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Hydrogels as local depots for on-demand therapeutic delivery: potential therapeutic approaches for tumor metastasis

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Tumor metastasis, the spread of tumor cells from their place of origin to surrounding tissues and then distant organs through vasculatures, is the major cause of cancer mortality. Despite the recent advances in therapeutic approaches for tumor metastasis, the therapeutic efficacy is still unsatisfactory. Fruitful treatment strategies for tumor metastasis largely depend on targeting tumor cells, the molecular and cellular features of circulating tumor cells, the TME, and the regulatory components of the TME. However, traditionally administered therapeutic agents in biological fluids are highly prone to inactivation, often fail to reach the target site, cause adverse effects, and exhibit poor pharmacokinetics with a short half-life. To overcome these limitations, hydrogel-based delivery systems are investigated as local depots for sustained and stable release to combat tumor metastasis. Herein, we review the extensive application of hydrogels in the local delivery systems of potential therapeutic agents for tumor metastasis therapy. This review summarizes the recent advances in tumor metastasis inhibition strategies and potential therapeutic approaches using hydrogels for the local delivery of various therapeutic agents.

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1. Introduction

Metastasis is a multistep process in which cancer cells spread from a primary tumor to colonize distant organs.[1] It is a major cause of death in cancer patients. Metastatic cancer patients have limited treatment options and significantly lower survival rates than patients with localized cancer. Systemic chemotherapy, the first line of treatment for metastatic cancer, fails to target metastatic cancer cells; has other serious side effects such as off-target accumulation, toxicity, and rapid renal and hepatic clearance; and has the potential to induce metastasis.[2,3] It has been reported that over 90% of failures in chemotherapy occur during the invasion and metastasis of cancers.[4] Recently, advanced treatment options such as immunotherapy, epigenome-modifying agents, and combination therapy have reduced toxicity in metastatic cancer patients but have limited efficacy in inhibiting tumor metastasis.[5] Despite the advances in therapeutic modalities and innovations in the development of active therapeutic options, the complexity of the multistep process creates a huge burden for the development of effective therapies.[6–8] However, the growing knowledge of the metastatic cascade has a significant impact on guiding therapeutic innovation and delivery systems.[5,6,9]

Localized biomaterial-assisted delivery systems for metastatic cancer therapeutic agents have received much attention to overcome the limitations of systemic chemotherapy and have the potential to directly deliver therapeutic agents to target pathological sites.[10,11] This provides an efficient delivery strategy to prevent post-surgical tumor recurrence and metastasis by achieving precise, high-dose controlled release and prolonged exposure of cancer cells to therapeutics. Meanwhile, a single local administration of therapeutics can reduce the side effects of systemic therapy and improve patient compliance.[12] Thus far, among various biomaterial-supported delivery systems, hydrogels are promising materials for various biomedical applications, including drug and other therapeutic agent delivery systems. Hydrogels are 3D polymeric network materials with structural similarity to natural extracellular matrixes that are frequently investigated as delivery vehicles for therapeutic agents. They are an ideal material for encapsulation and utilized as localized depots for therapeutic agents and offer improved delivery efficiency and specificity to the area of interest.[13,14] Moreover, they have been used as 3D models of different diseases such as tumor models,[15] cell encapsulation for enabling highly efficient tissue regeneration,[16] and functionalization with special materials for bioimaging and biosensing.[17] A hydrogel can be engineered from natural or

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synthetic materials to have distinct properties and features desirable for biomedical applications *via* various preparation methods. The steps and mechanisms of metastasis as well as the application of hydrogels have been extensively reviewed. This review discusses hydrogel-based local delivery systems for current and potential therapeutic approaches that control or prevent metastases. It highlights the recent advances in the use of hydrogels as local depots for the sustained delivery of therapeutic agents for tumor metastasis by targeting various steps in the metastatic process.

2. Research methodology

A search for original and review articles was conducted from various indexed journals reporting hydrogel-based local therapy for tumor metastasis. The following search terms were used for the literature search: hydrogel, delivery system, tumor metastasis, local delivery, *in situ* gel, chemotherapy, immunotherapy, phototherapy, and metastasis cascade from search engines, PubMed, Scopus, Google Scholar, and Web of Science databases. Advanced searches were performed from these databases such as (((hydrogel)) and (local delivery)) and (tumor metastasis). This review included original peer-reviewed studies based on the following criteria: (1) publication in an English-language journal; (2) papers related to local delivery systems for tumor transplantation; (3) all papers were included based on therapeutic approaches, inhibition of metastasis, and long-term local treatment delivery; and (4) no limitation has been placed on the date of publication.

3. Targeting metastatic cascade

Metastasis is a highly complex process in which cancer cells detach from the primary site and go through the following steps (metastatic cascade): local invasion, intravasation, circulation, extravasation, and colonization, to form a secondary tumor in distant parts of the body (Fig. 1). Infiltration of tumor cells into adjacent tissues begins with complete loss of intercellular adhesion molecules of tumor cells, which allows the cells to move together as detached clusters or single cells.[18] Several factors such as external stress, nutrient and oxygen deficiencies, chromosomal instability, and morphological and phenotypical changes of tumor cells create favorable conditions for tumor cells to invade the surrounding tissues.[19] For the most part, metastasis initiation genes play a critical role and can promote cell motility, epithelial–mesenchymal transition (EMT), extracellular matrix degradation, angiogenesis, or evasion of the immune system.[20] The epithelial-to-mesenchymal transition plays a role in invading and invasive properties of tumor cells, which reduces the adhesion of tumor cells with each other and the extracellular matrix (ECM), resulting in detachment, invading adjacent tissues and intravasation of cancer cells into the circulation.[21]

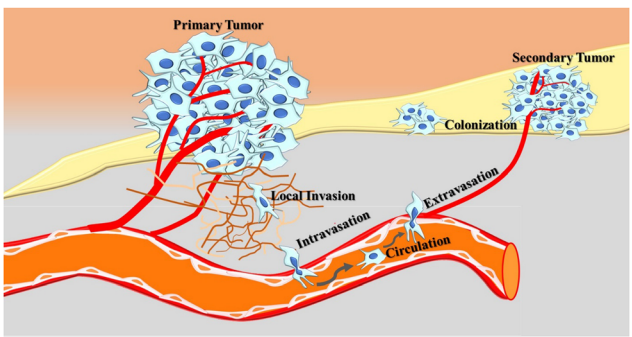

Fig. 1 Metastatic cascade: invasion, intravasation, circulation, extravasation, and colonization.

