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Hydrogel local drug delivery systems for postsurgical management of tumors: *Status Quo* and perspectives

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ABSTRACT

Surgery is one of the primary treatments for solid tumors. However, the incomplete resection of tumor cells and the immunosuppressive microenvironment make the issue of postsurgical tumor recurrence a great challenge. Furthermore, a wide range of requirements, including ensuring effective hemostasis, implementing prophylactic measures against infection, and promoting wound healing, were also raised in the postsurgical management of tumors. To fulfill these demands, multiple hydrogel local drug delivery systems (HLDDS) were developed recently. These HLDDS are expected to offer numerous advantages in the postsurgical management of tumors, such as achieving high local drug concentrations at the lesion, efficient delivery to surgical microcavities, mitigating systemic side effects, and addressing the diverse demand. Thus, in this review, a detailed discussion of the diverse demands of postsurgical management of tumors is provided. And the current publication trend on HLDDS in the postsurgical management of tumors is analyzed and discussed. Then, the applications of different types of HLDDS, *in-situ* HLDDS and *non-in-situ* HLDDS, in postsurgical management of tumors were introduced and summarized. Besides, the current problems and future perspectives are discussed. The review is expected to provide an overview of HLDDS in postsurgical management of tumors and promote their clinical application.

1. Introduction

Tumors refer to a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. They exhibit a range of characteristics, such as tumor-promoting inflammation microenvironment, replicative immortality, evasion of immune recognition and growth suppressions, leading to the intricacy of their treatment [1]. Tumors are categorized as solid tumors and non-solid tumors, which are divided according to the possibility of being palpated through clinical examinations. Solid tumors refer to visible masses that can be palpated while non-solid tumors, such as leukemia in blood diseases, cannot be palpated [2]. Among them, solid tumors accounted for more than 90 % of all tumor cases [3]. By 2040, the global cancer burden is anticipated to increase to 27.5 million new cases and 16.3 million deaths as the population growth and aging [4]. Thus, tumors have emerged as a formidable global challenge, and cancer treatment plays a pivotal role in determining the quality of life for tumor patients.

There are many types of cancer treatment approaches, including localized therapies and systemic therapies. Localized therapies are limited to tumor lesions of the body, which include surgery, radiation and cryotherapy [5]. Systemic therapies, such as chemotherapy, hormone therapy, and immunotherapy, are delivered through the bloodstream and may affect all parts of the body, which can be used alone or in combination with localized therapies [5]. Due to the unique characteristics of different types of tumors, such as solid tumors having a certain shape and size while non-solid tumors are generally amorphous, different treatment approaches are taken in clinical treatment. Localized therapy, especially surgical resection, remains the primary consideration for solid tumor treatment. For example, surgical resection is the main treatment method for lung cancer and pancreatic cancer. The surgical resection ratio of lung cancer ranged from 60 % to 90 % [6]. Besides, the ratio of R0 resection, which refers to the complete removal

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of the tumor during surgery with the negative observed margins, for minimally invasive surgery for pancreatic cancer was relatively high, reaching 67 %. And even the R0 resection ratio for pancreatic cancer patients receiving perioperative treatment was as high as 88 % [7,8]. Thus, surgery is one of the most common and effective solid tumor treatment approaches.

However, the postsurgical management of tumors continues to present a significant challenge, encompassing issues such as local tumor recurrence and other complex pathological conditions. Local tumor recurrence and metastasis after surgery is a frequently encountered issue, which is considered the primary concern in postsurgical management. It has been reported that the residual tumor cells and the immunosuppressive microenvironment resulted in the tumor recurrence [9]. The surgical trauma caused by hepatic wedge resection made the liver more prone to experimental tumor metastasis, while the residual tumor cells implanted near the wound show more aggressiveness than those grown in the original environment [10]. For example, the recurrence rate of patients with hepatocellular carcinoma after surgery was about 54 %, and the median survival time from recurrence to death was about 21 months [11]. Therefore, preventing postsurgical tumor recurrence is significant for ensuring the efficacy of tumor treatment. Furthermore, there are other diverse requirements that hold significant importance in the management of postsurgical managements, such as ensuring effective hemostasis, implementing prophylactic measures against infection, and promoting wound healing [12,13]. These issues raise sophisticated demands for improving patient prognosis and life quality.

