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Recent advances in hydrogel-based therapeutics for lung cancer

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Lung cancer is one of the most commonly diagnosed types of cancer worldwide, attracting significant attention from researchers due to its high mortality rate and limited treatment options. The complex biological mechanisms associated with lung cancer pose substantial challenges for effective treatment. In recent years, hydrogels have emerged as a promising therapeutic material, garnering considerable interest due to their excellent biocompatibility and biodegradability. These hydrogels can mimic the extracellular matrix of the alveolar microenvironment and have the capability to reduce inflammation while promoting the repair and regeneration of lung tissue. This dual functionality may help mitigate the progression of lung cancer. In this review, we summarize the latest advances and applications of various types of hydrogels in the treatment of lung cancer. We begin by providing an overview of the fabrication methods and characteristics of different hydrogels designed explicitly for lung cancer therapy. Next, we systematically explore their emerging applications in clinical interventions, focusing on their roles in enhancing the therapeutic effectiveness of chemoradiotherapy drugs. Finally, we discuss the current limitations of these hydrogel-based systems and suggest potential directions for future research in this evolving field.

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1 Introduction

Lung cancer is a diverse disease that exhibits a variety of clinicopathological features. It is mainly divided into two major cellular subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC makes up 85% of all lung cancer cases and includes several histological subtypes, such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[1–3] SCLC accounts for about 15% of lung cancer cases and is characterized by distinct neuroendocrine features.[3,4] Lung cancer is one of the most common malignancies worldwide, with the poorest prognosis among all types of cancers. The five-year survival rate is only 10% to 20%, making it the leading cause of cancer-related mortality.[5,6] Early-stage lung cancer often shows no clear clinical symptoms, leading to most patients being diagnosed only at advanced stages when symptoms appear.[7] Most lung cancer patients show nonspecific symptoms, with only 20% experiencing hemoptysis. However, as the disease progresses, it may lead to respiratory symptoms or signs associated with metastasis.[8,9]

Conventional therapeutic approaches for NSCLC have been well established in clinical practice. The principal therapeutic modalities for advanced lung cancer, including precision targeted therapy, immunotherapy, and chemotherapy, are primarily aimed at controlling tumor growth, alleviating symptoms, improving quality of life, and prolonging survival.[10–12] However, most conventional chemotherapeutic agents have significant limitations that affect their effectiveness, including low therapeutic indices, nonspecific targeting, instability, poor bioavailability, and the development of drug resistance. These pharmacological challenges not only cause systemic toxicity to healthy cells but also lead to severe side effects such as nausea, diarrhea, and other complications. As a result, these issues greatly limit the clinical utility of these treatments in managing lung cancer.[13] In response to these challenges, research has increasingly focused on strategies that utilize biomaterials.[14] Among these, hydrogels have emerged as a promising therapeutic platform in pulmonary oncology due to their biocompatibility and ability to release drugs over time, effectively addressing the critical limitations of traditional chemotherapy.[15] Hydrogels, as advanced drug carriers, offer significant advantages in therapeutic delivery systems. Primarily, hydrogels are characterized by a 3D network structure and hydrating capacity analogous to the native extracellular

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matrix (ECM), coupled with superior biocompatibility, chemopermeability, tunable biodegradation, mechanical adaptability, and high drug-loading efficiency.[16–19] These intrinsic properties enable sustained drug release kinetics, thereby reducing acute toxicity associated with high drug concentrations while enhancing therapeutic stability and efficacy through decreased metabolic clearance, crucial attributes for optimizing lung cancer chemotherapeutics.[20,21] Hydrogels have been shown to possess tumor-suppressive activity against lung cancers. When combined with synergistic treatment regimens, they enhance anti-tumor effects through various mechanisms that inhibit tumor growth, ultimately improving treatment results.

Hydrogels used in lung cancer therapeutics can be systematically classified based on various criteria. First, they are categorized by size into macroscopic hydrogels, microgels, and nanogels. In terms of responsiveness to stimuli, hydrogel systems can be classified as thermosensitive, pH-responsive, X-ray-responsive, or dual pH/temperature-responsive hydrogels. Functionally, these hydrogels are categorized into two types: those for lung cancer therapy and those for lung cancer monitoring and diagnosis. These engineered matrices utilize specialized physicochemical properties to enable spatiotemporal control over drug targeting and precise drug release. This approach enhances therapeutic efficacy while reducing systemic toxicity. This review provides a comprehensive examination of fabrication strategies, inherent properties, and emerging therapeutic applications of different hydrogel platforms in pulmonary oncology. Additionally, it critically addresses the translational challenges that arise from preclinical development to clinical deployment, with a particular focus on overcoming biological barriers and engineering biocompatible interfaces. By synthesizing current technological advancements and identifying significant knowledge gaps, this work aims to offer strategic insights for advancing hydrogel-based precision oncology in the management of lung cancer.

2 Fabrication strategies and functional attributes of multiscale hydrogels for lung cancer therapy

Multiscale hydrogels are increasingly recognized as a transformative platform in pulmonary oncology. They are engineered across various dimensional regimes, including macroscopic hydrogels, microgels, and nanogels.[22] These systems offer clinically relevant advantages due to their natural biocompatibility, adjustable biodegradation rates, and controlled drug release profiles over time and space. Their hierarchical architecture enables the precise targeting of cancerous lesions while ensuring the consistent delivery of therapeutic agents. These features have contributed to their widespread use in treating thoracic cancers.

2.1 Macroscopic hydrogel

Macroscopic hydrogel refers to hydrogel systems that are typically millimeter-scale and are administered through direct implantation into or around tumors. This method addresses significant limitations of conventional chemotherapy in treating localized lung cancer. By bypassing systemic circulation, which is a major factor in the rapid loss of drugs from tumor sites, these macroscopic hydrogels facilitate prolonged drug retention within malignant lesions. This localized delivery approach not only enhances the effectiveness of chemotherapy but also significantly reduces off-target toxicity through two synergistic mechanisms.[23,24]

2.1.1 Hyaluronic acid-based hydrogels. As a principal polysaccharide component of the ECM, hyaluronic acid (HA) and its derivatives are widely employed in fabricating macroscopic hydrogels with tunable properties, owing to their exceptional water-binding capacity, low immunogenicity, non-inflammatory nature, biocompatibility, controlled biodegradability, and negligible toxicity (Table 1). While native HA hydrogels exhibit slow gelation kinetics, potentially leading to precursor migration from injection sites and premature drug leakage, limitations have been ingeniously addressed through molecular engineering. By employing tyramine-functionalized HA as a carrier matrix, researchers developed an injectable endostatin (ES)-loaded hydrogel system (ES/HA-Tyr). The hydrogel was synthesized *via* a two-step process. First, tyramine-modified hyaluronic acid (HA-Tyr) was prepared through a chemical conjugation method. Subsequently, under physiological conditions (PBS, pH 7.3), a three-dimensional network hydrogel was formed by utilizing horseradish peroxidase (HRP) and hydrogen peroxide (H_2O_2) as a catalytic system. This system catalyzes the free radical coupling reaction between the tyramine moieties on the HA-Tyr chains, resulting in cross-links primarily comprised of dityrosine linkages. The horseradish peroxidase-mediated crosslinking system, combined with tyrosine coupling, accelerates gelation kinetics, allowing rapid *in situ* hydrogel formation after injection. This rapid gelation significantly enhanced localized ES retention while reducing systemic exposure. As shown in Fig. 1A, H&E staining was performed to evaluate the toxicity of ES/HA-Tyr in tumor-bearing mice. The results demonstrated that ES/HA-Tyr reduced the potential systemic toxic side effects of ES.[25] Furthermore, Anlotinib (AL) can be encapsulated in injectable HA-Tyr hydrogels under acidic conditions, with optimized synthesis parameters achieving sustained *in vitro* drug release.[26] However, conventional injectable hydrogel systems often suffer from uncontrolled burst release and off-target drug accumulation, which may lead to overdosing and compromised therapeutic efficacy. To address this, Tang *et al.* developed a novel Ara-C-conjugated HA-Tyr hydrogel system that is capable of sustained, tumor-targeted drug delivery. This system was rigorously evaluated in both *in vitro* and *in vivo* lung cancer models for its radiosensitizing capacity and biosafety. The results demonstrated enhanced radiosensitivity of tumor xenografts with minimal systemic toxicity.[27]

Furthermore, HA-based hydrogels have gained extensive utilization in oncological applications due to their robust self-healing capacity and precise injectability, demonstrating transformative potential in lung carcinoma therapeutics.[28–30] Hyaluronidase plays a pivotal role in tumorigenesis, progression, and therapeutic interventions, which has prompted

Table 1 Applications of various types of hydrogels in lung cancer treatment

Types	Name	Components	Advantages	Limitations	Citations
Multiscale hydrogel	Macroscopic hydrogel	HA hydrogel	High water-binding capacity, immunogenicity, non-inflammatory properties, biocompatibility, biodegradability, and non-toxicity	Slow gelation in natural hyaluronic acid hydrogels risks precursor migration and premature drug leakage	25 and 26
		RADA16-based hydrogel	Facilitates cell adhesion, proliferation, and differentiation, with sustained drug release from intratumoral or peritumoral hydrogels	RADA16-based hydrogel exhibits relatively weak mechanical properties	36
	Microgel	A poly(ethylene oxide)-gelatin methacryloyl	These microgels demonstrated enhanced capabilities in supporting lung cancer cell proliferation, migration, and phenotypic maintenance	It is limited in its ability to model the lung tumor microenvironment compared to organoids	40
		The photo-polymerizable poly(ethylene glycol) diacrylate	Exhibits high binding affinity and excellent selectivity, specifically confining cancer cells within microgel cavities to achieve localized cytotoxic elimination while maintaining extracellular cell viability	The complex synthesis and characterization of this material pose significant challenges	41
	Nanogel	Copolymerization of carboxymethyl chitosan and diallyl disulfide hydrogel	The treatment significantly reduced systemic cisplatin toxicity while overcoming MDR	The complicated synthesis and quality control of this material hamper precise regulation of drug release	46
		RNA nanohydrogels	The combinatorial system exerted synergistic antitumor efficacy by concurrently disrupting drug efflux pumps (*via* microRNA-mediated MDR gene silencing) and enhancing photodynamic-chemotherapeutic crosstalk, demonstrating precision targeting in lung cancer models	The complex synthesis and characterization of this material pose significant challenges	47
Stimuli-responsive hydrogel	Thermoresponsive hydrogel	PEG/MXene hydrogel	NIR irradiation triggered on-demand drug release and eradicated immunoevasive tumor cells	The development of this material is hampered by complexities in synthesis, quality control, and clinical translation	49
		The *N*-isopropylacrylamide (NIPAM), potassium persulfate (KPS), *N*,*N*′-methylenebisacrylamide (MBA), and cysteine hydrochloride hydrogel	This nanotheranostic platform enabled multimodal imaging and combinatorial therapy while preventing tissue damage from excessive heating, achieving optimal antitumor efficacy in lung cancer models	This material faces significant challenges in its translation from the laboratory to the clinic	50
		HMSNs and thermosensitive poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide) hydrogel	This design resolved challenges in drug loading uniformity and capacity for hydrophobic agents in high-water-content hydrogels	The gel presents uncertainty in its mechanical strength and *in vivo* stability	52
	pH-responsive hydrogel	Oxygen-loaded albumin hydrogel	DOX induced apoptosis *via* nuclear DNA damage and ROS generation, while RNase A degraded cytoplasmic RNA, synergistically enhancing antitumor efficacy	This material presents significant challenges in its complex, multistep synthesis and rigorous quality control	56
		Polyvinylpyrrolidone (PVP) and chitosan hydrogel	This hydrogel accelerated drug release in acidic tumor microenvironments, effectively inhibiting the proliferation of KRAS-mutant lung cancer cells while reducing systemic toxicity and treatment duration	The clinical translation of this material remains a major hurdle	57

Table 1 (*Contd.*)