Once the cell loses polarity and detaches from surrounding cells, it migrates through the extracellular matrix (ECM) into the blood and lymphatic vessels.[22] Determining factors for the intravasation of tumor cells into the circulation could be the intrinsic properties of cancer cells, tumor microenvironment, mechanical cues, a feature of newly formed blood vessels, and accessibility of tumor cells to vessels.[23] Rapid cellular division and growth of cancer cells increase the need for nutrition (change in metabolism) and oxygen (hypoxia) for each cell, which is believed to be the main reason for the formation of blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis). Newly formed blood vessels of primary tumors are malformed, highly branched, and leaky, allowing tumor cells to escape from the primary site.[24,25] Once tumor cells enter the bloodstream as single cells or in a clustered form, most circulating tumor cells (CTCs) die in the circulation, possibly due to physical stress, oxidative stress, anoikis, and the lack of growth factors and cytokines, and only a small percentage (0.01%) of cells can give rise to metastases. To escape from ensuing barriers in the bloodstream and generate a metastatic lesion, CTCs acquire key specific features: stem-like phenotype, hybrid epithelial–mesenchymal transition (EMT) state, escape from the immune system, low sensitivity to therapy, resistance anoikis and circulatory shear stress.[26–28] In addition, it has been reported that platelets adhering to CTCs act as a shield against fluid sheer stresses (FSS), prevent cytolysis by natural killer cells, hide CTCs from immune cell recognition, and secrete growth factors that help CTCs grow in the circulation.[29] Besides protection from immune cell attack and cytolysis, platelet adhesion to CTCs also reveals valuable impacts for tumor cell adhesion and extravasation to distant organs.[30]

The metastatic potential of tumor cells is not limited to surviving the hostile intravascular environment but also relies on their ability to exit the bloodstream and cross the endothelium to invade the surrounding tissue. The process of tumor cells exiting the bloodstream through transendothelial migration and invading the surrounding tissue is called extravasation. This process involves three major events that include adhesion of CTCs to vessel walls, remodeling of the endothelial barrier, and transendothelial migration (TEM).[31] In most cases, extravasation of tumor cells is paracellular migration, where tumor cells migrate between two endothelial cells. Such form of extravasation relies on the interaction of tumor cells with blood

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cells, ligands, and receptors.[32] In rare cases, tumor cells can migrate transcellularly by penetrating individual cell bodies. After successful extravasation, most cancer cells do not result in metastases but form micrometastases and become dormant. When micrometastases escape from dormancy, cancer cells interact with the microenvironment to form a pre-metastatic niche that helps to restart the growth of tumor cells at the secondary site. A suitable pre-metastatic niche creates favorable conditions for cancer cells to develop angiogenic switches and recruit various cells that enhance local tissue and microenvironments that facilitate the growth and expansion of the metastases.[24,33]

4. Therapeutic approaches for tumor metastasis

Unlike primary tumors, treating metastasis is challenging and every therapeutic approach does not effectively target metastatic cancers, often limited by their inability to eliminate already-seeded non-proliferative, growth-arrested, or therapy-resistant tumor cells. Although metastases are still the leading cause of cancer death, advances in cancer biology and the science of the metastatic cascade have the potential to improve the treatment of tumor metastasis (Table 1). This growing knowledge of the science of the stages of metastasis provides an opportunity to identify key drivers of metastasis and regulators of cancer cell migration, to distinguish the biological differences between micro- and macro metastases, to target the susceptibility of metastatic cancer cells, and to exploit the properties of metastatic tumor microenvironments, which provide an excellent basis for a therapeutic approach to metastasis.[34,35]

Effective therapeutic approaches to metastatic cancer should not only target the disseminated cancer cells themselves but also consider the mechanisms of cancer cell transformation and the processes involved in the metastasis cascade. Strategies such as targeting tumor microenvironment, molecular and cellular features of circulating tumor cells, cancer–immune interactions, and other regulator components of the metastatic tumor microenvironment are particularly promising therapeutic approaches.[36] The tumor microenvironment consists of various cellular components including tumor cells, cancer-associated fibroblasts, mesenchymal stromal cells, pericytes,

Table 1 Potential anti-metastatic therapeutic approaches

Target	Approach	Advantages	Limitations	Ref.
Primary lesions/ postoperative residual cancer	Chemotherapy PTX-NPs-DN hydrogel	→ Idea implantation at tumor resection cavity → Sustained-release PTX over ten days and higher accumulation in local tissue → Avoids systemically side effects	→ Limited by their inability to target metastatic cancer cells and eliminate seeded non-proliferative, growth-arrested, and therapy-resistant tumor cells	56
	Immunotherapy (iSGels@aOX40)	→ Relieving the immunosuppressive microenvironment at the tumor resection bed → Effective stimulating systemic antitumor immune responses and memory effects	→ Low response rate → Immune-related adverse events	57
	Combination therapies CTX&aPDL1@Gel	→ Sequential release of CTX and aPDL1 → Selective depletion of regulatory T cells (Treg) → Inhibition of cancer recurrence after surgery → Stimulation in systemic immune and T memory cells	→ Low response rate for circulating cancer cells	58
	Phototherapy	→ Ultrasimple synthesis and administration procedures	→ Low photostability	59
	ICG–alginate hydrogel	→ Excellent biocompatibility avoidance of the leakage from injection sites → Improvement of the accumulation in tumors → High-performance PTT	→ Potential toxicity of ICG → Poor aqueous stability	
Reprogramming tumor microenvironment	Chemo-immunotherapy	→ Reduces the numbers of both myeloid derived suppressor cells and Tregs in tumor microenvironment	→ Initial burst release of DOX from the hydrogels leads to toxicity of normal cells	60
	ATC/DOX@mPEG-*b*-PELG	→ Promotes the efficacy of adoptively transferred T cells against solid tumors		
	Hypoxia inhibitors	→ Combination of hypoxia alleviation and photodynamic therapy (PDT) to improve anticancer efficacy	→ Hypoxia can be expressed in some normal tissues and drugs targeting hypoxia can have serious side effects	61
	Prolonged oxygen-generating phototherapy hydrogel (POP-Gel)	→ POP-Gel elevate the oxygen level and significantly increasing immune efficacy		
	Angiogenesis inhibitors	→ Downregulates the expression of VEGF-A and Ang-2, destroys angiogenesis in tumors and reduces the density of micro-vessels	→ Anti-angiogenic therapies reduce drugs delivery to tumors	62
	PDLX-PMI hydrogel	→ Inhibit the proliferation of cancer cells and inhibit tumor metastasis		

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adipocytes, vasculature, lymphatic networks, myeloid populations, myeloid-derived suppressor cells, immune cells, and inflammatory cells, and non-cellular components such as extracellular matrix, matrix remodeling enzymes, cytokines, chemokines, exosomes, growth factors, and inflammatory enzymes.[37] Angiogenesis promotes tumor growth by providing oxygen and nutrients and is essential for tumor metastasis as a route for cancer cell dissemination.[24] Therefore, targeting tumor-induced angiogenesis has been suggested as a potential tumor metastasis prevention strategy. Another potential approach in metastasis therapy/prevention is targeting the molecular and cellular features of metastatic circulating tumor cells.[38] Similarly, targeting different steps in the metastatic cascade with therapeutics, such as antibodies, are promising candidates for inhibiting tumor cell metastases.[39] Not all disseminated tumor cells (DTCs) are guaranteed to metastasize, as a few DTCs enter a growth arrest (dormancy) until conditions are favorable to reactivate and reinstate their cancerous nature. At this stage, the cells are non-dividing and resistant to therapeutics, as most anti-tumor treatments target cell division. Therefore, targeting dormant tumor cells through their metastasis suppressors has been of therapeutic interest in treating metastasis. Metastasis suppressor inhibits metastasis by keeping the disseminated tumor cells in a state of dormancy.[40] RECK is a membrane-anchored protein regulator, which is often downregulated in several types of cancers. As described by Yoko *et al.*, enforced expression of RECK in tumor cells by a potent RECK-inducer, DSK638, inhibits metastasis.[41] Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells that are important for PMN formation and accumulate in patients with cancer. Pre-metastatic niche (PMN) is a preconditioned microenvironment that is a key determinant of cancer metastasis.[42] Since MDSCs play a critical role in PMN formation, it is realistic to design MDSC-based strategies to combat PMN.[43] Lu *et al.* demonstrated that targeting myeloid cells using adjuvant epigenetic therapy disrupts pre-metastatic microenvironment formation and prevents metastasis through a selective effect on myeloid-derived suppressor cells (MDSCs).[44] In general, identifying and targeting the key drivers of tumor metastasis, such as epithelial–mesenchymal transition (EMT),[45,46] angiogenesis,[47] the ECM,[48–50] circulating cancer cells,[51,52] micro- and macro-metastasis, and their molecular-drivers[53] (including their interaction with cancer cells at the various stages of metastasis), are the potential therapeutic strategies for metastatic cancer.[54,55]