To prevent postsurgical tumor recurrence, multiple therapeutical approches have been proposed by eradicating residual tumor cells and alleviating the immunosuppressive microenvironment. Chemotherapy, which has a high therapeutic efficacy, is usually used as adjuvant therapy together with surgery in clinical with a broad treatment spectrum and wide applicability [14]. However, traditional chemotherapy is easy to causes systemic adverse effects including organ toxicity, bone marrow suppression and alopecia. To address these issues, active pharmaceutical ingredients (APIs) have been developed in the past decades, with some even advancing to clinical trials. And the APIs have been employed into varieties of novel therapeutic approaches, such as phototherapy and immunotherapy. Nevertheless, despite the significant anti-relapse efficacy demonstrated in these postsurgical management approaches, there remain several critical issues that require resolution. On the one hand, these therapeutical approches may primarily focus on preventing tumor recurrence with limited impact on hemostasis, antiinfection, and wound healing promotion [15]. On the one hand, the main administration of these novel therapies is still systemic administration, which inevitably gives rise to systemic side effects [16,17]. Hence, in addition to the imperative of developing novel therapies or APIs to prevent tumor recurrence, it is equally crucial to investigate approaches for exquisite drug delivery systems that possess multiple functions and minimize adverse effects on patients. Extensive research on drug delivery systems holds immense significance.

Compared to traditional systemic drug delivery systems, hydrogel local drug delivery systems (HLDDS) exhibit extensive application prospects in postsurgical managements of tumors. HLDDS are insoluble biomaterial scaffolds with three-dimensional networks, which are formed by physical or chemical crosslinking [18]. HLDDS offer advantages in the field of drug delivery such as high drug loading capacity, precise drug targeting, reduced systemic side effects, and the potential for integrating multiple therapies [19]. In the field of postsurgical management of tumors, HLDDS possess numerous distinctive characteristics. For example, HLDDS with specific three-dimensional structure and porous structure are excellent exceptional vehicles for various APIs for multiple functions, such as antitumor, antiinfection and wound healing promotion [20]. Specifically, for the delivery of biological macromolecules, HLDDS can serve as a drug reservoir to effectively preserve their functionality as well [18]. Besides, HLDDS constructed by environmentally responsive materials enable *in-situ* gelation to adapt to postoperative cavities, enhancing the drug delivery efficiency [21–23]. In addition, the high water contents of HLDDS itself facilitate the hemostasis and wound healing promotion in the postsurgical cavity [12,15]. Therefore, these unique properties make HLDDS suitable for postsurgical management of various types of tumors, such as breast cancer [24,25], glioblastoma [26,27], and melanoma [15,28]. However, there is still a lack of systematic summary and analysis of its application in this area and the limitations and prospects of its development need to be deeply discussed to facilitate clinical translation.

Based on the above insights, this review provided a comprehensive overview of the etiology of tumor recurrence, strategies for postsurgical management of tumors, and the current applications of HLDDS. The challenges and limitations encountered by HLDDS were further analyzed, and future development directions as well as recommendations were proposed. This review is expected to promote the application of HLDDS in the postsurgical management of tumors.