Types	Name	Components	Advantages	Limitations	Citations
	X-ray-responsive hydrogels	Methoxy-poly(ethylene glycol) hydrogel	The on-demand delivery of radiotherapy-triggered chemotherapeutic drugs is employed to synergistically enhance the therapeutic efficacy of CCRT while minimizing adverse effects	The precision and efficiency of the X-ray-triggered drug release remain a major challenge for this material	58
	Dual pH/temperature-responsive hydrogels	Chondroitin sulfate nanogel	The characteristics of hydrogels with dual pH and temperature-sensitive properties	The development of this material is hindered by its poor clinical translatability	43
Multi-functional hydrogels with task-specific responsiveness	Hydrogels for lung cancer therapy	Pectin/cellulose hydrogel	*In vivo* experiments demonstrated that the ursolic acid and cisplatin loaded in the hydrogel enhanced antitumor activity and reduced systemic toxicity	The complex drug release kinetics of this material pose significant challenges to achieving synergistic effects	61
		FGFR1-specific dehydrogenation hydrogel	Following *in situ* administration, Nap-Y within the Y/Nin hydrogel undergoes FGFR1-mediated phosphorylation, generating the hydrophilic product Nap-Phe-Phe-Phe-Glu-Thr-Glu-Leu-Tyr (H_2PO_3)-OH (Nap-Yp), which triggers dehydrogenation-triggered gel dissolution and sustained Nin release	The efficacy of this material is hampered by an inefficient release mechanism and tumor heterogeneity	62
	Hydrogels for lung cancer monitoring and diagnosis	Polyvinyl alcohol–sucrose hydrogel	Achieves non-invasive, portable, and high-frequency monitoring during tumor treatment, demonstrating highly sensitive and specific detection capabilities	The practical application of this material is limited by the questionable reliability of sweat biomarkers	63
		Wrinkled cellulose hydrogel	Exhibits elevated specificity and biosafety profiles, enabling precise interrogation of both the quantitative correlation of heterogeneous CTCs in NSCLC-staged patients' blood and the metastatic potential through distant metastasis detection	The detection sensitivity and quantitative accuracy of this material remain fundamentally challenging	64
		Polyethylene glycol hydrogel	Possesses superior scalability and functions as an *in situ* therapeutic platform for pulmonary carcinoma, demonstrating validated antitumor efficacy	The analytical specificity of this material may be compromised by cross-reactivity	66 and 67

extensive investigation in both *in vivo* and *in vitro* settings. However, the current lack of highly sensitive *in situ* detection methodologies limits its functional characterization. To overcome this challenge, Ge *et al.* engineered a fluorescence resonance energy transfer (FRET)-based HA hydrogel system specifically designed for hyaluronidase detection.[31] As shown in Fig. 1B, the working principle involves fluorescence quenching through FRET when HA derivatives are crosslinked into hydrogel networks, where donor fluorophores are brought into proximity. Upon exposure to hyaluronidase, enzymatic degradation of the hydrogel disrupts FRET, resulting in fluorescence recovery that is proportional to the enzyme activity. This system was further employed to assess real-time fluorescence responses during 3D culture of lung cancer cells, enabling non-invasive monitoring of enzymatic activity.

2.1.2 RADA16-based hydrogels. RADA16-I represents the most canonical member of the ion-complementary self-assembling peptide family. Its molecular structure comprises positively charged arginine (Arg, R) and negatively charged aspartic acid (Asp, D) as hydrophilic residues, along with the non-polar alanine (Ala, A) as the hydrophobic component. In aqueous solution, RADA16-I undergoes spontaneous self-assembly into β-sheet-rich secondary structures driven by ionic complementarity and hydrophobic interactions. This arrangement positions all hydrophobic and hydrophilic amino acids on opposite sides of the structure, facilitating further organization into stable nanofibers. In its higher-order architecture, the hydrophobic domains are capable of encapsulating hydrophobic therapeutic agents, while the hydrophilic regions contribute to the overall stability of the system in aqueous environments.[32] RADA-16, a self-assembling peptide with high hydration capacity, spontaneously forms β-sheet-rich hydrogels in aqueous environments.[33] These hydrogels not only mimic the ECM microenvironment of cartilage but are also enzymatically degradable *in vivo*. RADA16-based hydrogels exhibit excellent biocompatibility, supporting cell adhesion, proliferation, and differentiation.[34] To enhance functional versatility, Yang *et al.*[35] engineered a copper-binding peptide glycyl-histidyl-lysine-

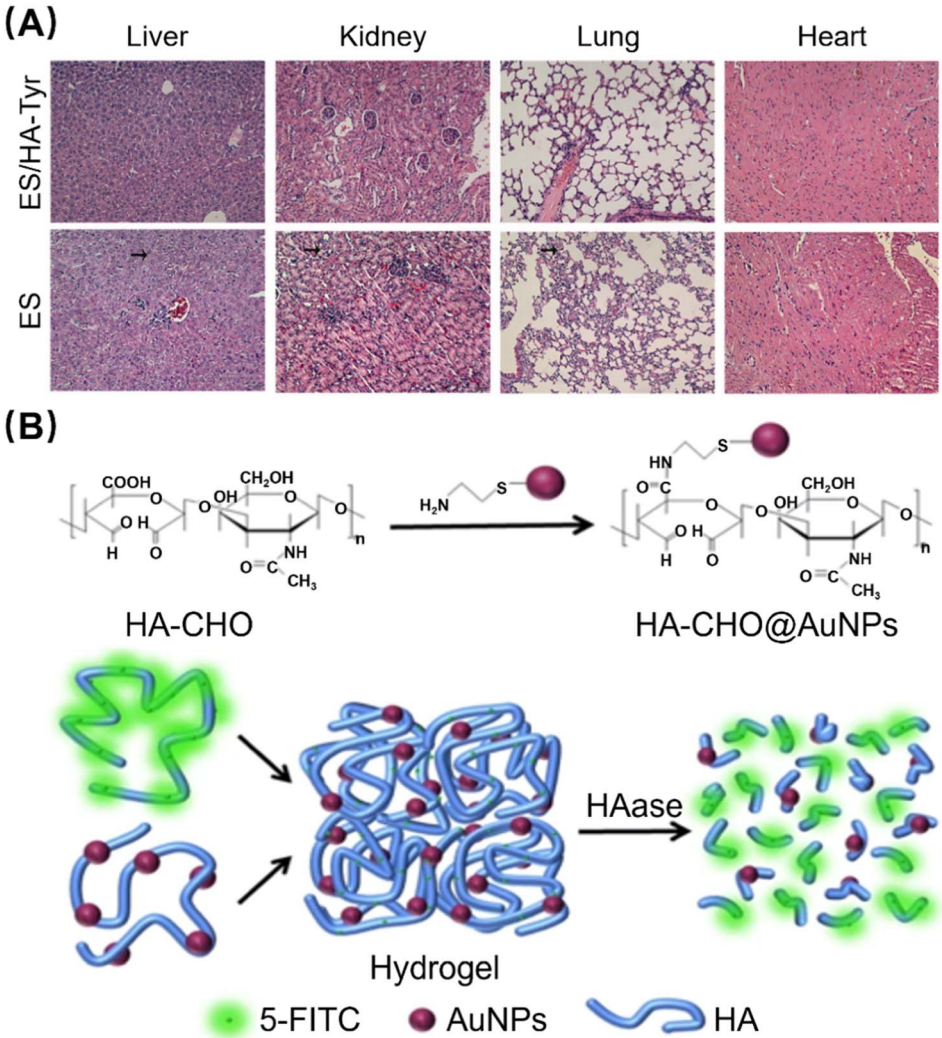

Fig. 1 (A) Hematoxylin and eosin staining pictures of visceral tissue after ES and ES/HA-Tyr treatment. Reproduced from ref. 25 with the permission of Informa UK Limited, copyright 2021. (B) Preparation of HA-CHO@AuNPs and schematic illustration of the HA fluorescent hydrogel based on FRET for the detection of HAase activities. Reproduced from ref. 31 with the permission of Springer Nature, copyright 2020.

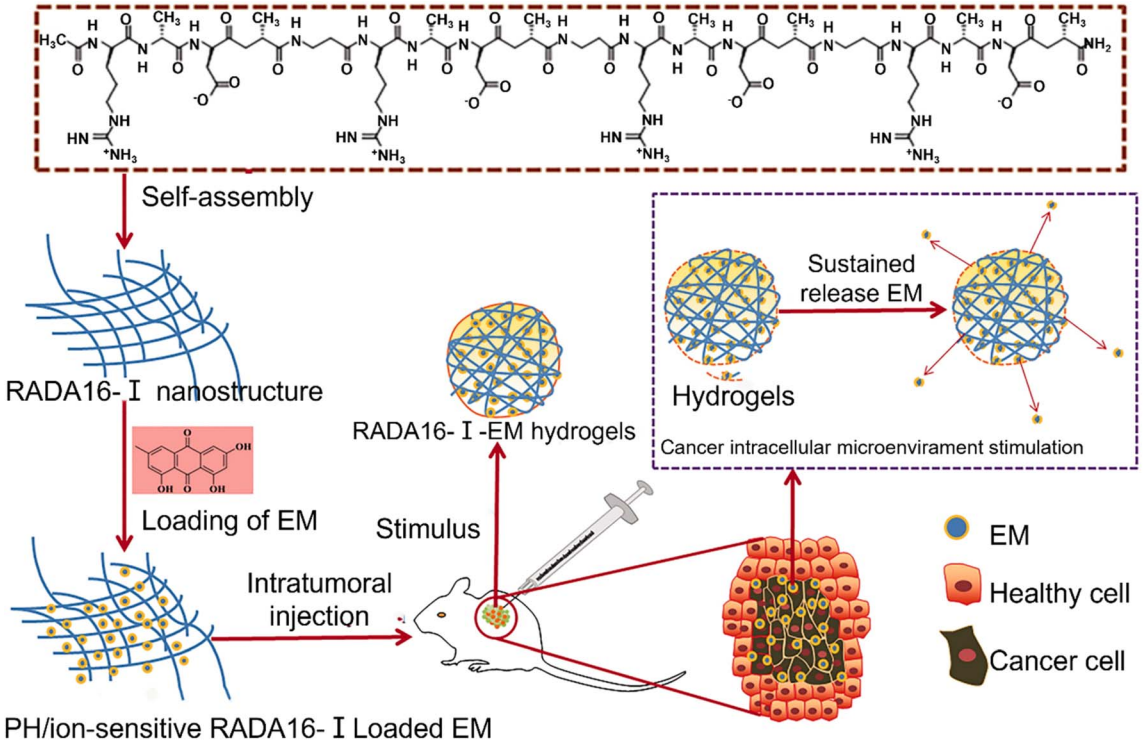

Fig. 2 Illustration to develop pH/ion-responsive RADA16-I hydrogels loaded with an anti-cancer drug – EM for cancer treatment. The RADA16-I-EM suspension was injected into a cancer-bearing mouse model *via* intra-tumoral injection, where it immediately formed hydrogels *in situ* in response to the stimulation of the microenvironment within the cancer. Sustained release of EM from the hydrogels inside or beside the cancer exerts inhibitory effects on the cancer cells. Reproduced from ref. 36 with the permission of Informa UK Limited, copyright 2021.

functionalized RADA16 hydrogel. This innovative system leverages functionalized RADA16 nanofibers to chelate copper ions, forming composite hydrogels that promote angiogenesis by enhancing endothelial cell adhesion and proliferation *in vitro*, as well as neovascularization *in vivo*. Recent advances in RADA16-based hydrogel design for lung cancer therapy include the encapsulation of hydrophobic emodin (EM) within RADA16-I hydrogels. Specifically, as shown in Fig. 2, colloidal suspensions of RADA16-I-EM were prepared under magnetic stirring and subsequently triggered to form *in situ* hydrogels upon exposure to physiological pH/ionic conditions. Intratumoral injection studies demonstrated sustained EM release from the hydrogel depot, achieving localized cytotoxicity against cancer cells.[36] These findings highlight the growing potential of RADA16-I hydrogels as precision drug delivery platforms for treating lung cancer (Table 1).

These findings demonstrate that macroscopic hydrogels enable localized drug delivery to tumor sites, thereby minimizing systemic side effects. Furthermore, the sustained release kinetics maintain therapeutic drug concentrations within the tumor microenvironment, significantly enhancing treatment efficacy. Looking forward, macroscopic hydrogel systems could be integrated with multimodal therapeutic strategies. Such as chemotherapeutic agents, immunomodulators, and gene therapy vectors, to potentiate synergistic effects. This combinatorial approach holds promise for improving patient survival rates and redefining precision oncology paradigms.