5. Hydrogels for the local delivery of drugs for tumor metastasis therapy

Hydrogels are three-dimensional water-swollen networks of physically or chemically linked polymers, proteins, small molecules, or colloids. They can be prepared from natural or synthetic materials, *via* physical or chemical interactions, in different sizes (nano-gels, micro- and macroscopic gels), and conventional and stimuli-responsive forms.[63–65] Hydrogels are a suitable and versatile platform for delivery due to their ability to encapsulate and preserve pharmaceuticals and provide sustained and remotely programmable release.[64,66] In biomedical applications, hydrogels mostly offer four basic properties: biocompatibility, biodegradability, drug-loading ability, and controlled drug release.[67] Due to these and other unique properties, hydrogels have gained considerable interest in therapeutic agent delivery systems. Delivery approaches for therapeutic agents require outstanding improvements to achieve the desired therapeutic effect and avoid side effects. In the therapeutic area, hydrogel-based local delivery systems are promising platforms and have received tremendous attention due to their advantages over conventional delivery systems.[68,69] Maximizing the efficacy of the treatment depends on the dose of drug that reaches the target site, so therapy is carried out at the target site through localized delivery platforms.[70] Local delivery systems have the ability to deliver high doses of therapeutic molecules at the target site and provide controlled and sustained drug molecule release with minimized nonspecific distribution of therapeutics in healthy tissues.[71,72] Hydrogel-based local drug delivery system is one of the long-acting drug delivery formulations that allow controlled drug release over days, weeks, months, and years after single-dose administration and a stable pharmacokinetic profile. It is best suited for patients who require long-term therapy, such as prostate cancer patients who receive 365 injections of Lupron Depot Therapy per year. Hydrogels can strongly entrap and encapsulate drugs and short-half-life molecules such as proteins and small particles through networks of mesh size and molecular interaction, which reduces clearance rate and increases retention time at the injection site.[73] It can be the protective delivery vehicle of therapeutics and avoid premature degradation. As a local delivery platform, hydrogels can increase the concentration of therapeutics at the injection site, which improves antitumor efficacy, stimulates local immune response, and reduces off-target effects, systemic toxicity, and systemic reactions. Hydrogels can be used to encapsulate hydrophilic and hydrophobic molecules and release both molecules simultaneously, sequentially, or at completely different times, making them ideal for the codelivery of therapeutics for synergistic effects. Hydrogels are attractive for the controlled delivery of therapeutic agents such as chemotherapeutic drugs, immunosuppressive agents, antibodies, vaccines, cytokines, and immune cells.[70] Despite the interesting properties of hydrogels in drug delivery systems, some limitations still exist (Table 2). Because they are soft, hydrophilic, and wet materials, hydrogels are limited to encapsulating hydrophobic drugs and have relatively low tensile strengths. Therefore, strengthening and appropriate modification of their (supra)molecular structures and physicochemical properties have been the main focus of research on hydrogel biomedical applications. Extensive research has been conducted on strategies to develop hydrogels with (supra)mechanical properties and improve their tissue adhesiveness, drug loading capacities, environmental responsiveness, and drug release kinetics. Various designing strategies have been developed to overcome these limitations and to

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Table 2 Limitations of hydrogels as drug delivery systems and possible solutions

Limitations and disadvantages	Types of hydrogel material/example	Possible solutions	Ref.
Non-biocompatible and non-biodegradable properties	Poly(*N*-isopropylacrylamide) based hydrogels	Introduce biodegradable, biocompatible linker into PNIPAM backbone	78
Toxicity of small cross-linkers molecules	Glutaraldehyde cross-linked polymeric hydrogels	Polymer–polymer cross-linking or hybrid polymer networks (HPN)	79
Slow stimuli response and	Poly(*N*-isopropylacrylamide-*co*-2-hydroxyethylacrylate (HEA)) hydrogels cross-linked *via* di-selenides	Fine-tuned by adjusting the stimuli and incorporating of several stimuli in a single polymer	80
Initial burst drug release	Poly(ethylene glycol) hydrogels	Designee hybrid membranes of hydrogel to prolong drug release and better encapsulate hydrophobic drugs	
Poor encapsulation of hydrophobic drugs	Hydroxypropyl methylcellulose (HPMC) hydrogels	Introduction of molecules capable of forming inclusion complexes and/or the incorporation of hydrophobic moieties	80
Weak mechanical characteristics	Poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogel	Copolymerization and development of hybrid materials with natural polysaccharides	81
Loaded drugs may alter responsiveness of hydrogels	Ibuprofen and salicylate sodium salts loaded 2-(2-methoxyethoxy) ethyl methacrylate (MEO MA), 2-hydroxyethyl methacrylate (HEMA) and ethylene glycol 2 dimethacrylate (EGDMA) (100 : 2 : 1 mol ratio)	Understanding of drugs and polymer ratio, interaction of drugs and hydrogel moieties, and drug binding moieties	82
Drug deactivation and during polymer binding	Chemical bonding loading strategies proteins, peptides and small molecules in chitosan hydrogels	Understanding of the trends and cross-linking technologies hydrogels formation	83

achieve high stretchability and toughness, including the modification of network structures,[74] such as the formation of double networks and dual physical contact, as well as the incorporation of different nanomaterials in the hydrogels.[75] Hydrogels with tunable properties are intended to achieve desired local drug delivery systems and exhibit the necessary mechanical and biochemical properties for controlled drug release without side effects. The most explored strategy to achieve on-demand localized drug delivery is the formation of ''smart'', dynamic hydrogels that can respond to environmental stimuli.[76,77] These smart hydrogels can provide a controlled and sustained delivery system of therapeutics in a time-dependent manner and minimally invasive procedures. Among the potential hydrogel designs, smart injectable hydrogels that respond to external stimuli are gaining attention and are optimal candidates for on-demand local delivery systems with minimally invasive procedures.