2. Etiology and strategies for postsurgical management of tumors

The demands for postsurgical management of tumors are diverse, including inhibited postsurgical tumor recurrence and others demands. Postsurgical tumor recurrence is believed to be closely related to the residual tumor seeds in the surgical cavity (edge) and the immunosuppressive microenvironment that may be caused by surgery (Fig. 1a) [9,29]. The presence of residual tumor seeds facilitates the potential for tumor recurrence, while the immunosuppressive microenvironment fosters conducive conditions. On the one hand, for some superficial solid tumors, it is highly possible to achieve a cure by surgical resection of the whole tumor in the early stage [30]. However, for deep-seated solid tumors with high aggressiveness and irregular shape, it is difficult to completely remove the whole tumor by surgery, and the residual tumor cells in the hidden corner provide the possibility of recurrence. For example, the rapid surgical recurrence of glioma, a highly aggressive intracranial malignant tumor, has been proven to be directly related to the residual tumor tissue in the surgery [31]. On the other hand, tumor cells can be protected from attack by establishing immunosuppression, which has long been considered a key step in tumor formation and progression [9]. What's worse, surgery can also lead to a variety of factors, such as inflammation, blood transfusion and anesthetics, which further enhance the systemic immunosuppression state, creating a "soil" for tumor recurrence. Therefore, eliminating residual tumor cells and regulating the immune microenvironment is considered an effective strategy to prevent tumor recurrence.

To prevent postsurgical tumor recurrence, various therapies such as chemotherapy, phototherapy, immunotherapy, and embolization therapy have been proposed and demonstrated certain efficacy in suppressing tumor recurrence (Fig. 1b). Chemotherapy is the traditional postsurgical treatment for tumors with its high effectiveness, especially in the treatment of inaccessible or unknown tumors due to the drugs that can even affect cancer cells outside the primary area [32]. For example, paclitaxel is one of the most effective anti-cancer drugs for treating various advanced and refractory cancers such as ovarian cancer, breast cancer, lung cancer, cervical cancer and so on. Paclitaxel binds with β-tubulin to prevent polymerization and stabilize microtubules, thereby preventing normal microtubule assembly and affecting the mitotic process of tumor cells to inhibit cell proliferation [33]. However, traditional chemotherapy still faces some challenges. As the content of drugs reaching the tumor site is low, it is often necessary to overdose to ensure adequate drug delivery to the tumor site [34]. Patients receiving overdose chemotherapy always experience side effects such as liver failure, myelosuppression, cardiotoxicity, hair loss and vomiting, which significantly reduce the quality of life [35]. To address these problems of chemotherapy, novel therapies have been developed, including phototherapy, immunotherapy and vascular embolization therapy.