2.2 Microgels

Microgels, defined as hydrogels with dimensions ranging from 0.5 to 10 μm, exhibit tunable crosslinking densities that critically govern their mesh porosity, morphological features, mechanical compliance, swelling ratios, structural stability, and degradation kinetics.[37] The structural programmability of microgels enables the precise modulation of their physicochemical properties by optimizing their biochemical composition, adjusting crosslinking density, and selecting suitable fabrication methods. As a new category of hydrogel materials, microgels have advantages over macroscopic hydrogels due to their higher surface-to-volume ratios. This makes them versatile platforms for applications such as localized drug delivery, contrast-enhanced imaging, and tissue engineering/regeneration. These qualities have positioned microgels at the forefront of biomedical research. Furthermore, compared to organoids, which aim to allow cells to self-organize under suitable conditions into miniature tissues that mimic organ structure and function, microgels are designed to create a highly controllable, actively regulated 3D microenvironment to guide cell behavior. Relative to organoids, microgels offer unparalleled tunability and controllability of the microenvironment, as well as exceptional manufacturing reproducibility and scalability. Additionally, when organoids grow beyond a certain size, the diffusion of oxygen and nutrients to their core becomes limited, leading to central necrosis. In contrast, the macroporous channels formed between microgel particles

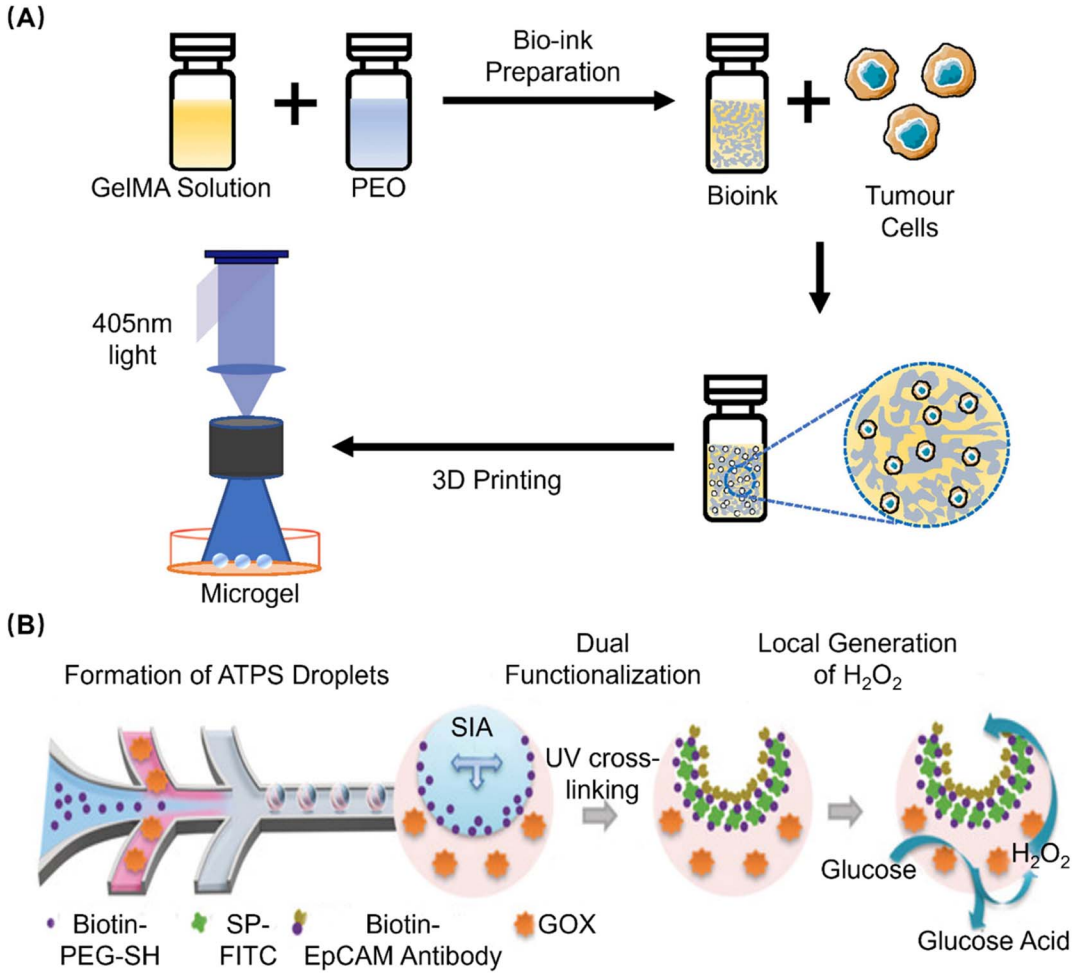

Fig. 3 (A) Schematic diagram of digital light processing-based 3D bioprinting for cell-laden PEO/GelMA porous microgels customization. After mixing the bio-ink components and living cells, the cell-laden PEO/GelMA porous microgels are constructed utilizing a digitally light-processed-3D printer based on digital 3D images from computer. Reproduced from ref. 40 with the permission of Elsevier, copyright 2021. (B) Schematic of the fabrication of dual-functionalized crescent microgels in a microfluidic device and their local generation of H_2O_2 based on the catalytic oxidation of glucose by GOX. Reproduced from ref. 41 with the permission of John Wiley and Sons, copyright 2020.

greatly facilitate fluid convection and diffusion, effectively supporting long-term cell survival and function within large-scale constructs, thereby fundamentally avoiding the issue of internal necrosis.[38,39]

In cancer research, conventional 2D *in vitro* culture systems often fail to recapitulate TME, contributing to high attrition rates in clinical translation. In contrast, 3D culture models better mimic physiological conditions. Addressing this gap, Hu *et al.* developed digitally light-processed 3D-printed porous microgels for the cultivation of lung cancer cells, simultaneously elucidating mechanotransductive pathways involving actin cytoskeletal reorganization in 3D microenvironments. Specifically, as shown in Fig. 3A, a poly(ethylene oxide)-gelatin methacryloyl aqueous two-phase emulsion technique was employed to fabricate monodisperse GelMA microgels with hierarchically porous architectures. These microgels demonstrated enhanced capabilities in supporting lung cancer cell proliferation, migration, and phenotypic maintenance,[40] establishing a robust platform for pathophysiologically relevant *in vitro* tumor modeling (Table 1). To achieve selective *in situ* capture and elimination of lung cancer cells *in vivo* without harming healthy cells, Liu *et al.*[41] developed crescent-shaped microgels through a microfluidic-based phase-separation strategy. As shown in Fig. 3B, this process involved ultraviolet-induced crosslinking of photopolymerizable polyethylene glycol diacrylate and the removal of non-polymerizable dextran phases from the emulsion droplets. The microgels were engineered through a sequential functionalization process: surface modification with biotin groups, encapsulation of glucose oxidase (GOX) within the hydrogel matrix, and conjugation of epithelial cell adhesion molecule (EpCAM) antibodies, resulting in dual-functionalized microgels. These bifunctional microgels exhibited high specificity and affinity for lung cancer cells, selectively trapping target cells within their cavities and inducing localized cytotoxicity *via* GOX-mediated reactive oxygen species (ROS) generation, while sparing surrounding non-target cells. The synergistic integration of cell capture (*via* EpCAM targeting) and on-demand killing (*via* enzymatic ROS

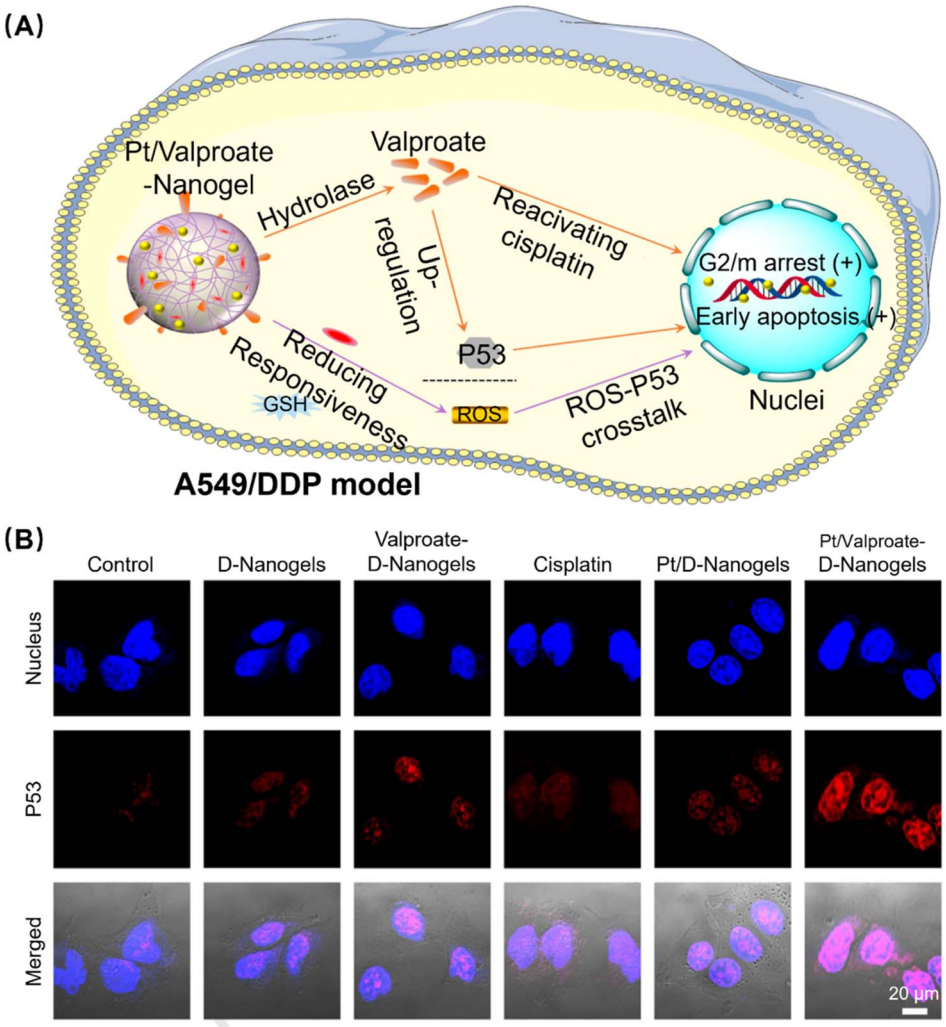

Fig. 4 (A) Schematic model showing how Pt/Valproate (VPA)-D-Nanogel reactivates cisplatin and enhances early apoptosis in A549/DDP cell. Reproduced from ref. 46 with the permission of Elsevier, copyright 2020. (B) Intracellular P53 content observed by CLSM after treatment for 24 h. The scale bar is 20 μm. Nuclei were stained with Hoechst 33 258 (blue), and red fluorescence represented P53. The highest amount of P53 was observed from cells treated with Pt/Valproate-D-Nanogels, which was consistent with the results of the above cytotoxicity tests. Reproduced from ref. 46 with the permission of Elsevier, copyright 2020.

production) within a single microgel particle establishes a novel platform for precision cancer therapy. This approach demonstrates significant potential for applications in smart biomaterials, biomedical engineering, and combinatorial cancer treatment strategies, particularly in minimizing systemic toxicity (Table 1).

Although microgels show great potential in 3D bioprinting and tissue engineering, their application in the specific field of lung cancer therapy faces non-negligible challenges and limitations. For instance, targeted delivery efficiency is low and pulmonary retention time is short, while low drug-loading capacity may necessitate the administration of large quantities of microgels, potentially increasing toxic side effects. The long-term safety of their retention in the lungs still requires comprehensive evaluation. Additionally, their ability to penetrate and modulate the complex tumor microenvironment in the lungs remains inadequate.[42]

2.3 Nanogels

Nanogels, defined as nanoscale hydrogel particles (<200 nm) composed of crosslinked hydrophilic or amphiphilic polymer networks, are synthesized through physical (ionic interactions, hydrogen bonding) or chemical crosslinking strategies. Their submicron dimensions enable intravenous administration while protecting encapsulated hydrophilic/hydrophobic therapeutics from degradation during systemic circulation, thereby reducing off-target toxicity. Characterized by a high surface area-to-volume ratio, excellent biocompatibility, superior hydration capacity, and low immunogenicity, nanogels exhibit exceptional potential as advanced drug carriers. These systems enhance pharmacokinetic profiles through TME-responsive drug release mechanisms, while their inherent hydrophilicity, structural deformability, and colloidal stability optimize biodistribution.[43] Such attributes position nanogels as transformative platforms for precision oncology applications.[44,45] To

reactivate cisplatin sensitivity and potentiate early-stage apoptosis, as shown in Fig. 4A, Sun *et al.* engineered nanogels *via* copolymerization of carboxymethyl chitosan and diallyl disulfide, followed by valproate functionalization to confer cisplatin-reactivation capabilities.[46] Cisplatin was subsequently loaded into the VPA-functionalized nanogels using a pH-responsive swelling-diffusion method for targeted delivery to A549/DDP cisplatin-resistant xenografts. In contrast, a higher level of P53 was observed from A549/DDP cells treated with Valproate-D-Nanogels (17.25) or Pt/Valproate-D-Nanogels (33.74). Meanwhile, the caspase 3 contents in all groups were also measured (Fig. S9), which were consistent with the fact that Pt/Valproate-D-Nanogels possessed the highest caspase 3 enzyme activity compared to the other groups (Fig. 4B). The resulting Pt/VPA-D-Nanogel system significantly reduces systemic cisplatin toxicity while overcoming multidrug resistance (MDR) through synergistic modulation of histone deacetylase inhibition and platinum-DNA adduct repair pathways, offering a promising strategy for treating refractory cancers (Table 1).