6. Hydrogels for the local delivery of chemotherapeutics for tumor metastasis

Locally targeted chemotherapy offers an opportunity to overcome the limitations of conventional systemic chemotherapy: off-target delivery with significant adverse effects of chemotherapeutic agents. Drug carriers such as hydrogels have attracted much attention for effective local delivery of drugs to achieve therapeutic efficacy with low administration frequency, thereby alleviating systemic toxicity, avoiding the inconvenience of multiple injections, and preventing the development of resistance during repeated drug administration.[73,84] Most notably, the properties of hydrogels can be tuned and improved according to the raw materials used and preparation methods. The most important property of local drug delivery is their injectability, which is minimally invasive and targeted implantation even in poorly accessible tissue sites. An injectable hydrogel is a type of *in situ* gel-forming material that requires the sol (pre-gel) to be transported to the target site and sol–gel transition at a specific time interval at the implanted site.[85] It has been widely explored as a local drug delivery system for single drug delivery, multidrug co-delivery, and other combination therapies.[86–88]

In recent decades, various injectable hydrogels have been investigated as local delivery platforms for tumor metastasis chemotherapy. Leng *et al.* designed an injectable hyaluronic acid (HA)-based hydrogel loaded with paclitaxel (PTX) nanoparticles and epirubicin (EPB) (PPNPs/EPB@HA-Gel) for the treatment of tumor recurrence and metastasis.[89] Encapsulated drugs (paclitaxel (PTX) and epirubicin (EPB)) were steadily released from the hydrogel to inhibit the proliferation and migration of tumor cells, thereby preventing long-term tumor recurrence and metastasis in a post-operative breast tumor model. As a nutrient delivery pathway for tumor cells, angiogenesis has been a hot target for metastasis therapeutic approaches to inhibit tumor growth and dissemination. When the nutrition continuously travels through the blood vessels to the tumor cells, the tumor cells also spread through it, which ultimately results in cancer cell growth and metastasis. Thus, disruption of nutrient supply and prevention of angiogenesis is a promising strategy to prevent tumor metastasis. Wang *et al.* prepared a photo-responsive injectable hydrogel using a polydopamine cross-linked collagen/silk fibroin composite to deliver thrombin to occlude blood vessels and prevent angiogenesis.[90] Localized delivery of vascular disrupting agents through an injectable thermosensitive PLGA–PEG–PLGA copolymer to tumor-bearing mouse models has been investigated as a promising tumor metastasis preventive strategy.[91] These vascular disruptive agents can significantly inhibit the

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proliferation of cancer cells and prolong the survival rate of tumor-bearing mouse models.

Pancreatic cancer is an aggressive form of cancer with a dismal prognosis. The lack of any reliable early diagnostic marker of the disease makes early diagnosis challenging, and most patients are diagnosed at a later stage after the disease has advanced or metastasized.[92,93] Surgical resection and chemotherapy are front-line treatments for local stages of pancreatic cancer. A remarkable feature of injectable hydrogels in the treatment of metastasis is the minimally invasive local implantation in such poorly accessible tissues with a fine needle. Yang *et al.* designed an endoscopic ultrasound-guided thermosensitive injectable hydrogel (PLGA–PEG–PLGA, PPP) for local sustained chemotherapy to pancreatic tumors.[73] This fine-needle-injectable *in situ* gel-forming material demonstrated sustained delivery of the drug and the best therapeutic effect, significantly reducing the proliferation, invasion, and migration of pancreatic cancer cells. Similarly, Braet *et al.* demonstrated a pH-sensitive hydrogel-based intraperitoneal drug delivery approach for the treatment of peritoneal metastases, which was a more promising drug delivery method for unresectable peritoneal metastases, maintaining cytotoxicity and delaying tumor growth.[94]

Although surgery is currently considered one of the main treatment modalities for cancer, local post-surgical cancer recurrence and metastasis formation of disseminated cancer cells through cut blood vessels greatly affect the prognosis of cancer and the patient's survival rates. Cancer-associated adipocytes and angiogenesis in the postoperative tumor microenvironment significantly affect the recurrence and metastasis of tumor cells. Effectively killing residual tumor cells, simultaneously inhibiting the function of cancer-associated adipocytes and angiogenesis, may be a promising strategy to prevent tumor recurrence and metastasis after surgery. Li *et al.* studied anticancer drugs (doxorubicin and metformin) encapsulated in pH-responsive dopamine and 3-aminobenzeneboronic-acid-grafted hyaluronic acid hydrogels for implantation into the tumor surgical cavity.[95] Sustained-release drugs effectively killed residual tumor cells, hindered adipocyte-stimulated tumor proliferation and migration, and inhibited tumor angiogenesis, leading to significant inhibition of tumor recurrence and metastasis after surgery. Injectable *in situ* formed hydrogel is a suitable local drug delivery alternative post-surgical cavity implant for the prevention of cancer recurrence and distant metastasis.[96–99] Overall, hydrogel-based local delivery of chemotherapy can combat tumor metastasis by eradicating tumor cells,[100] remodeling the tumor microenvironment,[101,102] such as blocking the function of cancer-associated adipocytes to inhibit adipocyte-stimulated tumor cell proliferation, cell migration, and angiogenesis,[66] and inducing immunogenic cell death[103] (Fig. 2).

7. Hydrogels for the local delivery of phototherapeutic agents for tumor metastasis

Phototherapy, which includes photodynamic therapy (PDT) and photothermal therapy (PTT), is a treatment modality that has been widely used in recent years to destroy tumor cells by exposure to light without damaging normal tissue. Both PDT and PTT are minimally invasive antitumor approaches that are applied in combination with light activation of a photosensitizer (PS) and a photothermal agent (PTA), respectively (Fig. 3). After activation by light, PS produces reactive oxygen species (ROS), which can oxidize nearby biological macromolecules on tumor cells, causing cytotoxicity of tumor cells, while the photothermal agent (PTA) converts light energy into heat energy and kills tumor cells, as the tumor cells are more sensitive to high temperatures than normal cells.[104–106] Although phototherapy has been highly successful in tumor therapy, traditional phototherapeutic administrations have been associated with phototoxicity, limiting clinical applications. Sustained and controlled delivery of phototherapeutic agents directly to tumor sites is an effective antitumor phototherapy that minimizes off-target effects in normal tissues. In recent years, hydrogels in antitumor phototherapy have gained great interest due to their ability to deliver phototherapeutic agents in a localized site and minimize the distribution of phototherapeutic agents in non-target sites.[107–109] The application of hydrogels as photothermal agents and photosensitizer carriers has been extensively investigated for antitumor PTT

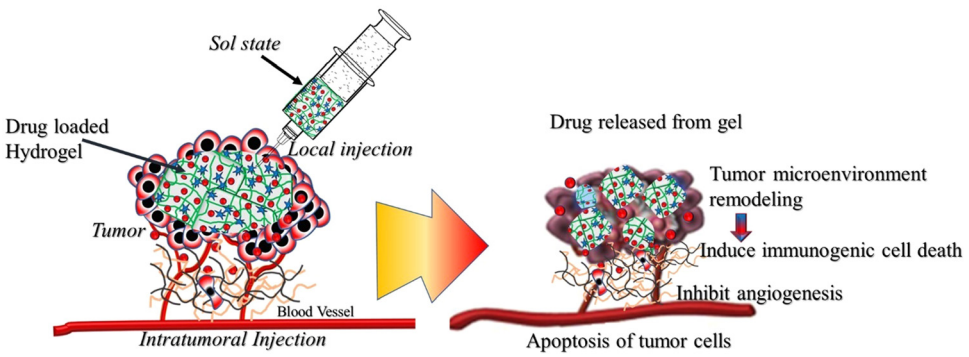

Fig. 2 Hydrogel-based chemotherapeutic approaches to metastatic cancer *via* targeting tumor microenvironment, inducing immunogenic cell death and inhibiting angiogenesis.

