by murine sarcoma cells), PCgel exhibits pore sizes (0.5–1 μm) better suited for active T cell migration than Matrigel's 0.1–0.5 μm range. This structural optimization restricts nonspecific cellular dispersion while enabling sustained cytokine release and persistent tumoricidal efficacy. Simultaneously, as discussed in Section 3.3, hydrogels can incorporate cytokines to functionally enhance encapsulated cells for synergistic immunomodulation.[117] Grosskopf *et al.* engineered a hydroxypropyl methylcellulose (HPMC-C12) hydrogel co-delivery system that locally releases IL-15 to promote CAR-T cell memory phenotype (TSCM) expansion. This strategy enhances solid tumor therapeutic efficacy while circumventing systemic toxicity.[118]

Natural biomaterials such as fibrin mimic the ECM to facilitate cellular proliferation, migration and functional maintenance, while their tunable concentrations enable precise regulation of gel porosity, degradation rate and cell release kinetics. Furthermore, natural-source materials exhibit inherent modifiability, allowing their engineering into hydrogel scaffolds with biochemical signaling functions through versatile strategies:[119] (1) Chemical modifications incorporating integrin-binding peptides (*e.g.*, RGD, YIGSR) enhance cell adhesion, spreading and signaling; (2) coupling with heparin or incorporating synthetic peptides (*e.g.*, BMP2/VEGF-binding sequences) recapitulates ECM-mediated spatial enrichment and regulation of growth factors; (3) introducing enzyme-sensitive peptides containing matrix metalloproteinase-cleavable sites enables enzyme-triggered hydrogel degradation.

4. Conclusions

Hydrogel-based delivery systems fabricated from naturally derived materials demonstrate remarkable versatility and promising clinical potential. These biocompatible materials, characterized by their hierarchical assembly structures and abundant surface functional groups, enable precise modulation of dynamic crosslinking networks to meet specific mechanical requirements for diverse drug administration routes. Simultaneous co-loading of multiple drugs or therapeutic agents is achievable (Fig. 8). In antitumor therapeutic applications, such hydrogel systems not only significantly mitigate toxicity risks associated with conventional therapies but also provide an ideal platform for precision drug delivery through their tunable physicochemical properties, exhibiting favorable translational potential.[120,121]

Hydrogels as emerging drug delivery platforms demonstrate significant preclinical advantages. Compared to conventional administration methods, their unique controlled and sustained-release characteristics not only enhance therapeutic efficacy but also reduce dosing frequency, substantially improving patient compliance.[122] As multifunctional bioscaffolds, hydrogel systems integrate drug reservoirs with immunomodulatory capabilities: they actively recruit immune cells through encapsulated cytokines/chemokines to remodel the tumor immune microenvironment,[123] while precisely synchronized degradation kinetics and therapeutic agent release optimize immune cell infiltration processes.[124] Notably, natural material-based hydrogels leverage abundant ionizable groups to selectively regulate the distribution of negatively-charged proinflammatory factors and positively-charged anti-inflammatory mediators through charge interactions, enabling intelligent immune microenvironment modulation.[121,125] Furthermore, injectable hydrogels fabricated from these materials exhibit unique value in cellular therapy due to their ECM-mimetic structural and mechanical properties. Their semipermeable porous architecture supports cell adhesion and protein chelation while selectively permitting small molecule diffusion (*e.g.*, ROS and cytokines), yet effectively blocks direct immune cell-graft contact to mitigate rejection risks. These attributes establish natural hydrogels as ideal platforms for precision therapy and regenerative medicine.[126,127]

Injectable antitumor hydrogels derived from natural materials face multifaceted technical challenges during clinical translation. Regarding mechanical properties, balancing injectability for minimally invasive procedures with mechanical supportiveness at tumor sites typically requires composite modifications or crosslinking process optimization to achieve performance equilibrium. In drug-controlled release, tumor microenvironment heterogeneity (*e.g.*, pH gradients, enzyme activity variations) hinders precise prediction of drug release kinetics, demanding enhanced environmental responsiveness in material design.[128] For targeted delivery, the limited universal applicability of receptor-mediated strategies stems from significant interpatient variability in tumor biomarker expression. Safety control challenges primarily arise from inherent endotoxin (LPS) contamination in natural materials, where TLR-4-mediated inflammatory responses impair both biocompatibility and therapeutic efficacy, while conventional sterilization methods inadequately address the dual requirements of preserving material bioactivity and eliminating endotoxins.[129] Industrialization hurdles emerge from biological source-induced batch-to-batch variability, complicating quality control in large-scale production.[121] Notably, current research predominantly relies on short-term animal studies,[6] lacking in-depth investigation into three critical aspects: (1) long-term behavior of hydrogels in orthotopic tumor models; (2) material-tumor microenvironment interaction mechanisms; (3) systemic impacts of degradation byproducts. Addressing these critical gaps demands multidisciplinary collaboration encompassing novel functionalization strategies, standardized manufacturing protocols and systematic preclinical evaluation frameworks. Injectable hydrogels are classified as class III medical devices with high-risk profiles, requiring rigorous preclinical evaluation in accordance with FDA guidelines and ISO 10993 standards. Comprehensive biological evaluation must

include hemocompatibility, pyrogenicity, carcinogenicity, genotoxicity, cytotoxicity, systemic toxicity, and localized tissue responses post-implantation to establish *in vivo* biosafety profiles through comprehensive risk-benefit analysis.[130,131]

Developing clinically translatable antitumor hydrogels necessitates deep integration of material merits with clinical imperatives to ensure both biosafety and therapeutic precision. Current hydrogel carrier development has evolved from single-drug delivery to combinatorial loading of diverse therapeutic agents. Future systems should leverage synergistic designs of biodegradability and stimulus-responsive degradation mechanisms within gel networks to engineer temporal-release architectures, enabling precision-controlled drug liberation across varied clinical scenarios. Simultaneously, advancing clinical translation requires optimization of natural material self-assembly techniques, coupled with establishment of GMP-compliant manufacturing protocols, to overcome persistent translational barriers for injectable hydrogel platforms.

Author contributions

C. Z., H. L., and Z. L contributed equally to this work. All authors contributed to the article and approved the submitted version.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare no conflicts of interest.

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