Addressing carrier toxicity and off-target effects, Li *et al.*[47] leveraged the programmability of DNA nanotechnology and rolling circle transcription to construct multifunctional RNA nanogels. These carriers co-encapsulated doxorubicin (DOX), porphyrin derivatives, and tumor-suppressive microRNAs (let-7a, miR-34a, miR-145) within a single RNA nanoparticle architecture. The combinatorial system exerted synergistic antitumor efficacy by concurrently disrupting drug efflux pumps (*via* microRNA-mediated silencing of the MDR gene) and enhancing photodynamic-chemotherapeutic crosstalk, thereby demonstrating precision targeting in lung cancer models. A549 cells (human lung adenocarcinoma cells), HeLa cells (human cervical adenocarcinoma cells), and L02 cells (human hepatocytes) were incubated with RNA-loaded NHs at 37 °C for 2 hours. Following incubation, the cytoplasmic green fluorescence intensity in A549 cells was significantly higher than that observed in HeLa and L02 cells. These results demonstrate that hydrogel nanoparticles equipped with aptamers can achieve enhanced cellular uptake efficiency (Table 1).

While preclinical studies have validated the therapeutic potential of nanogels in both *in vitro* and *in vivo* settings, critical challenges remain for clinical translation. Key limitations include insufficient long-term biosafety data, batch-to-batch variability in hydrogel formulation, and scalability constraints of complex manufacturing processes. Future research must prioritize standardized characterization protocols and good manufacturing practice-compliant production methods to bridge the gap between laboratory-stage investigations and clinical-grade therapeutic applications in lung oncology.

2.4 Future perspectives

Although macroscopic hydrogel, microgels, and nanogels used for lung cancer treatment have shown considerable promise as drug delivery systems, their clinical application and future development still face several unresolved challenges. These include, for example, complex manufacturing processes, difficulties in ensuring batch-to-batch consistency, insufficient long-term stability, the need for further optimization of drug release kinetics, and the requirement for deeper investigation into their response mechanisms within the complex tumor microenvironment.[48]

3 Stimuli-responsive hydrogels for lung cancer therapy: fabrication strategies and functional attributes

3.1 Thermosensitive hydrogels

Thermosensitive hydrogels enable rapid *in situ* gelation at target sites through simple temperature stimulation, eliminating the need for organic solvents, crosslinkers, or external devices. The sol–gel phase transition of thermoresponsive polymer solutions occurs instantaneously when the temperature rises or falls below a critical threshold, accompanied by volumetric expansion or contraction of the matrix. This enables localized hydrogel formation for precise drug delivery, thereby enhancing local drug concentrations while minimizing systemic toxicity or side effects associated with conventional administration. Despite therapeutic advancements, limitations such as single-modality efficacy and residual adverse effects persist. To address these challenges, Ma *et al.* developed a temperature-sensitive hydrogel-based localized injection system encapsulating cisplatin and imiquimod within 2D MXene nanosheets, forming PEG-MXene@DDP@R837@SHDS. Near-infrared (NIR) irradiation triggered on-demand drug release and eradicated immunoevasive tumor cells[49] (Fig. 5A) (Table 1). Similarly, Jiang *et al.*[50] innovatively integrated chemotherapy and magnetic induction hyperthermia by formulating an intelligent thermosensitive hydrogel using nano-realgar and Fe_3O_4 combined with gelatin. This nanotheranostic platform enabled multimodal imaging and combinatorial therapy while preventing tissue damage from excessive heating, achieving optimal antitumor efficacy in lung cancer models (Table 1). Furthermore, to overcome inherent limitations of thermosensitive hydrogels, such as poor drug solubility, rapid degradation, and transient bioactivity-Zhou *et al.* engineered a nanocarrier delivery system by encapsulating erlotinib within hollow mesoporous silica nanoparticles (HMSNs) embedded in a thermosensitive poly(D, L-lactide)-poly(ethylene glycol)-poly(D, L-lactide) hydrogel. This design resolved challenges in drug loading uniformity and capacity for hydrophobic agents in high-water-content hydrogels. As shown in Fig. 5B, *in vivo* imaging revealed prolonged intratumoral and peritumoral drug retention with the ERT@HMSNs/hydrogel composite. The injectable system demonstrated robust antitumor activity and systemic safety in xenograft models, accelerating drug efficacy by elevating tumor drug concentrations.[51,52] This study pioneers a scalable platform for localized anticancer nanodelivery systems[52] (Table 1).

Thermosensitive hydrogels, as an advanced drug delivery system, have demonstrated considerable promise in the local treatment of lung cancer. Compared to pH-responsive hydrogels, thermosensitive hydrogels offer a more stable and reliable triggering signal, enabling physical sequestration and spatial

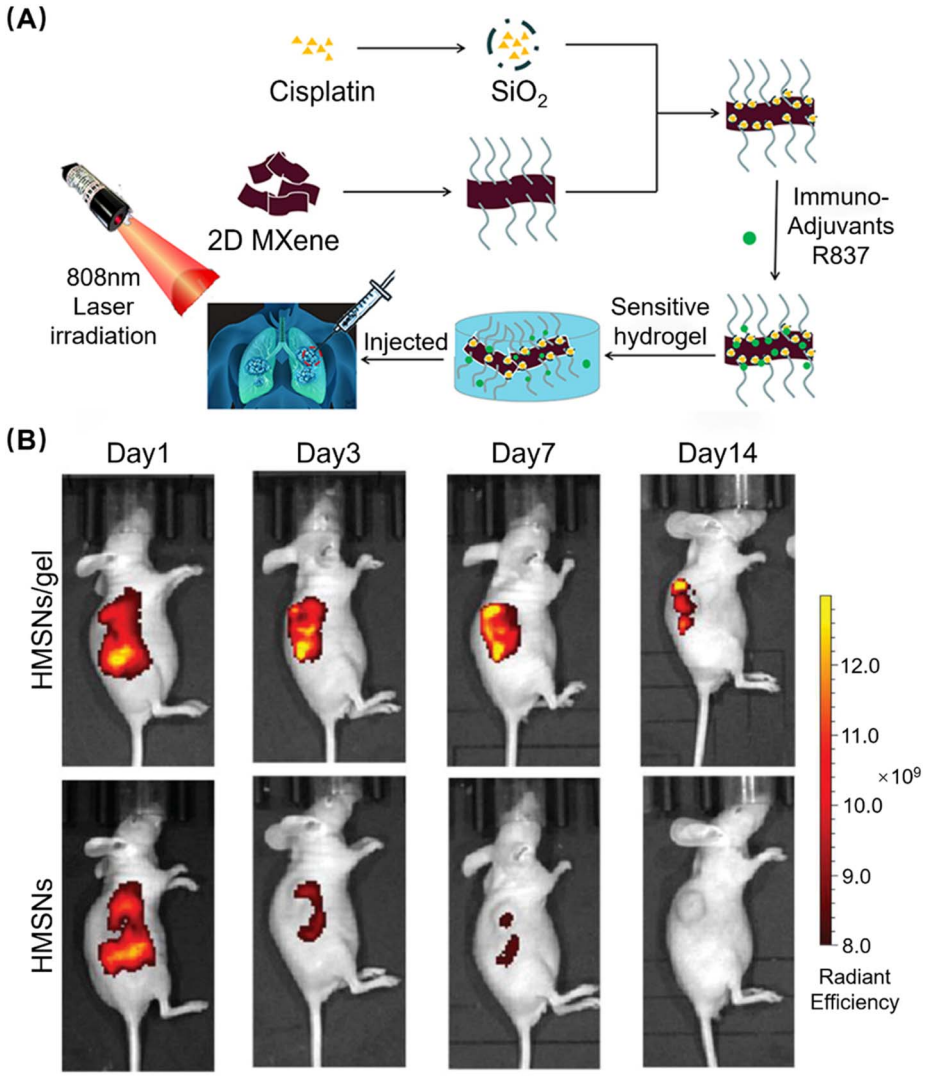

Fig. 5 (A) Schematic illustration of the preparation process of MDR@SHDS. Reproduced from ref. 49 with the permission of Dove Medical Press Limited, copyright 2024. (B) The NIR real-time images of A549 xenograft models after injection of DiR@HMSNs formulation and DiR@HMSNs/hydrogel composite at 1st, 3rd, 7th, and 14th days. MDR@SHDS. Reproduced from ref. 52 with the permission of John Wiley and Sons, copyright 2020.

confinement. The liquid hydrogel precursor can be delivered to the tumor site, whereupon gelation, it effectively entraps the therapeutic agents at the target location. This mechanism significantly minimizes drug diffusion into the systemic circulation, thereby mitigating systemic toxicity. In contrast, pH-responsive hydrogels inherently struggle to form such a long-term, stable scaffold capable of providing physical support and isolation. However, thermosensitive hydrogels are also associated with non-negligible limitations and challenges. These include, but are not limited to, obstacles in clinical translation and application, as well as an incomplete understanding of their interactions with the complex tumor microenvironment. In conclusion, due to their unique advantages, thermosensitive hydrogels hold significant potential to emerge as a crucial platform for localized drug-controlled release in the future.[53]

3.2 pH-Responsive hydrogels

pH-Responsive hydrogels enable selective drug release under acidic conditions and targeted delivery to tumor tissues, achieving integrated diagnostic and therapeutic functions while exhibiting excellent biocompatibility and biodegradability.[54,55] These hydrogels typically contain weakly acidic or alkaline functional groups (*e.g.*, amines, carboxylic acids, imines) capable of donating or accepting protons. Variations in external pH trigger protonation/deprotonation of these groups, inducing phase transitions (*e.g.*, solubility changes, volumetric swelling/shrinking) and controlled drug release. Covalent organic frameworks (COFs), with their ordered structures, open channels, tunable porosity, and lipophilicity, have emerged as promising platforms for combinational therapies, including chemotherapy, photothermal therapy (PTT), and photodynamic therapy (PDT). However, existing research predominantly

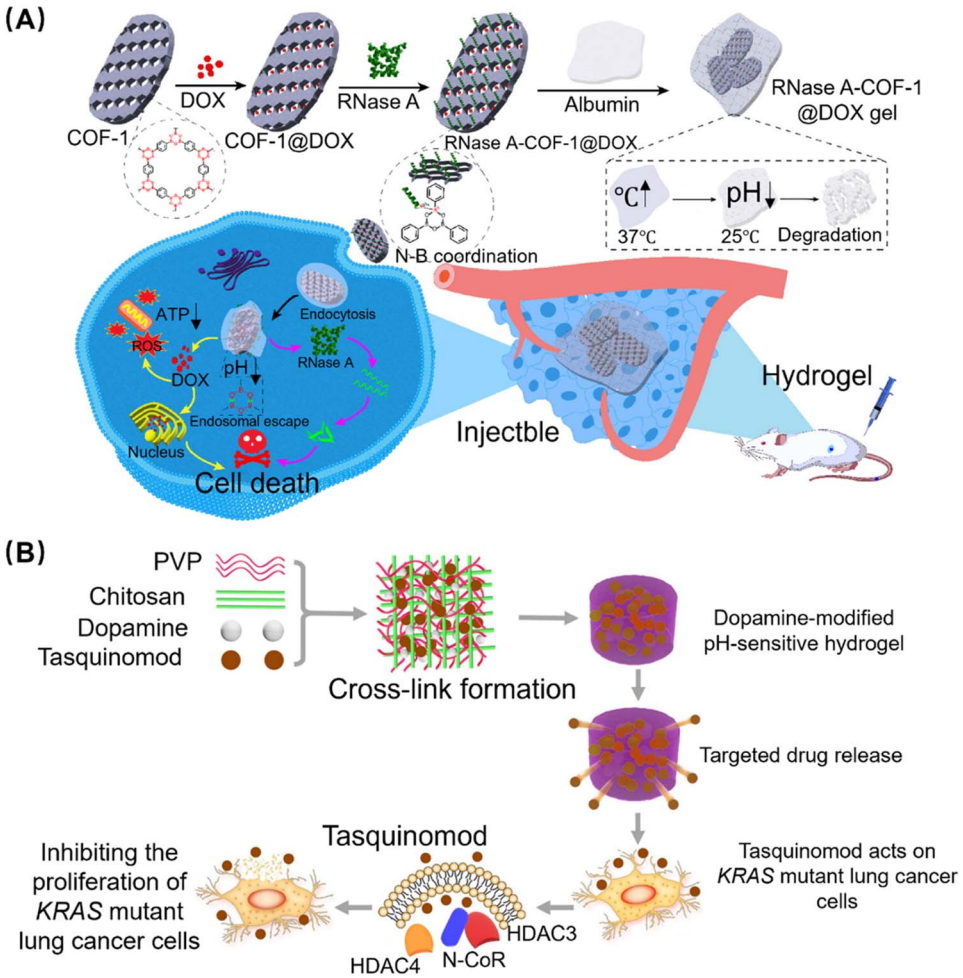

Fig. 6 (A) Schematic illustration of the RNase A-COF-1@DOX Gel carrier and its mechanism for releasing protein and small-molecule drugs. Reproduced from ref. 56 with the permission of American Chemical Society, copyright 2023. (B) Schematic diagram of dopamine-modified pH-responsive hydrogel. Reproduced from ref. 57 with the permission of Sage Publications, copyright 2022.

focuses on integrating COFs with small-molecule drugs and PTT/PDT agents, neglecting their potential for co-delivering proteins and small-molecule therapeutics. As shown in Fig. 6A, to address this gap, Meng *et al.* developed an injectable, albumin-based synergistic nanogel platform (RNase A-COF@DOX Gel) for lung cancer treatment, simultaneously encapsulating the chemotherapeutic DOX and the cytotoxic protein ribonuclease A[56] (RNase A). Under acidic tumor conditions, pH-responsive cleavage of boronate ester bonds in the COF triggered its disintegration, releasing DOX and RNase A into the cytoplasm. DOX induced apoptosis *via* nuclear DNA damage and ROS generation, while RNase A degraded cytoplasmic RNA, synergistically enhancing antitumor efficacy. This system pioneers a novel strategy for intracellular protein-small molecule co-delivery[56] (Table 1).