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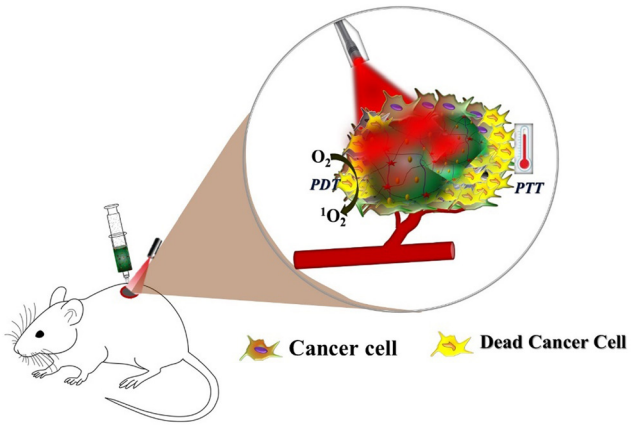

Fig. 3 Schematic illustration of the hydrogel-based localized delivery platform for anti-tumor PTT/PDT.

and PDT. Jin *et al.* achieved a successful combination of photothermal therapy (PTT) and photodynamic therapy (PDT) incorporating gold nanorods (AuNRs) and methylene blue (MB) into a multifunctional hydrogel.[110] Yao *et al.* synthesized thermosensitive Pluronic F127 hydrogels and loaded with titanium carbide nanoparticles as photothermal agents to achieve excellent photothermal therapeutic effects against breast cancer.[111] In another study, Pan and co-workers developed an indocyanine green-alginate hydrogel for local tumor ablation. The *in situ* synthesized hydrogel exhibits strong indocyanine green accumulation ability in tumors and performs remarkable local PPT of tumors.[59] Similarly, Zhang *et al.* designed an injectable thermosensitive hydrogel as an effective carrier of UZC ($NaYF_4$:Yb^{3+}, Tm^{3+} (UCPs), Zn_2GeO_4:Mn^{2+} (ZGM), and g-C_3N_4); photosensitizers, under 980 nm laser irradiation, can generate ROS and lead to the destruction of tumor cells.[112] Moreover, Wang *et al.* successfully incorporated photosensitizer chlorin e6 and manganese dioxide (MnO_2) nanoparticles into the stimulus-responsive injectable hydrogel to achieve synergistic photodynamic/photothermal therapy of breast cancer.[113]

8. Hydrogels for the local delivery of immunotherapeutic agents for tumor metastasis

The immune system can recognize, target, and eliminate cancer cells, whereas cancer cells struggle to resist the immune system and develop tumors. Cancer cells that overcome immune defense can grow into tumors and interact with a variety of host cells to create a pro-tumor microenvironment that promotes invasion and metastasis. Cancer cells that survive against the elimination by immunosurveillance accumulate various genetic and epigenetic changes, which provide cancer cells the stealth ability to escape immune system.[114,115] Those that escape from the immune system form a tumor, establish a tumor micro-environment, and accumulate malignant properties to settle in a metastatic niche, eventually forming metastatic tumors.

Recently, immunotherapies have been considered revolutionary therapeutic strategies and breakthrough in the treatment of metastatic disease.[116,117] Representative types of immunotherapeutic strategies used in tumor metastasis are immune checkpoint blockade, cytokine therapy, cancer vaccines, and adoptive T cell therapy.[118–121] Immunotherapies combat tumor metastasis either by limiting the immunosuppressive ability of cancer cells or boosting the host immune system to promote their ability to target cancer cells.[122] Targeting cancer stem cells, tumor microenvironment, and key signaling pathways through immunotherapy can yield dramatic results in preventing metastasis. Tumor-initiating cells play a crucial role in cancer metastasis, though immunotherapy is an ideal treatment option to eliminate cancer stem cells and halt cancer metastasis.[123]

Immunosuppressive tumor microenvironment (TME) has a significant impact on tumor metastasis, so modulating the tumor microenvironment is one way to improve immune function and inhibit tumor metastasis. Remodeling the tumor microenvironment promotes immune cell infiltration, suppresses tumor angiogenesis, and enhances the anti-tumor effects of drugs, thereby restraining tumor metastasis.[124] Recently, remodeling the tumor microenvironment has attracted the attention of researchers as a therapeutic target for cancer metastasis (Fig. 4). Han *et al.* investigated the delivery of anti-tumor drugs and immunostimulants (baicalin, antigen, and CpG-ODN) to a melanoma-bearing mouse model, thereby remodeling the tumor microenvironment and killing tumor cells.[125]

Although immunotherapy has attracted tremendous attention as a treatment modality, low response rates and severe systemic immune-related adverse events limit the efficacy and overall impact of therapy.[127] Such drawbacks are mainly attributed to the systemic administration of high dosages or multiple injections of immunotherapeutic agents. The intratumoral delivery approach is a promising method for immunotherapeutic agents to reduce systemic side effects and combat mechanisms of tumor immune suppression within the tumor microenvironment. In particular, smart hydrogels are highly desirable for local delivery, allowing controlled and sustained release of immunotherapeutic agents to tumor sites to enhance antitumor immune responses and inhibit metastasis and tumor recurrence.[128–130] Most previous studies have used injectable hydrogels as local delivery platforms for immune-mediated and immunotherapeutic agents. Immunotherapeutic agents, chemotherapeutic drugs, photosensitizers, combinational chemo-immunotherapy, and photoimmunotherapy can be encapsulated into injectable hydrogels, resulting in sustained and controlled release at target sites to mediate immunotherapy. For instance, Song *et al.* developed a PEGylated polypeptide injectable hydrogel for local co-delivery of tumor vaccine and immune checkpoint inhibitors.[131] Sustained release of vaccines and immune checkpoint inhibitors efficiently recruited endogenous dendritic cells and elicited strong humoral and cellular responses, thereby inhibiting tumor growth and attenuating the immunosuppressive tumor

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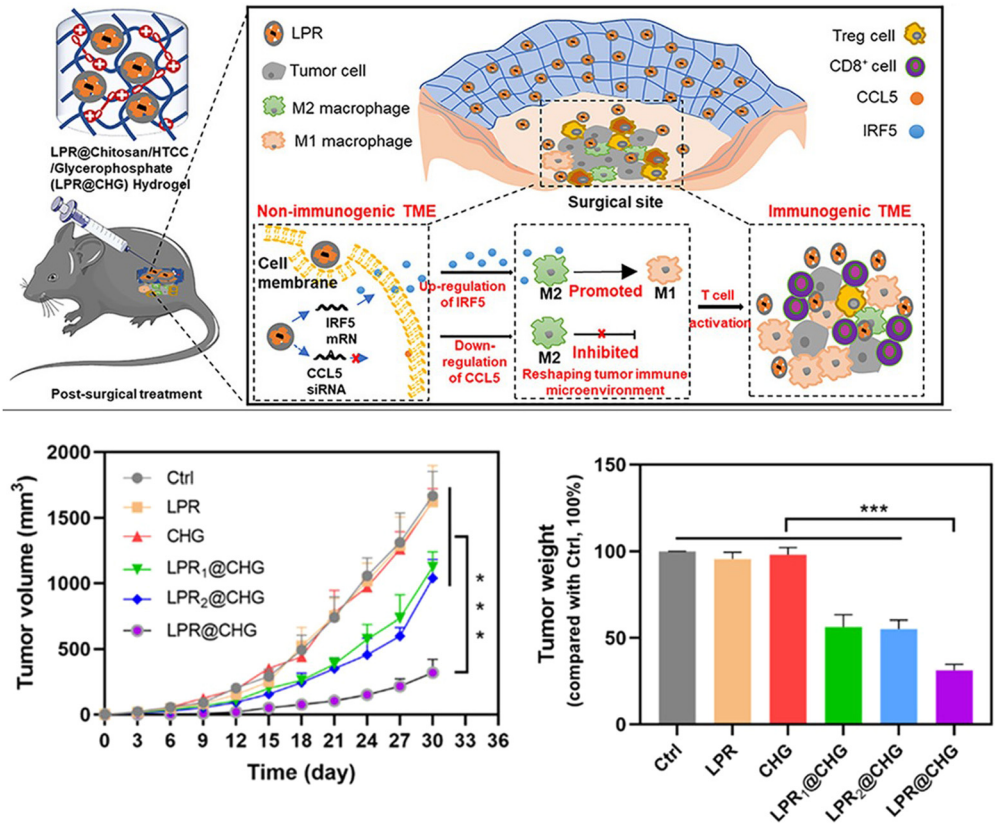