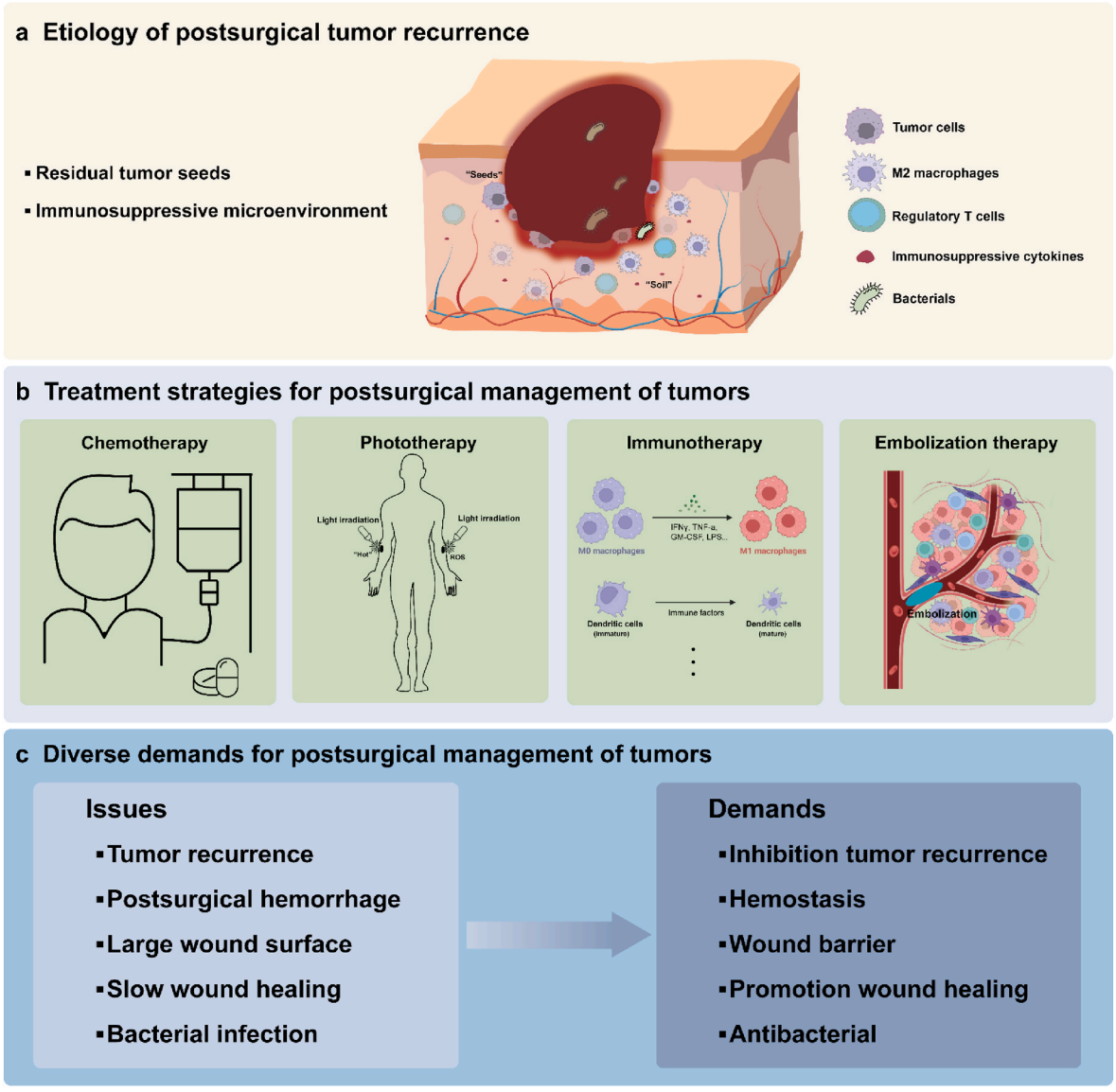


Fig. 1. Current situation for postsurgical management of tumors. (a) Etiology of postsurgical management of tumors. (b) Treatment strategies for postsurgical management of tumors. (c) Diversec demands for postsurgical management of tumors.

Phototherapy is a treatment approach that converts light energy into reactive oxygen species or heat energy to achieve tumor treatment effects under local light irradiation, including photodynamic therapy (PDT) [36,37] and photothermal therapy (PPT) [15,38]. Under light irradiation, PDT transfers energy to the surrounding oxygen through the photosensitive agent to generate reactive oxygen species (ROS), which cause oxidative damage to the surrounding biomolecules and kill tumor cells [39]. PTT is an approach of rapid local high temperature induced killing of tumor cells by photothermal agent [40]. Both of these two phototherapies have the advantages of strong specificity, negligible drug resistance, and negligible toxic side effects on non-irradiated sites [41]. In addition to phototherapy, immunotherapy has garnered significant attention. Immunotherapy exerts anti-tumor effect mainly by enhancing the body's immune system to recognize tumor cells, thus clearing tumor cells with the durability of treatment. Local immunotherapy is expected to effectively prevent tumor recurrence by enriching immune cells in tumor sites and directly killing tumor cells. Compared to phototherapy and immunotherapy, vascular embolization therapy exhibits unique antitumor mechanism. Vascular embolization therapy is an anti-tumor therapy that kills tumor cells by selectively inducing thrombosis in tumor blood vessels. It has been proved that the formation of a single blood clot is enough to fill the whole blood vessel and subsequently cause the death of thousands of tumor cells, which endow the vascular embolization therapy with high anti-tumor efficiency [42,43]. In summary, these therapies exhibit great potential in preventing postsurgical tumor recurrence.