To overcome limitations of conventional chemotherapy, such as inadequate intratumoral drug retention and frequent dosing. Xu *et al.*[57] engineered a pH-responsive hydrogel system using dopamine-modified chitosan-polyvinylpyrrolidone loaded with the chemotherapeutic agent tasquinimod (Fig. 6B). This hydrogel accelerated drug release in acidic TME, effectively inhibiting the proliferation of KRAS-mutant lung cancer cells while reducing systemic toxicity and treatment duration. The study provides a clinically translatable approach for localized, precision chemotherapy (Table 1).

3.3 X-ray-responsive hydrogels

X-ray-responsive hydrogels enable the on-demand delivery of radiotherapy-triggered chemotherapeutic drugs, synergistically enhancing the efficacy of concurrent chemoradiotherapy (CCRT) while minimizing systemic toxicity. Conventional chemotherapy alone may cause severe damage to organs such as the heart, liver, and kidneys, necessitating synergistic CCRT approaches. Although CCRT is the standard treatment for inoperable stage III NSCLC, current regimens often fail to achieve optimal therapeutic synergy and instead exacerbate toxicity. To address this, as shown in Fig. 7A and B, Wang *et al.* developed an X-ray-responsive polypeptide nanogel (PNG) for targeted delivery of the chemotherapeutic agent DOX.[58] The PNG/DOX system demonstrated prolonged circulation time and enhanced intratumoral accumulation in A549 lung cancer-

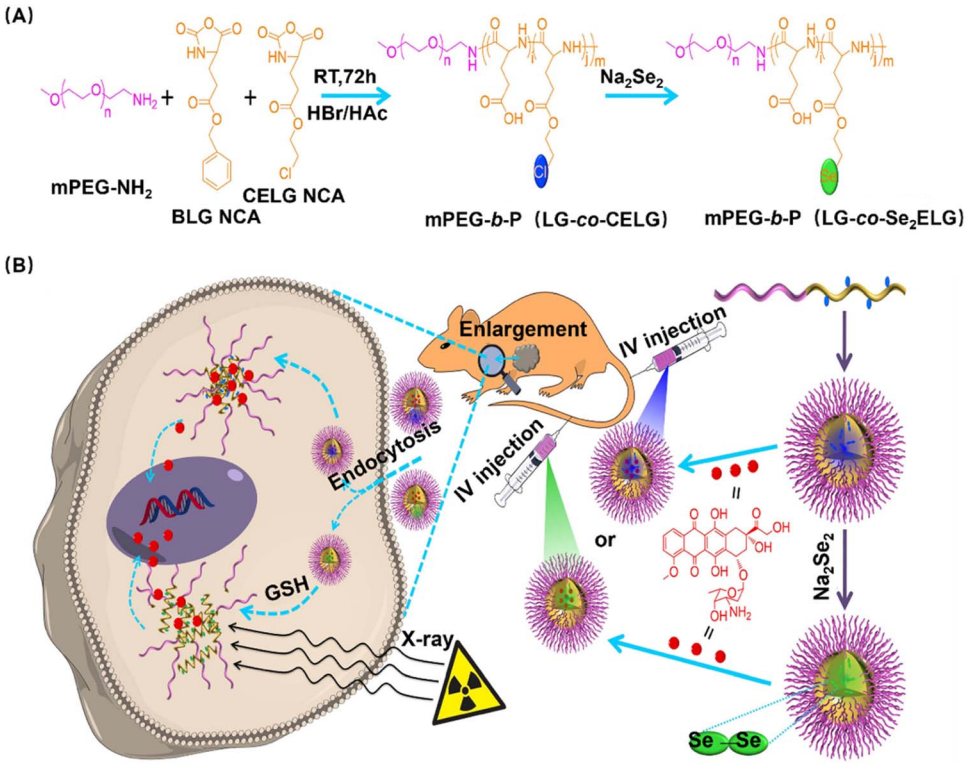

Fig. 7 (A) Synthesis of mPEG-b-P(LG-co-CELG). Reproduced from ref. 58 with the permission of Elsevier, copyright 2021. (B) Schematic diagram of DOX loading, intravenous administration, enhanced retention in tumor tissue, enhanced internalization by tumor cells, and stimuli-responsive drug release. Reproduced from ref. 58 with the permission of Elsevier, copyright 2021.

bearing nude mice. Combined with X-ray irradiation, PNG/DOX exhibited superior synergistic antitumor efficacy and reduced off-target toxicity compared to monotherapies. This X-ray-responsive nanogel bridges chemotherapy and radiotherapy, providing a promising platform for optimizing CCRT for clinical translation (Table 1).

X-ray-responsive hydrogels represent an emerging class of smart materials that, although showing potential for lung cancer treatment, remain confined to laboratory research. Further studies are essential before clinical translation can be achieved. Furthermore, this strategy has inherent limitations in its applicability, as it is only suitable for patients with lung cancer who are scheduled to undergo radiotherapy. It holds limited value for early-stage diseases that do not require radiation or tumor types that are insensitive to radiotherapy. Moreover, due to the penetrating nature of X-rays, inevitable damage to surrounding healthy lung tissue, the heart, and the esophagus persists. Future research should focus on developing safer and more efficient materials and establishing reliable pulmonary delivery strategies to overcome these current drawbacks.[59]

3.4 Dual pH/temperature-responsive hydrogels

Dual pH/temperature-responsive hydrogels are materials whose physical properties (*e.g.*, swelling capacity, structure, morphology) dynamically respond to specific pH and temperature conditions. These hydrogels combine the characteristics of pH- and thermoresponsive systems: under acidic pH (6.1) and low temperature (23 °C), the nanogel–hydrogel precursor exists as a sol due to ionic interactions, whereas it transitions into a viscoelastic gel under physiological conditions (37 °C, pH 7.4). To overcome CDDP resistance, Soo Gil *et al.* synthesized chondroitin sulfate nanogels loaded with cisplatin *via* chelate ligand–metal coordination crosslinking. These nanogels were subsequently incorporated into a pH- and temperature-responsive bioabsorbable poly(ethylene glycol)-poly(β-amino ester urethane) (PEG-PAEU) hydrogel for cancer cell-specific drug delivery.[43] When exposed to A549 lung cancer cells or administered in murine models, the nanogels exhibited no significant inflammatory response and were fully bioabsorbed. The *in vivo* gelation, morphology, and biodegradability of PEG-PAEU copolymers and hydrogel–nanogel mixtures were evaluated by subcutaneous injection into the back of SD rats. The *in situ* gel formation of hydrogels and hydrogel + CS-nanogel mixtures, as well as the degradation rate over time, which was measured by tracking the change in size. Both formed a well-defined spherical shape gel in a short time due to changes in the pH and temperature under physiological conditions, which can become a hydrogel depot encapsulating the drug (Table 1). This injectable nanogel system thus serves as a promising platform for targeted CDDP delivery, addressing the challenges of chemoresistance in lung cancer therapy.

3.5 Future perspectives

Despite the great promise of stimuli-responsive hydrogels in the treatment of lung cancer, several limitations remain, including concerns regarding the long-term biocompatibility and safety of the materials, insufficient responsive precision due to the complex tumor microenvironment, and bottlenecks in production and clinical translation. Consequently, substantial future research is still required to overcome these current challenges.[60]

4 Engineered hydrogel systems for lung cancer therapy: fabrication methodologies and functional characteristics

Hydrogels for lung cancer applications can be categorized, based on their primary function, into two distinct groups: those designed for therapeutic purposes and those developed for monitoring and diagnosis.

4.1 Hydrogels for lung cancer therapy

Numerous types of hydrogels for lung cancer therapy have been developed, most of which exhibit potent inhibitory effects on lung cancer cells *in vitro* and suppress tumor growth or eliminate cancer cells *in vivo*. This section highlights hydrogel categories not previously mentioned above.

Ursolic acid significantly inhibits the proliferation and migration of LA795 cells while promoting cancer cell apoptosis. Mechanistic studies reveal that ursolic acid suppresses lung cancer through the MAPK and EMT pathways, inducing DNA and membrane damage. Subsequently, a degradable and self-healing hydrogel-based drug delivery system was designed to enhance the targeted efficacy of combination therapy with ursolic acid and cisplatin. *In vivo* experiments demonstrated

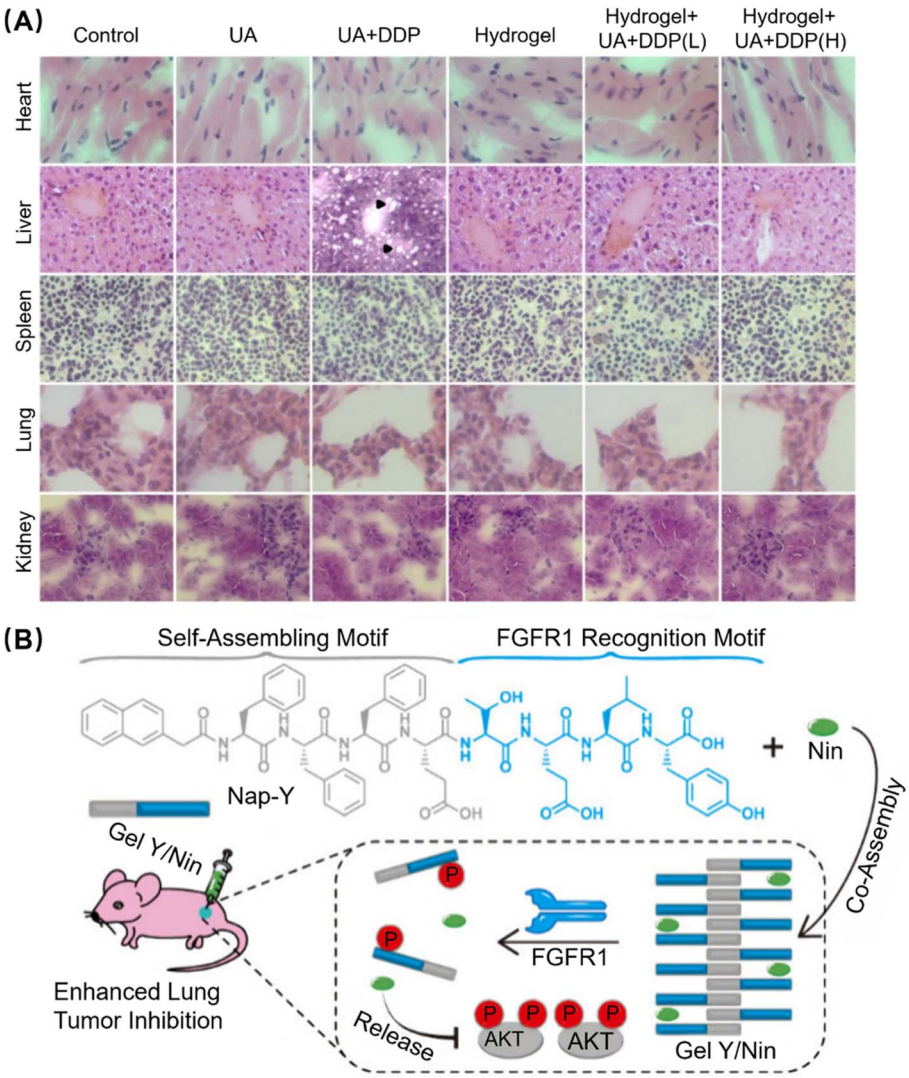

Fig. 8 (A) Representative histological sections of organs and tumor tissues from different administration groups with combined UA and DDP treatment. Reproduced from ref. 61 with the permission of Elsevier, copyright 2024. (B) Schematic illustration of targeted FGFR1 inhibitor release *via* dehydrogenase-responsive hydrogel for potentiating lung cancer therapy. Reproduced from ref. 62 with the permission of American Chemical Society, copyright 2024.