Fig. 4 Approach used to target the TME for tumor metastasis: modulating the immunosuppressive tumor microenvironment *via* macrophage infiltration and controlling the tumor growth by initiating T-cell-mediated immune responses.[126] Copyright © 2022, American Chemical Society.

environment. Zhuang *et al.* developed hydrogel-based combinational therapy (photothermal agents, chemotherapeutics, and immune adjuvants) for metastasis inhibition. Similarly, Liu *et al.* demonstrated the local delivery of an immunogenic cell death (ICD) inducer and immune checkpoint blockade (ICB) therapy through injectable hydrogels to induce antitumor immune response and T-cell-mediated immune responses.[132]

Immunogenic cell death (ICD): a crucial mechanism of action of tumor immunotherapy is induced by various chemotherapies.[133] The general principles of chemotherapies to stimulate immunotherapy efficacy are: (1) controlled and sustained release of chemotherapeutics from locally implanted hydrogels, (2) tumor cell immunogenic cell death (ICD) with tumor-associated antigens (TAAs) and damage-associated molecular pattern (DAMPs), (3) maturation of dendritic cells, and (4)

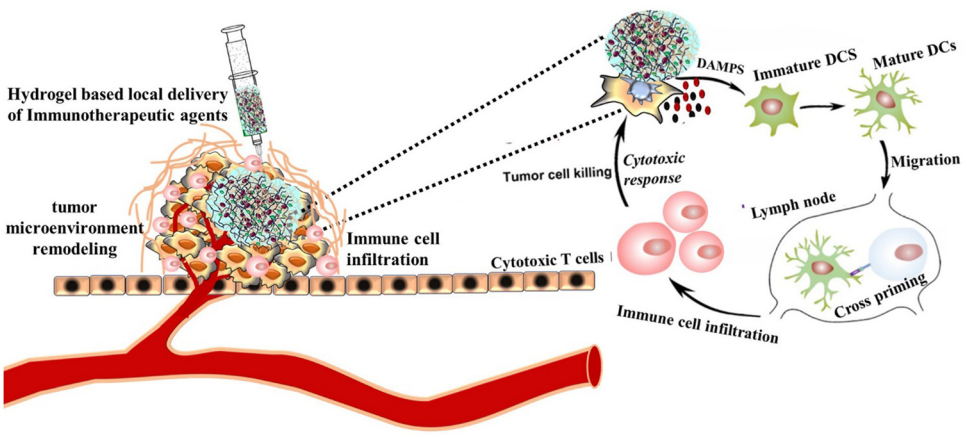

Fig. 5 Schematic illustration of immunogenic cell death (ICD) induction on tumor cells *via* hydrogel-based local delivery of therapeutics to improve the efficacy of immunotherapy.

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release damage-associated molecular patterns (DAMPs) attracted by dendritic cells (DCs), thereby stimulating the maturation of lymphocytes and the anti-tumor immune response[134] (Fig. 5). Wang *et al.* designed an injectable thermosensitive hydrogel loaded with oxaliplatin (OxP) and resiquimod (R848) to induce immunogenic cell death. Upon local injection, the hydrogel exhibits sustained release of the drugs that are cytotoxic and enhance the immunogenicity of tumors by inducing immunogenic cell death.[135]

9. Hydrogel-based local delivery of combination therapeutics for tumor metastasis

Despite continuous improvements in tumor metastasis inhibition and tumor therapeutic approaches, tumor cells' adaptive mechanisms to escape the host's immune system, drug resistance, and toxicity are the basis of treatment failure and tumor progression. Combination therapy is the most effective therapeutic approach that combines two or more therapeutic agents to target different pathways within tumors and the tumor microenvironment, which aids in tumor progression and metastasis. It is more effective in targeting target tumor heterogeneity, drug resistance, and killing cancer stem cells. Over mono-therapeutic approaches, combination therapy enhances efficacy and decreases toxicity due to the synergistic or additive principle of action that requires lower dosage of each therapeutic agent, addresses heterogeneous nature of tumors, and strikes cancer cells in more than one place. In combination therapy, the therapeutic potential of some drugs to produce a synergistic effect depends on the sequence, making it difficult to design simultaneous combinations. In addition, the synergistic effects of combination therapies strongly depend on the effective combination of multiple therapeutic molecules in a single platform rather than simple mixing (Fig. 6). With recent advances in drug delivery systems, hydrogels have the potential to assemble multiple therapeutic agents (drugs, cells, growth factors, and particles) into a single platform without losing bioactivity *via* chemical or simple physical interactions.[86,136–138]

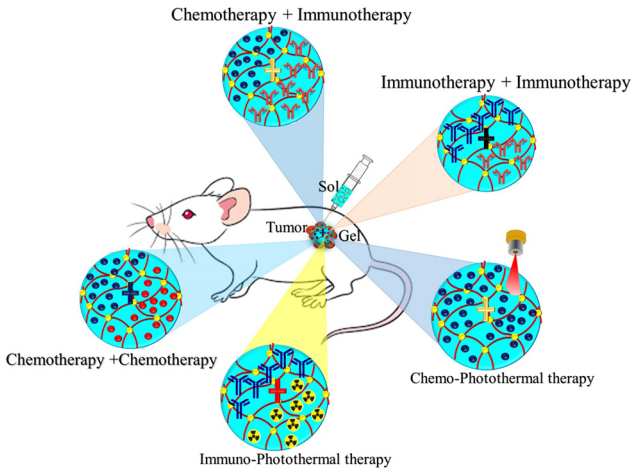

Fig. 6 Schematic illustration of the potential application of hydrogels for local delivery of combination therapeutics of tumor metastasis.