Moreover, due to the unique feature of surgery, postsurgical tumor management becomes considerably more intricate (Fig. 1c). Specifically, following surgical intervention, destruction of the tumor's vasculature necessitates prompt and efficient hemostasis as a paramount prerequisite for effective postsurgical tumor management. In addition, due to the inflammatory microenvironment and large-area skin defects after surgery, the postsurgical wound is prone to microbial colonization and becomes an infected wound, slowing down wound healing [44,45]. Thus, antibiotics and wound healing promotion are also essential for postsurgical tumor management. Therefore, delivering antirecurrence drugs effectively into the surgical tumor cavity and manage the pathological environment of the wound simultaneously is more beneficial for postsurgical tumor management.

To fully optimize the effectiveness of the postsurgical management of

tumors, the design of drug delivery systems is crucial. Currently, drug delivery approach in clinical practice is mostly systemic drug delivery system. For example, chemotherapy drugs and immune checkpoint inhibitors are mostly given orally or intravenously, which leads to reduced drug delivery to the tumor site and poses challenges in maintaining the efficacy of biological macromolecule drugs. Besides, to ensure efficacy of phototherapy and vascular embolization therapy, it is imperative to confine the drug exclusively to the lesion site, thereby minimizing potential harm inflicted on surrounding normal tissues. However, this requirement cannot be met through systemic drug delivery system. Compared with systemic drug delivery system, local drug delivery system will be another beneficial alternative. Local drug delivery system directly localizes the drugs to the cancer lesions, avoiding excessive drug circulation and serious damage to normal tissues [46–48]. More importantly, local drug delivery system provides the possibility for the integrating of multiple tumor therapies, such as PDT, PTT, immunotherapy [26,49] and vascular embolization therapy [50,51], and other postsurgical management needs. In conclusion, developing local drug delivery system is promising for achieving the therapeutic effects of various therapies and meeting the needs of postsurgical tumor management.

3. HLDDS for postsurgical management of tumors

A suitable local drug delivery system should fulfill several requirements, including proper drug loading capacity, tunable drug release profile and desired mechanical performance [52,53]. Specially, HLDDS, a local drug delivery system, has attracted great attention in postsurgical tumors management due to its advantages of high drug loading, controllable drug release profile, adjustment of physicochemical properties, and excellent biocompatibility [54–56]. The matrix of HLDDS is originally derived from natural materials, including sodium alginate, chitosan, hyaluronic acid, and gelatin. The high biological safety of these natural materials ensures the HLDDS produce negligible toxic effects when directly contacting the wound after tumor surgery [57]. In the past 20 years, natural HLDDS have gradually been replaced by synthetic hydrogels. Synthetic polymers usually have a clear structure, which can be easily modified for specific degradability and functionality. Researchers can synthesize polymer hydrogel materials according to the needs of different tissues and organs or to achieve a certain therapeutic purpose, aiming to customize the physicochemical properties of hydrogels, such as mechanical properties, responsiveness, and degradability [58,59]. Therefore, the widespread accessibility of HLDDS matrix establishes a fundamental basis for their multifaceted applications.