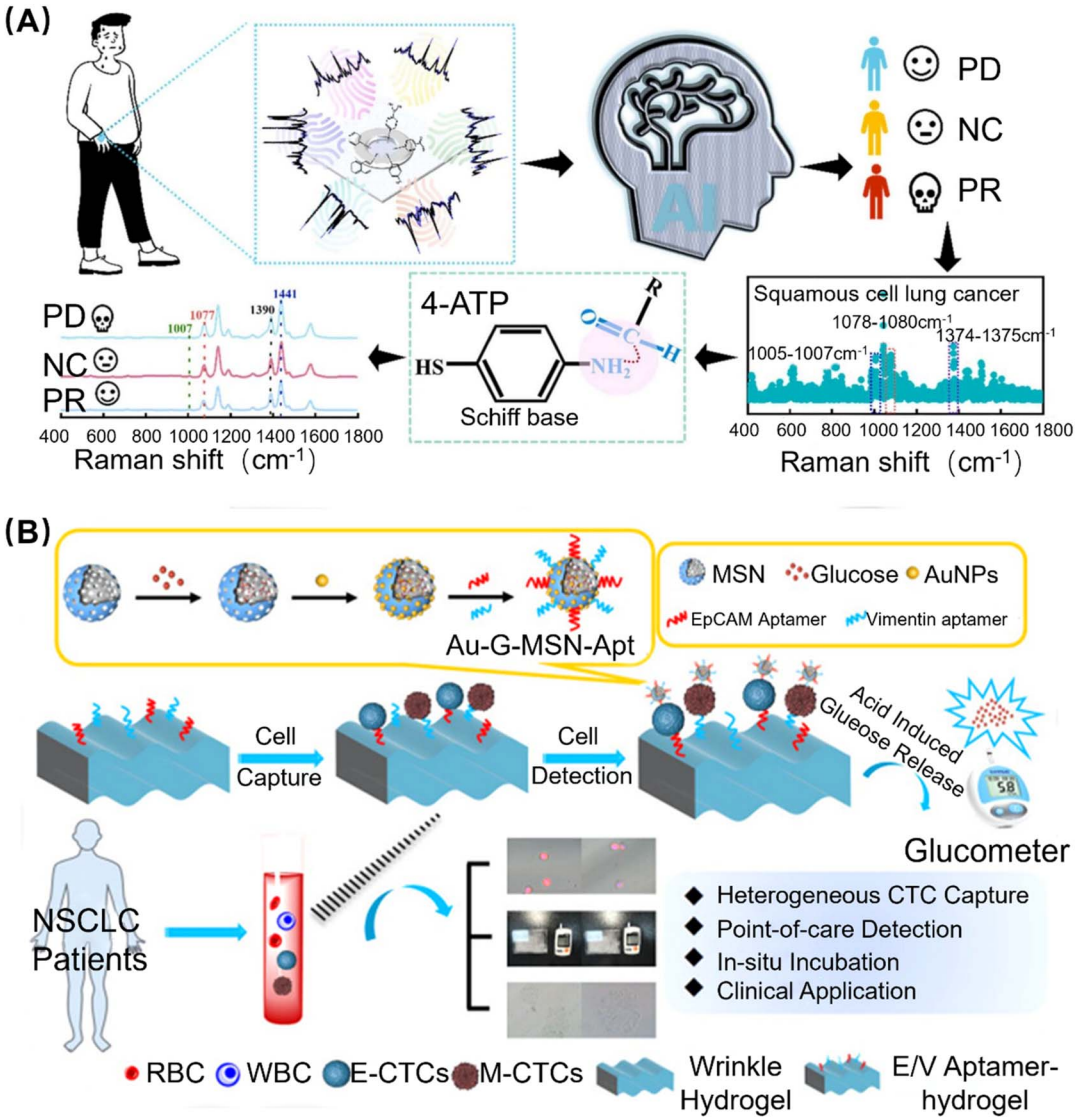

Fig. 9 (A) Schematic illustration of hydrogel-based flexible wearable sweat sensor for SERS-AI-powered monitoring of lung cancer therapeutic efficacy. Reproduced from ref. 63 with the permission of Elsevier, copyright 2024. (B) Fabrication of E/V aptamer-hydrogel and Au-G-MSN-Apt nanoprobes and applications in capture, detection, and *in situ* culture of CTCs in NSCLC patients. Reproduced from ref. 64 with the permission of American Chemical Society, copyright 2022.

that the ursolic acid and cisplatin loaded in the hydrogel enhanced antitumor activity and reduced systemic toxicity. As shown in Fig. 8A, the histopathological analysis of H&E-stained sections demonstrated marked hepatic lesions in the high-concentration UA + DDP group, whereas no significant pathological alterations were observed in other experimental groups. This study proposes a novel multi-target combination therapeutic approach using ursolic acid and cisplatin, which, when integrated with the hydrogel system's targeted delivery capabilities, significantly improves therapeutic outcomes for lung cancer[61] (Table 1).

Additionally, as shown in Fig. 8B, a "smart" supramolecular hydrogel was developed that undergoes FGFR1-specific dehydrogenation-triggered gelation for the localized delivery and sustained release of the FGFR1 inhibitor at the lung tumor site. To achieve this, the octapeptide hydrogelator Nap-Phe-Phe-Phe-Glu-Thr-Glu-Leu-Tyr-OH (Nap-Y) was rationally designed to comprise three distinct components: (i) Nap-Phe-Phe-Phe, serving as the self-assembling backbone; (ii) a negatively charged glutamic acid (Glu) residue, acting as a spacer to modulate charge balance; and (iii) the FGFR1-recognizing tetrapeptide Thr-Glu-Leu-Tyr, derived from the phosphorylation site (Y471) of the FGFR1 substrate FRS2. Owing to its abundant aromatic groups, the FGFR1 inhibitor Nin can readily co-assemble with Nap-Y to form the supramolecular hydrogel Y/Nin. Following *in situ* administration, Nap-Y within the Y/Nin hydrogel undergoes FGFR1-mediated phosphorylation, generating the hydrophilic product Nap-Phe-Phe-Phe-Glu-Thr-Glu-Leu-Tyr (H_2PO_3)-OH (Nap-Yp), which triggers gel dissolution and sustained Nin release. Consequently, the released Nin

effectively inhibits FGFR1 and its downstream signaling proteins, achieving enhanced therapeutic efficacy against lung tumors[62] (Table 1).

4.2 Hydrogels for lung cancer monitoring and diagnosis

4.2.1 Polyvinyl alcohol–sucrose hydrogel. Comfortable treatment of malignant tumors represents a current clinical priority in cancer therapy, which imposes stringent demands for noninvasive, portable, and high-frequency monitoring of tumor status during treatment. In recent years, flexible wearable sweat sensors have rapidly emerged, capable of adhering to human skin for health assessment and medical diagnosis. However, these wearable sweat sensors, based on diverse mechanisms, suffer from limitations such as poor sensitivity, temporal variability, and complex data calibration. To address these shortcomings, as shown in Fig. 9A, researchers have introduced surface-enhanced Raman spectroscopy (SERS), which enables highly sensitive and specific detection of trace analytes in sweat. To further enhance the sensitivity and specificity of SERS, a polyvinyl alcohol–sucrose hydrogel-based wearable sweat sensor was developed, incorporated with multiple molecular receptors for SERS monitoring of therapeutic efficacy in lung cancer. By integrating SERS technology with artificial intelligence algorithms (including LightGBM, Gaussian Naive Bayes, Linear Discriminant Analysis, Random Forest, and Support Vector Machine), a novel and precise diagnostic model was established to monitor treatment outcomes. Based on 12 617 clinical SERS spectra, this model successfully diagnosed three therapeutic response categories (disease progression, partial remission, and stable disease) with an accuracy of 89.7%. Leveraging data mining *via* AI algorithms, key Raman spectral features within clinical spectra were identified to explore lung cancer-specific biomarkers associated with diverse comorbidities[63] (Table 1).

4.2.2 Wrinkled cellulose hydrogel. NSCLC accounts for approximately 85% of all lung cancer cases. While traditional biopsy remains the gold standard for cancer diagnosis, its invasive nature imposes physical trauma on patients, leading to low compliance. Additionally, repeated biopsies to obtain spatiotemporal samples from metastatic cancer patients are clinically challenging. In contrast, liquid biopsy based on circulating tumor cells (CTCs), which involves capturing and enumerating CTCs from peripheral blood, is widely recognized as a minimally invasive and patient-friendly approach. It has been extensively validated for its clinical significance in cancer diagnosis, prognosis, and the provision of biological insights into tumor evolution and heterogeneity, guiding therapy. Despite advancements in CTC detection, accurately and specifically identifying CTCs in patient blood remains a formidable challenge due to the complexity of the blood matrix and the low abundance of CTCs. As shown in Fig. 9B, to address this, an integrated analytical strategy was proposed for CTC capture, portable detection, and *in situ* culture based on wrinkled cellulose hydrogels and mesoporous silica nanoparticles (MSNs). Compared to widely reported immunomagnetic separation techniques for CTCs, the key innovations of this study are highlighted as follows: (1). A dual-aptamer-functionalized capture probe, a wrinkled cellulose hydrogel modified with dual aptamers targeting EpCAM and vimentin, was engineered to simultaneously capture both epithelial and mesenchymal circulating tumor cells from non-small cell lung cancer patients with high specificity. (2). Glucose-encoded detection probe: The detection probe (Au-G-MSN-Apt) was fabricated by encapsulating glucose within amino-functionalized MSNs coated with L-cysteine-modified gold nanoparticles (AuNPs), followed by conjugation with EpCAM and vimentin aptamers. Upon target cell recognition, the AuNP caps disassemble, releasing glucose from the MSNs. Captured CTCs were quantified using a commercial portable glucose meter, enabling rapid and user-friendly readouts. (3). *In situ* reculture capability: leveraging the inherent biocompatibility of the hydrogel, captured CTCs were successfully recultured *in situ* without release, preserving their viability for downstream analysis. (4). Clinical correlation validation: the system demonstrated a strong correlation between heterogeneous CTC counts in NSCLC patient blood and disease staging (including distant metastasis status), underscoring its potential for personalized monitoring. Collectively, this strategy exhibits significant promise for early cancer diagnosis and dynamic therapeutic evaluation[64] (Table 1).

The core advantages of the hydrogel-portable glucose meter strategy lie in its ability to address CTC heterogeneity, offer portability and low cost, and maintain high cell viability, making it more suitable for subsequent culture and analysis of captured cells and for point-of-care testing in resource-limited settings. Compared to microfluidic strategies, which excel in high-throughput, high-purity automated processing and enable high-content molecular analysis of rare cells, the hydrogel-PGM strategy demonstrates exceptionally low clinical application costs, extremely high detection sensitivity and portability, and superior cell viability for downstream analysis, thereby carving out a distinctive and complementary niche. However, the hydrogel-PGM strategy is currently at the laboratory proof-of-concept stage and lacks large-scale clinical validation, whereas microfluidic technology is relatively mature, with many platforms having advanced to extensive clinical research stages.[65]

4.2.3 Polyethylene glycol (PEG) hydrogel. Chen *et al.*[66] developed an extraction-free quantitative method for multiplex serum miRNA detection using size-encoded hydrogel microbeads. This approach enabled the measurement of miR-21, miR-205, and miR-375 expression levels in candidate serum samples, allowing for the accurate and reliable classification of distinct lung cancer subtypes through machine learning. The reported method demonstrated high scalability, facilitated by adjustable microbead sizes and the coupling of diverse fluorescent dyes as detection signal channels. By integrating capture antibodies and detection antibodies conjugated with circular template DNA strands, the assay can be extended from miRNAs to protein biomarkers. This methodology exhibits significant potential for high-throughput biomarker quantification, advancing the development of noninvasive cancer assessment strategies.