Recently, various investigations have been conducted to explore the application of injectable hydrogels as local delivery platforms of combination therapeutics for tumor metastasis (Table 3). Xiao *et al.* designed multifunctional injectable alginate hydrogels for synergistic tumor combination therapy.[139] Hydrogels (GPI/R848@ALG) were prepared by simply mixing alginate (ALG) sols with glucose oxide (GOx)-conjugated polyacrylic acid stabilized-iron oxide nanoparticles (GPI NPs) and the Toll-like receptor 7/8 agonist resiquimod (R848). Glucose oxidase (GOx) blocks the glucose supply for starvation therapy, Fe_3O_4 NPs boost the Fenton reaction efficacy for enhanced chemodynamic therapy, and resiquimod (R848) reprograms the TAMs towards M1-like phenotype for the inhibition of tumor progression. Combined chemo-photothermal therapy has been reported to produce synergistic effects and enhance therapeutic index by enhancing cell membrane penetration, drug release at the target region, and drug cytotoxicity. Combined chemo-photothermal therapy has been reported to produce synergistic effects and enhance the therapeutic index by improving cell membrane penetration, drug release at the target region, and drug cytotoxicity. Sun *et al.* designed a hydrogel-based chemo-photothermal combination therapy for localized NIR-triggered drug release to enhance antitumor effects.[140] Similarly, Hu *et al.* synthesized tumor-microenvironment-responsive injectable nanocomposite hydrogels (Au NBPs&Pt NCs@DOX gel) for synergistic photothermal, chemotherapeutic, and chemodynamic cancer therapies.[141] Localized chemo-photothermal therapies are promising therapeutic strategies to eradicate primary tumor cells but not likely distant metastasis. Besides directly killing primary tumor cells, metastasis requires a systemic tumor-specific immune response. Zhuang *et al.* developed injectable hydrogel-based combinational therapy photothermal agents, chemotherapeutics, and immune adjuvants to inhibit metastasis.[142] Lu and coworkers investigated the combination of a hydrogel vaccine system containing a granulocyte-macrophage colony-stimulating factor (GM-CSF) and programmed death-ligand-1 antibody (αPD-L1) in a post-surgical mouse tumor model.[143] This locally implanted combination therapy induced the production of powerful antigen-specific T cells and stimulated an anti-tumor immune response, which effectively inhibited tumor recurrence and metastasis. Similarly, Wang *et al.* investigated hydrogel-based local delivery of combined sonodynamic therapy (SDT) and chemodynamic therapy (CDT) for breast cancer and inhibition of tumor metastasis[144] (Fig. 7). An *in situ* formed alginate-based hydrogel was loaded with manganese dioxide (MnO_2) nanoparticles, an organic polymer, and an SIS3 drug as the CDT agents, sonosensitizer for SDT and therapeutic drug for inhibiting tumor metastasis respectively. Upon exposure to ultrasound (US) radiation at the tumor site, the hydrogel generated hydroxyl radicals ($^{\bullet}OH$) and singlet oxygen ($^1O_2$) through CDT and SDT effects to induce tumor cell death. Zhou *et al.* also studied hydrogels loaded with a

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Table 3 Recent reports on hydrogel-based local delivery for cancer metastasis

Functional materials	Application/advantages	Limitations	Ref.
PDLLA-PEG-PDLLA	• Sustained co-delivery of 5-fluorouracil and *cis*-platinum • Thermo-sensitive and injectable • Synergistic combination chemotherapy • Communitive release time: more 30 days	→ *In vivo* burst release	99
Niche-like CS-FTP-gel (chitosan polymer)	→ *In situ* gel forming, ROS-responsive niche-like hydrogel for AQ4N prodrug sustained release → Utilized for remodeling of tumor hypoxic microenvironment → Use relatively non-toxic crosslinker	→ Not applicable in relatively low hypoxic or oxygenated tissue environment	146
DSDMA–SBMA zwitterionic hydrogels	→ Co-delivery of sunitinib (Sun) and chlorin e6 (Ce6) → Redox-responsive zwitterionic hydrogel → Injectable and *in situ* gel forming	→ Use of chemical crosslinker → Initial burst drug release within 2 hours	71
Poly(acrylic acid-*co*-4-vinylphenylboronic acid) nanohydrogels (P(AA-*co*-4-VPBA) NG)	→ Codelivery of combretastatin-A4 phosphate (CA4P) and doxorubicin (DOX) → Loading and release of hydrophilic drug and nanogel → Releasing time up to14 days	→ Poor encapsulation of hydrophobic drugs → Release of drug in normal physiology without nanogels	147
Chitosan LPR@CHG hydrogel	→ *In situ* injectable thermosensitive hydrogel → Release immunotherapeutic to reprogram the antitumoral immune niche → Less toxic and minimally invasive	→ Receptor dependent delivery system → Need to deliver in cellular organelle label	126
Uracil grafted *N*-isopropylacrylamide (NIPAM)	→ Achieve *in situ* gel formation at 37 °C → Free cross-linking agents due the presence of multiple hydrogen bonding → Minimally invasive material for tumor treatment	→ Less targeted and diffusion-based release	148
Bombyx mori silk fibroin (BMSF) and *Antheraea assamensis* silk fibroin (AASF) blended hydrogels	→ Injectable hydrogel for co-delivery of drugs	→ Drug–drug interaction and drug deactivation	149
Anticancer peptide (KL) based KPFD hydrogels	→ Used as therapeutic hydrogel → Surve as synergistic therapeutic effect (combinational photothermal–chemotherapy) → Inducing membrane destabilization and facilitating the cell uptake drugs	→ Less space for co-encapsulation of drugs with photothermal	150
Methacrylated polymers combinations (DexMa-CsMa)	→ Sustained and controlled release → For topical treatment approach → Bio-adhesive on a biological simulating membrane	→ Initial burst release → Drug–polymer interaction	151
ICG–alginate hydrogel	→ Ultrasimple synthesis and administration procedures → *In situ* fabrication of the photothermal hydrogel		59
PQ/PB-Gel	→ Simple preparation and administration method → Low production cost → Excellent efficacy and low toxicity		152
ERT@HMSNs/PLEL	→ *In situ* physically crosslinked non-flowing gel at physiological temperature → Long term sustained release → Nano-scaled delivery system for localized anticancer therapies	→ Stimuli responsiveness is influenced by loaded materials → Need cell membrane targeting and penetration moieties	153
PTX@BN/4aPEG-OPA	→ Tissue-adhesive ability → Immobilization of drug-loaded systems at tumor sites to increase local drug concentration → Long term release over 30 days	→ Polymer–drug interaction → Slow-release rate	154
CPN@GO-CET/CPT11@shRNA hydrogel	→ Multifunctional drug/gene delivery system → Ligand-mediated active targeting and the pH-triggered drug release features → *In situ* gel formation → Co-delivery of anticancer drugs and siRNA	→ Initial burst release within 2 h	155
ES/HA-Tyr hydrogels	→ Sustained release → Lower systemic toxicity, and better anti-tumor effects		156
GEM/(PLGA–PEG–PLGA, PPP) hydrogel	→ Exhibit excellent injectability, biocompatibility, and the capability of sustained drug delivery → *In situ* forming hydrogel	→ Slow stimuli response → Burst release	73
PVLA-PEG-PVLA hydrogel	→ Sustained delivery of drugs	→ Slow stimuli response	157