In a complementary study, Wu *et al.*[67] engineered a thermoresponsive hydrogel composite (abbreviated as PDMP) by

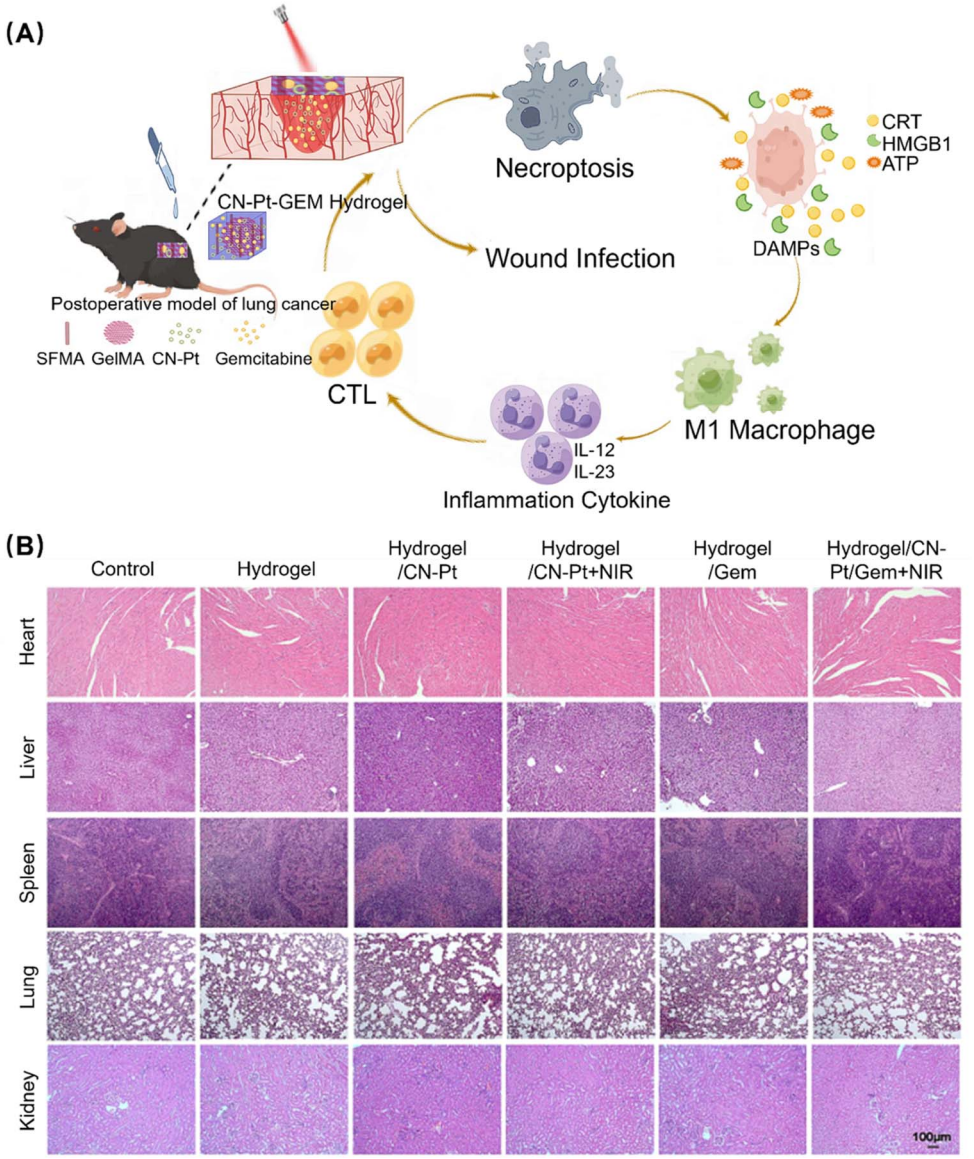

Fig. 10 (A) Schematic of CN-Pt-GEM hydrogel system for tumor surgical adjuvant treatment: inhibiting tumor recurrence and wound infection. Reproduced from ref. 68 with the permission of Springer Nature, copyright 2024. (B) Representative H&E staining images of the heart, liver, spleen, lung, and kidneys from mice in different hydrogel treatment groups. Reproduced from ref. 68 with the permission of Springer Nature, copyright 2024.

blending monomethoxy polyethylene glycol-polycaprolactone-paclitaxel micelles with cisplatin-loaded polyethylene glycol-poly(ε-caprolactone)-polyethylene glycol. The PDMP hydrogel displayed temperature-dependent sol–gel transition behavior, remaining freely injectable at room temperature and forming a stable gel at physiological temperatures. This system demonstrated potent antitumor efficacy as an *in situ* therapeutic depot for lung cancer. The PDMP hydrogel ultimately exhibited substantial promise for minimally invasive, localized lung cancer therapy through direct intratumoral injection (Table 1).

4.3 Other hydrogels

Additionally, numerous hydrogels have been applied in lung cancer therapy. While these systems do not directly kill tumor cells, they effectively prevent postoperative tumor recurrence and wound infection following lung cancer resection. For instance, as shown in Fig. 10A, a hydrogel system was developed based on single-atom platinum (CN-Pt) with exceptional photothermal conversion efficiency, combined with the delivery and controlled release of the chemotherapeutic drug gemcitabine (GEM). Post-resection, this system was coated onto the wound surface and activated by NIR PTT, effectively inducing necroptosis of residual cancer cells, amplifying levels of damage-associated molecular patterns, and increasing the population of M1 macrophages. The significantly elevated levels of phagocytic macrophages enhanced tumor immunogenicity and sensitized cancer cells to CD8+ T cell-mediated immunity, thereby suppressing postoperative recurrence, as validated in

an animal model of postoperative lung cancer recurrence. Furthermore, the NIR-responsive CN-Pt-GEM hydrogel also exhibited potent antibacterial activity to inhibit postoperative wound infections.[68] Finally, the HE staining analysis of the major organs also showed good biological safety in mice, as shown in Fig. 10B.

4.4 Future perspectives

Currently, these hydrogels still face significant limitations due to issues such as insufficient sensitivity, poor signal-to-noise ratio, and long-term biocompatibility concerns, making their translation from the laboratory to the clinic extremely challenging.

5 Applications of hydrogels with diverse compositions in lung cancer therapy

Significant advancements have been achieved in hydrogel-based therapeutic drug delivery. A growing body of literature has demonstrated that hydrogel biomaterials serve as powerful tools for investigating interactions between cells and the TME and localized drug delivery systems capable of maintaining therapeutic drug concentrations at tumor sites. Below, we summarize recent advances in the application of hydrogels for the treatment of lung cancer.

5.1 Application of poloxamer hydrogels in lung cancer therapy

Poloxamers are synthetic triblock copolymers composed of poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide). Poloxamer-based hydrogels remain in a fluid state at room temperature but transition into a highly viscous gel upon exposure to body temperature. In recent years, these hydrogels have garnered significant interest in tissue engineering and localized cancer therapy. A thermoresponsive poloxamer hydrogel (abbreviated as TGel)-extensively evaluated in preclinical settings-demonstrates superior performance due to its cancer cell specificity, minimal off-target toxicity, and intrinsic chemical ablation properties. Studies have confirmed the feasibility of intratumoral administration and retention of TGel, revealing its localized chemical ablation effects in xenograft mouse models of lung cancer. Notably, TGel exhibited pronounced tumor-suppressive activity with negligible systemic toxicity.[69,70] Compared to conventional systemic chemotherapy, intratumoral delivery of chemotherapy-loaded poloxamer hydrogels offers enhanced safety and efficacy for lung cancer treatment. This approach ensures sustained drug release at the tumor site while minimizing exposure to healthy tissues.[71]

5.2 Application of HA hydrogels in lung cancer therapy

Recent studies have focused on HA hydrogel-based strategies for lung cancer therapy to overcome the limitations of traditional chemotherapeutic drug injections.[72] HA-Tyr conjugates have been extensively utilized in lung cancer treatment due to their excellent biocompatibility, biodegradability, non-immunogenicity, and ability to serve as ligands for CD44 receptors overexpressed on tumor cell surfaces.[30] For instance, AL-loaded HA-Tyr hydrogels (AL-HA-Tyr), prepared by encapsulating AL within HA-Tyr conjugates, demonstrated controlled drug release, anti-tumor activity, and anti-angiogenic properties through localized tumor administration. This approach significantly reduced visceral toxicity compared to systemic AL injection, mitigating adverse effects such as hypertension, elevated triglycerides, increased thyroid-stimulating hormone levels, and cardiovascular toxicity. Additionally, AL-HA-Tyr downregulated the expression of Ki-67 and VEGF-A in tumor cells. In murine models, AL-HA-Tyr treatment markedly delayed tumor progression, with treated mice exhibiting significantly reduced tumor mass compared to controls.[26] Furthermore, a locally injectable ES/HA-Tyr demonstrated a prolonged half-life and reduced systemic toxicity relative to free ES, while enhancing anti-angiogenic and anti-tumor efficacy. ES/HA-Tyr enabled sustained drug release, persistently inhibiting endothelial cell proliferation, invasion, and neovascularization. Intratumoral injection of ES/HA-Tyr increased local ES concentrations while decreasing serum levels, thereby minimizing systemic side effects. Combined with radiotherapy, ES/HA-Tyr normalized aberrant tumor vasculature. CD31 staining revealed disorganized and distorted vessels in controls, whereas ES/HA-Tyr-treated tumors exhibited reduced vascular irregularity, tortuosity, branching, and sprouting after seven administrations. This vascular remodeling improved pericyte coverage, alleviated hypoxia, and enhanced radiosensitivity.[25] In another study, an injectable hydrogel composed of HA functionalized with levodopa and poly(ε-caprolactone-lactide) was developed to encapsulate immunomodulatory nanocomplexes containing ovalbumin-expressing plasmids and granulocyte-macrophage colony-stimulating factor for dendritic cell activation. Subcutaneous injection of this hydrogel facilitated the spontaneous self-assembly of a microporous network, mimicking the cellular microenvironment, which enabled localized immune cell recruitment and host cell programming. The microporous structure within the immune-enriched microenvironment permitted dendritic cell infiltration and trafficking to the injection site hydrogel. Controlled degradation of the injection site hydrogel triggered the release of OVA-expressing nanoscale polyplexes, inducing OVA-specific antibody production and effectively suppressing lung cancer progression *in vivo*.[73] HA's remarkable viscoelasticity, biocompatibility, and abundance in the ECM further establish it as a pivotal material for cell therapy, tissue engineering, and regenerative medicine.[29,30,74,75]

5.3 Application of chitosan-HA hydrogels in lung cancer therapy

To enhance the antitumor efficacy of hydrogels, chitosan and its chemically modified derivatives have been widely employed as antitumor components in hydrogel systems, with established applications in regenerative medicine.[76,77] For instance, a pH-responsive, controlled, and targeted chitosan-HA hydrogel-

based drug delivery system was developed by incorporating the chemotherapeutic agents cisplatin and DOX into chitosan modified with nitro salicylaldehyde and aldehyde HA. This dual-drug loading system demonstrated enhanced cytostatic effects against A549 lung cancer cells compared to single-drug-loaded systems, attributed to synergistic interactions between the two drugs and pH-triggered release kinetics.[71,78–80] *In vitro* cell viability studies of hydrogels, single-drug-loaded hydrogels, dual-drug-loaded hydrogels, free drugs, and drug combinations were conducted using the MTT assay. A549 lung cancer cells were treated with CSNSA/A-HA hydrogel, CS-NSA/A-HA/CDDP, CS-NSA/A-HA/DOX, CSNSA/A-HA/CDDP/DOX, free CDDP, free DOX and CDDP-DOX combinations at different concentrations such as 6.25, 12.50, 25.00 μg mL^{-1} and, 50.00 μg mL^{-1} and 100.00 μg mL^{-1}. The prepared dual-drug carrier itself shows remarkable cell inhibition at all concentrations. Single drug loaded hydrogels, CS-NSA/A-HA/CDDP and CS-NSA/A-HA/DOX show almost similar cell viability of 22.42% and 22.14% respectively. The final dual-drug-loaded material exhibits a cell viability of 18.8%.[81]

5.4 Application of pectin-cellulose hydrogels in lung cancer therapy

As shown in Fig. 11A, one study demonstrated that loading silibinin into a biodegradable hydrogel composed of pectin hydrazide and oxidized carboxymethyl cellulose resulted in a system with excellent biocompatibility, biodegradability, and sustained drug release properties. This formulation significantly reduced silibinin toxicity while enhancing therapeutic efficacy against lung cancer and minimizing systemic side effects, indicating broad clinical potential. Silibinin exhibits anti-tumor activity by inhibiting the proliferation and migration of cancer cells. The hydrogel-encapsulated silibinin achieved complete drug release, attaining therapeutic effects comparable to those of the free drug.[82] Furthermore, a novel self-healing biodegradable hydrogel was developed using acyl hydrazide-functionalized carboxymethyl cellulose and oxidized pectin, loaded with citrinin. This hydrogel demonstrated rapid gelation, prolonged citrinin release, and enhanced biocompatibility, effectively reducing citrinin-induced systemic toxicity. Notably, the hydrogel significantly amplified *in vivo* antitumor efficacy compared to free citrinin, attributed to localized drug retention and controlled release kinetics.[83]

5.5 Application of alginate hydrogels in lung cancer therapy

In recent years, alginate hydrogels have garnered significant scientific interest due to their unique capacity for localized delivery of immunomodulators, enhanced immune activation, and reduction of systemic toxicity. These hydrogels minimize systemic immune-related adverse effects and decrease dosing frequency, positioning them as strategic tools for localized immunotherapy.[84–86] Alginate-based hydrogels with improved mechanical properties and stability through physical or chemical modifications have been extensively explored.[29,30,74,78,87,88] Notably, alginate hydrogels have demonstrated substantial potential in lung cancer therapy.[89–91] In a recent study, an alginate-based hybrid hydrogel was developed for use as an injectable on lung resection surfaces during surgery. These hydrogel-encapsulated endoplasmic reticulum-modified liposomes are preloaded with signal transducer and activator of transcription 3 small interfering RNA and lidocaine hydrochloride. The endoplasmic reticulum-modified liposomes effectively downregulated activator of transcription 3 expression in the TME, inducing lung cancer cell apoptosis and polarizing tumor-associated macrophages toward an M1-like phenotype. Concurrently, sustained lidocaine hydrochloride release provided postoperative pain relief and activated natural killer cells, synergistically inhibiting tumor growth while improving patient quality of life. Immunohistochemical analysis of tumor tissues further demonstrated that the combination therapy significantly enhanced apoptosis rates while suppressing proliferation.[91,92]

Moreover, a biodegradable alginate hydrogel was engineered for the sustained and sequential co-delivery of sphingosine-1-phosphate and an anti-PD-L1 antibody. This delivery system potently suppressed tumor growth and minimized post-surgical recurrence *in vivo*. It also markedly increased the infiltration of dendritic cells, M1 macrophages, CD4+, and CD8+ T cells, showcasing a promising strategy to reshape the immunosuppressive tumor microenvironment.[93]

5.6 Application of poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide) hydrogels in lung cancer therapy

A novel injectable matrix based on HMSNs and a thermosensitive poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide) hydrogel was developed to encapsulate and localize the sustained release of erlotinib. This ERT-loaded hydrogel composite exhibits an injectable, flowable solution state at room temperature, transitioning into a physically crosslinked, non-flowable gel at physiological temperatures. Compared to conventional erlotinib administration, this system significantly enhances drug loading capacity, aqueous solubility, and oral bioavailability of ERT, while demonstrating prolonged intratumoral and peritumoral drug retention and reduced systemic toxicity, thereby improving therapeutic efficacy against NSCLC. As evidenced by tumor imaging and tumor growth curves, oral Tarceva®, locally injected ERT@HMSNs, and ERT@HMSNs/hydrogel all effectively inhibited the proliferation of A549 lung cancer cells. Notably, the hydrogel-based formulation combined with localized delivery significantly enhanced ERT's therapeutic outcomes while reducing the required doses.[52]

5.7 Application of albumin-oxygenated hydrogels in lung cancer therapy

Albumin-oxygenated hydrogels have been widely explored for lung cancer therapy in recent years.[54,94,95] A novel composite delivery system (RNase A-COF-1@DOX) was developed to enable simultaneous targeted delivery of proteins and small-molecule drugs *in vivo*. This system integrates: (1). Lipophilic covalent organic framework (COF-1) encapsulating the small-molecule chemotherapeutic DOX; (2). RNase A, a cytotoxic protein drug, immobilized on COF-1; (3). Albumin-oxygenated hydrogel

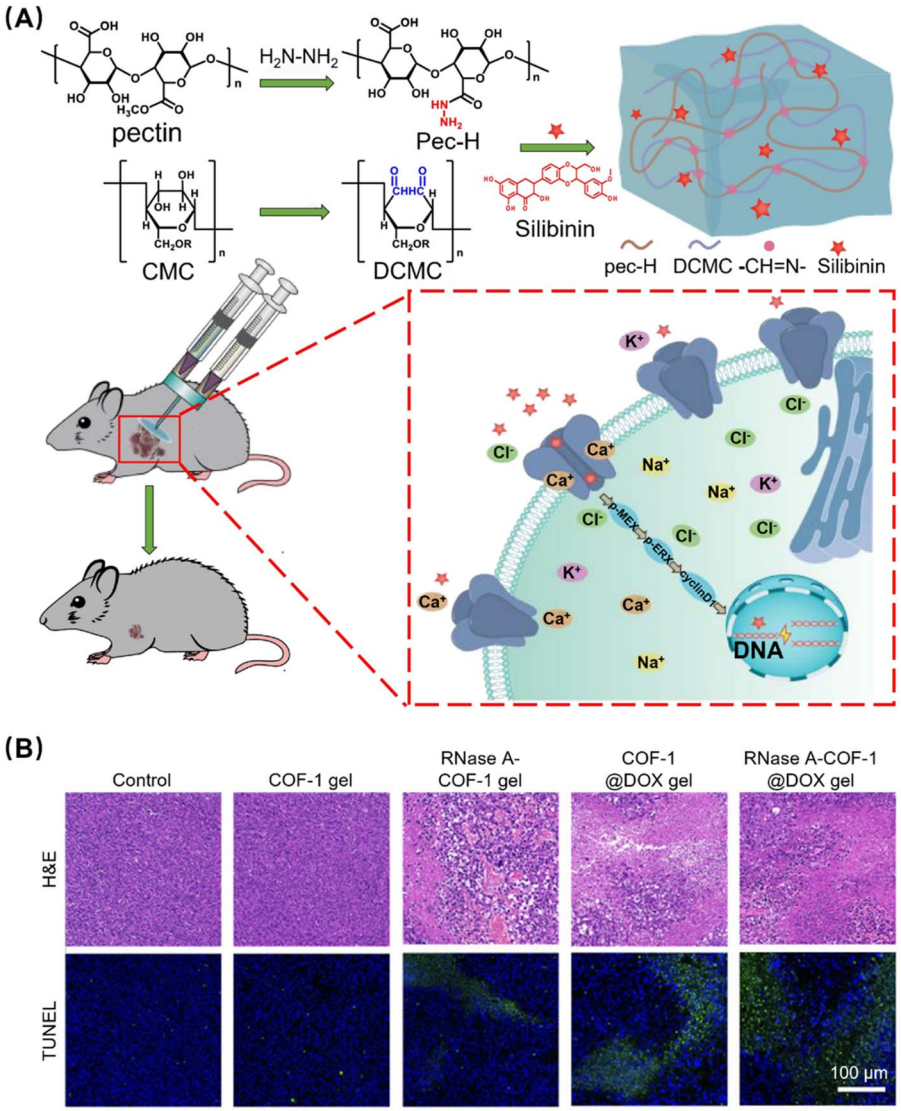

Fig. 11 (A) Schematic illustration of the synthesis of pec-H and DCMC, cross-linking mechanism of pec-H/DCMC hydrogel, and silibinin application for tumor growth inhibition. Reproduced from ref. 82 with the permission of Elsevier, copyright 2023. (B) TUNEL and H&E staining images of LLC tumor tissues treated on day 12 according to panel. Reproduced from ref. 56 with the permission of American Chemical Society, copyright 2023.

networks crosslinked within the pores of COF-1, the RNase A-COF-1@DOX hydrogel group exhibited significantly higher apoptosis levels compared to other treatment groups. The pH-responsive boronate ester bonds in COF-1 undergo cleavage in acidic TME, triggering the disintegration of COF-1 and the subsequent release of DOX and RNase A into the cytoplasm. DOX, a hydrophobic chemotherapeutic agent, penetrates tumor nuclei to induce apoptosis by disrupting nuclear DNA and elevating ROS levels. RNase A degrades cytoplasmic RNA in tumor cells, synergistically enhancing apoptosis and therapeutic efficacy. As shown in Fig. 11B, the antitumor efficacy of RNase A and DOX was evaluated by hematoxylin & eosin (H&E) and TUNEL staining of tumor tissues, with the RNase A-COF-1@DOX gel group demonstrating significantly elevated apoptosis levels compared to other treatment groups. This system provides a groundbreaking strategy for co-delivering protein and small-molecule drugs to tumor cells, addressing challenges in intracellular protein drug delivery.[56]

6 Conclusions and perspectives

Lung cancer remains a leading cause of global mortality, with current therapeutic strategies limited by insufficient efficacy, lack of specificity, and systemic complications such as hypertension, elevated triglycerides, and increased thyroid-stimulating hormone levels. These limitations stem from challenges including short pulmonary drug retention, poor solubility, low oral bioavailability, and off-target toxicity. Hydrogels, as promising biomaterials, have garnered significant attention due to their exceptional biocompatibility, hydrophilicity, controlled drug release, and intelligent drug delivery

capabilities, with broad applications spanning agriculture, tissue engineering, regenerative medicine, and oncology. Compared to free drug administration, hydrogel-based delivery systems enhance drug half-life, reduce systemic toxicity, improve patient compliance, and increase oral bioavailability, demonstrating remarkable potential in lung cancer therapy. Hydrogels exhibit distinct advantages in the treatment of lung cancer compared to liver cancer, primarily due to differences in anatomical accessibility and organ-specific pathophysiology. In lung cancer applications, hydrogels can be delivered directly to the trachea and bronchi through the oral and pharyngeal passages *via* bronchoscopy, allowing for precise localization at the tumor site. This route is inherently minimally invasive, associated with an exceptionally low risk of bleeding, and offers high potential for repeated administrations. In stark contrast, the treatment of liver tumors typically requires percutaneous puncture under ultrasound or CT guidance, where a needle must traverse the skin, muscle, and peritoneum to reach the hepatic lesion. This procedure carries a significantly higher risk of severe hemorrhage than the bronchoscopic approach. Furthermore, the exceptional adhesiveness and sealing properties of hydrogels enable the immediate occlusion of leaking alveoli and small bronchi. Post-operatively, they effectively seal alveolar fistulas, seamlessly integrating therapeutic and reparative functions. While post-hepatectomy complications primarily involve bleeding and bile leakage, the utility of hydrogels in managing these issues is less pronounced than their critical role in preventing pulmonary air leaks. Finally, peritumoral hydrogels can effectively "anchor" mobile lung tumors, which exhibit substantial movement with respiration. Compared to liver tumors, this strategy more significantly reduces tumor mobility, thereby facilitating the precise delivery of radiotherapy and chemotherapy.

However, translating hydrogel-based therapies from laboratory research to clinical applications remains challenging, requiring the resolution of several critical issues: (1). Long-term biocompatibility and biodegradability: while short-term biocompatibility can be assessed in animal models, long-term safety profiles for chronic conditions like lung cancer remain uncertain. (2). Inflammatory responses: injectable hydrogels may induce redox-active substance accumulation in the lungs, exacerbating inflammatory cascades and potentially accelerating tumor progression. (3). Mechanical integrity: many hydrogels exhibit compromised structural stability when encapsulating hydrophobic drugs, limiting their therapeutic efficacy. (4). Precise drug release control: inconsistent drug release kinetics risk overdosing or underdosing during treatment. (5). TME complexity: Incomplete understanding of TME dynamics hinders the optimization of stimuli-responsive hydrogels. (6). Technical barriers: stringent size requirements, undefined pharmacokinetics, and the need for surgical implantation or X-ray-guided procedures further impede clinical adoption. (7). Prior to commencing clinical trials, comprehensive data from *in vitro* and animal studies are required to substantiate the safety and efficacy of the product. (8). Following product commercialization, a comprehensive post-market surveillance system shall be established to collect and analyze adverse event reports and monitor the long-term performance of the material. The surveillance protocol must be approved by an Ethics Committee.

Despite these challenges, hydrogels continue to attract extensive research interest, with recent studies addressing critical gaps in their application for treating lung cancer. Future innovations must prioritize: advanced material engineering, developing hydrogels with tunable degradation rates, and adaptive mechanical properties. Smart release systems: integrating real-time monitoring and feedback mechanisms for dose precision. TME-targeted designs: leveraging multi-omics insights to engineer microenvironment-responsive hydrogels. Translational validation: conducting large-scale preclinical studies to assess long-term safety and efficacy. The unique attributes of hydrogels position them as transformative tools in oncology. Addressing current limitations through interdisciplinary collaboration will accelerate their transition from bench to bedside, offering new hope for precision lung cancer therapy.

Conflicts of interest

The authors declare no conflict of interest.

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.

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