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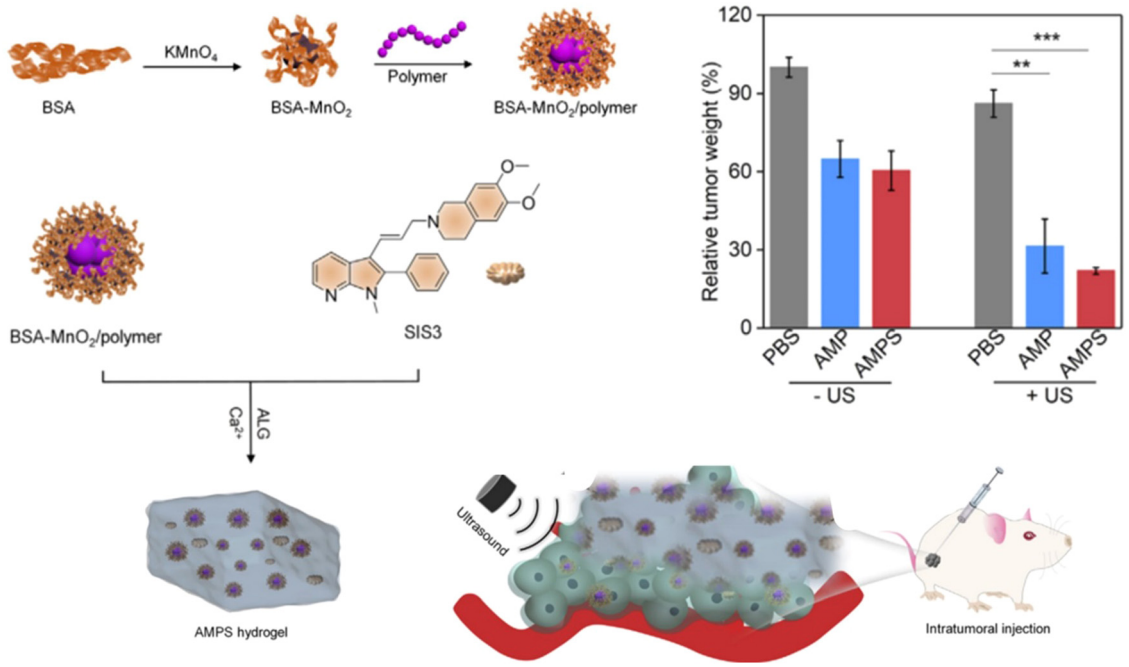

Fig. 7 Schematic illustration of the *in situ* formed alginate-based hydrogel for SDT-CDT combination therapy for tumor metastasis inhibition,[144] Copyright 2023, Wang *et al.*

combination of antitumor drugs and monoclonal antibodies for the inhibition of postoperative tumor recurrence and metastasis[145] (Fig. 8). Sustained release of the drug and monoclonal antibody resulted in CXCR4 inhibition, ICD induction, and PD-L1 blockage, which directly turned the residual tumor seeds into an *in situ* vaccine and remotely disturbed the PMN. Overall, local delivery of combination therapeutics has shown remarkable success in killing tumor cells, controlling the tumor microenvironment, and providing benefits over monotherapy in various tumor metastases.

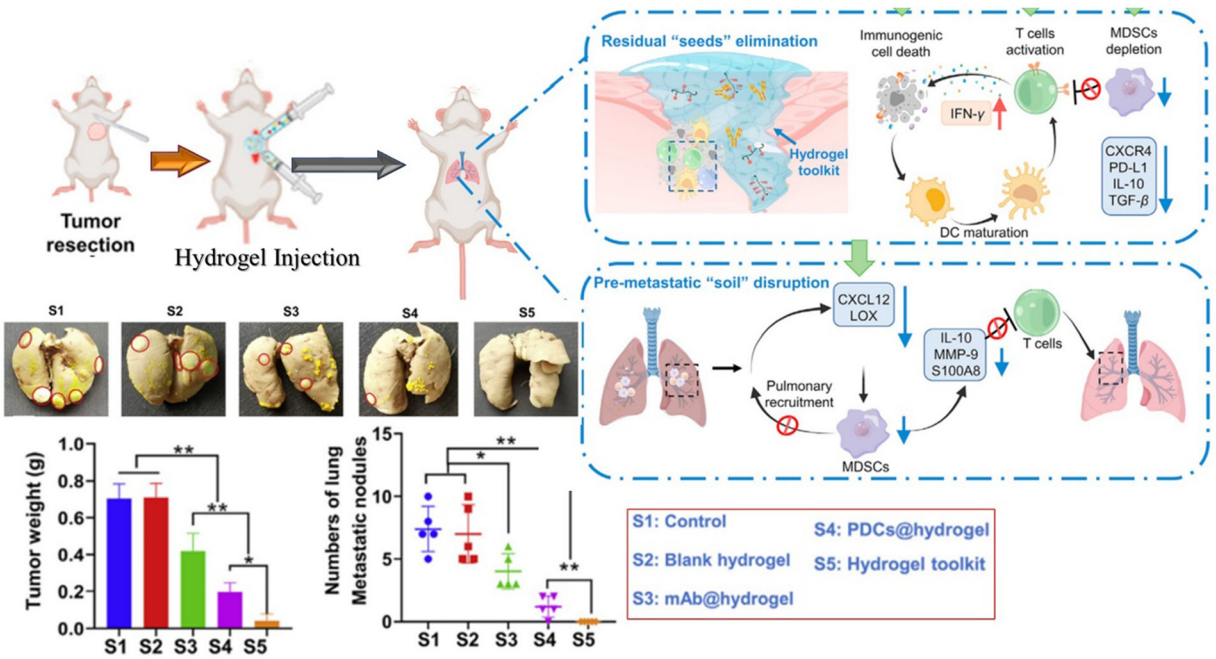

Fig. 8 Illustration of the *in situ* formed hydrogel for the inhibition of postoperative tumor recurrence and metastasis,[145] Copyright 2022, Chinese Pharmaceutical Association and Institute of Materia Medica.

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10. Conclusions and future perspectives

Tumor metastasis is a deadly event and a complicated problem in clinical tumor therapy. Despite the advances in therapeutic modalities and innovations in the field, metastasis remains the leading cause of cancer-related death. Several factors are involved in the migration of cancer cells and the formation of tumor metastasis. Targeting the entire process of metastasis is explored as a novel therapeutic approach to inhibit tumor metastasis by intervening in any steps of tumor cell migration. Various therapeutic agents have recently been developed with the potential to induce primary tumor cell apoptosis, modulate TME, and eradicate circulating tumor cells. However, off-target accumulation with severe side effects in the systemic administration of these therapeutic agents has impeded their therapeutic application. Owing to the unique properties of biocompatibility, embedding biologically active agents, and controlled release capacity, hydrogels have been shown to have great potential in the delivery of therapeutic agents in tumor metastasis. Moreover, hydrogel-based localized delivery systems have received much attention to overcome the limitations of systemic therapy and provide effective delivery to target pathological sites through a controlled release manner, resulting in long-term exposure to tumor cells to therapeutics. This review highlighted the recent applications of hydrogels as local delivery systems to inhibit tumor metastasis. Hydrogels, in particular smart hydrogels, can serve as a perfect platform for localized depots and sustained release of drugs in chemotherapy, radiotherapy, phototherapy, immunotherapy, and/or combination therapy to reduce the patient's multiple dose burden, making them promising for the future treatment of tumor metastasis. Smart hydrogels can intelligently respond to environmental stimuli and can be delivered less invasively, thereby enabling the remotely controlled and on-demand release of therapeutic agents. The significance of a hydrogel-based localized delivery approach over systemic therapy is to expand the range of therapeutic inhibition of tumor metastasis, reduce systemic toxicity and repeated dosing, and enhance patient compliance, which will improve the quality of clinical responses.

Conflicts of interest

The authors declare no conflict of interest.

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