HLDDS exhibit distinct advantages in postsurgical tumor management. For instance, the precursor solution can be easily injected into the surgical cavity of tumors in a liquid state and subsequently undergo gelation triggered by specific physical or chemical factors to form *in-situ* hydrogels. After gelation, these *in-situ* hydrogels seamlessly conform to the irregular surgical cavities, making them suitable for tumors of varying shapes and locations [60,61]. Thus, HLDDS facilitates the effective administration of drugs to the tumor site, which is a prerequisite for successful tumor therapy treatment. Importantly, when combined with novel tumor therapies, hydrogels exhibit substantial potential in preventing tumor recurrence. HLDDS can retain the biological activity of immunoactivity biomacromolecule, enabling full activation of anti-tumor immune responses upon localized administration, facilitating immune cell enrichment alongside sustained effects to induce robust immunological responses [62]. Additionally, by incorporating photosensitizers or photothermal agents into the hydrogel matrix for localized drug administration, the high local concentrations would lead to significantly enhanced light conversion efficiency thereby maximizing the effectiveness of PDT or PTT [36,38]. Furthermore, certain types of HLDDS can obstruct tumor blood vessels with defined shape and volume, exhibiting potential applications in vascular embolization therapy [51,63]. Notably, in addition to inhibiting tumor recurrence, HLDDS can also meet other requirements for postsurgical tumor management. For example, HLDDS have demonstrated remarkable benefits in tissue reconstruction and plasticity following tumor surgical, especially in breast-conserving surgery for breast cancer [64]. Though filling and repairing breast defects after visible lesion resection, HLDDS effectively inhibits tumor recurrence while restoring the original appearance of the breast. Moreover, owing to their exceptional water absorption capacity and air permeability properties, HLDDS offer a 3D microenvironment that provides biomechanical support for cell proliferation and migration, exhibiting potential applications as external wound healing auxiliary materials [65]. In conclusion, for their unique advantages, HLDDS have a broad application prospect in preventing postsurgical tumor recurrence.

To investigate the development of HLDDS in postsurgical management of tumors, a literature survey was employed based on the Web of Science (Fig. 2). The results demonstrated that approximately 370 publications in this field were presented in the past 5 years (Fig. 2a). The year 2023 was the peak of the number of publications, and 'article' was the main publication type (Fig. 2a–b). The number of citations related to HLDDS in postsurgical management of tumors has been steadily increasing in recent years, with a count of nearly 3987 citations for the year 2023 (Fig. 2c). The papers published by the researchers from China accounted for 343 (Fig. 2d). Additionally, the top 5 journals that have published papers pertaining to HLDDS in postsurgical management of tumor include *Advanced Functional Materials*, *Biomaterials*, *ACS Applied Materials Interfaces*, *Biomaterials Science* and *Journal of Controlled Release* (Fig. 2e). This observation signifies a growing emphasis and interest in this field. Thus, it is necessary to summarize and analyze the current publications on HLDDS in postsurgical management of tumors, enabling the scientific community to gain the latest development direction and research focus in this field more clearly.

4. None *in-situ* HLDDS

The HLDDS used for postoperative tumor management are categorized into *non-in-situ* HLDDS and *in-situ* HLDDS. Among these, *non-in-situ* HLDDS refers to a pre-gelled semi-solid or solid preparation before administration. They can be further classified into implantable HLDDS and injectable HLDDS. Implantable HLDDS is administered in a predetermined shape and volume, whereas injectable hydrogel possesses shear-thinning properties and can be administered *via* syringes. In contrast, the *in-situ* HLDDS typically exist as low-viscosity liquids prior to administration, which transit into a semi-solid gel due to the transformation of polymer dispersion state or conformation upon administration. The *in-situ* HLDDS in response to specific stimuli in the microenvironment of the lesions, such as temperature, pH, ions, light, etc., are considered as responsive *in-situ* HLDDS, while others were considered as non-responsive *in-situ* HLDDS. The *non-in-situ* HLDDS was initially discussed in this review (Fig. 3).

4.1. Implantable HLDDS

The implantable HLDDS is pre-gelled prior to administration and then implanted in a three-dimensional configuration at the lesion site. Implantable HLDDS is a stable three-dimensional network where polymer chains are cross-linked through physical or chemical interactions [66]. In addition to possessing general characteristics of hydrogels such as high biocompatibility, drug loading capacity and porosity, the irreversible cross-linking structure of implantable HLDDS endows them with superior mechanical strength to effectively support postoperative cavities and prevents repeated deformation within the dynamic mechanical environment of the human body. This feature is particularly advantageous for tissue regeneration applications, especially in breast cancer postoperative treatments [67,68]. Chen et al. developed an implantable hydrogel composed of cross-linked chitosan and pullulan

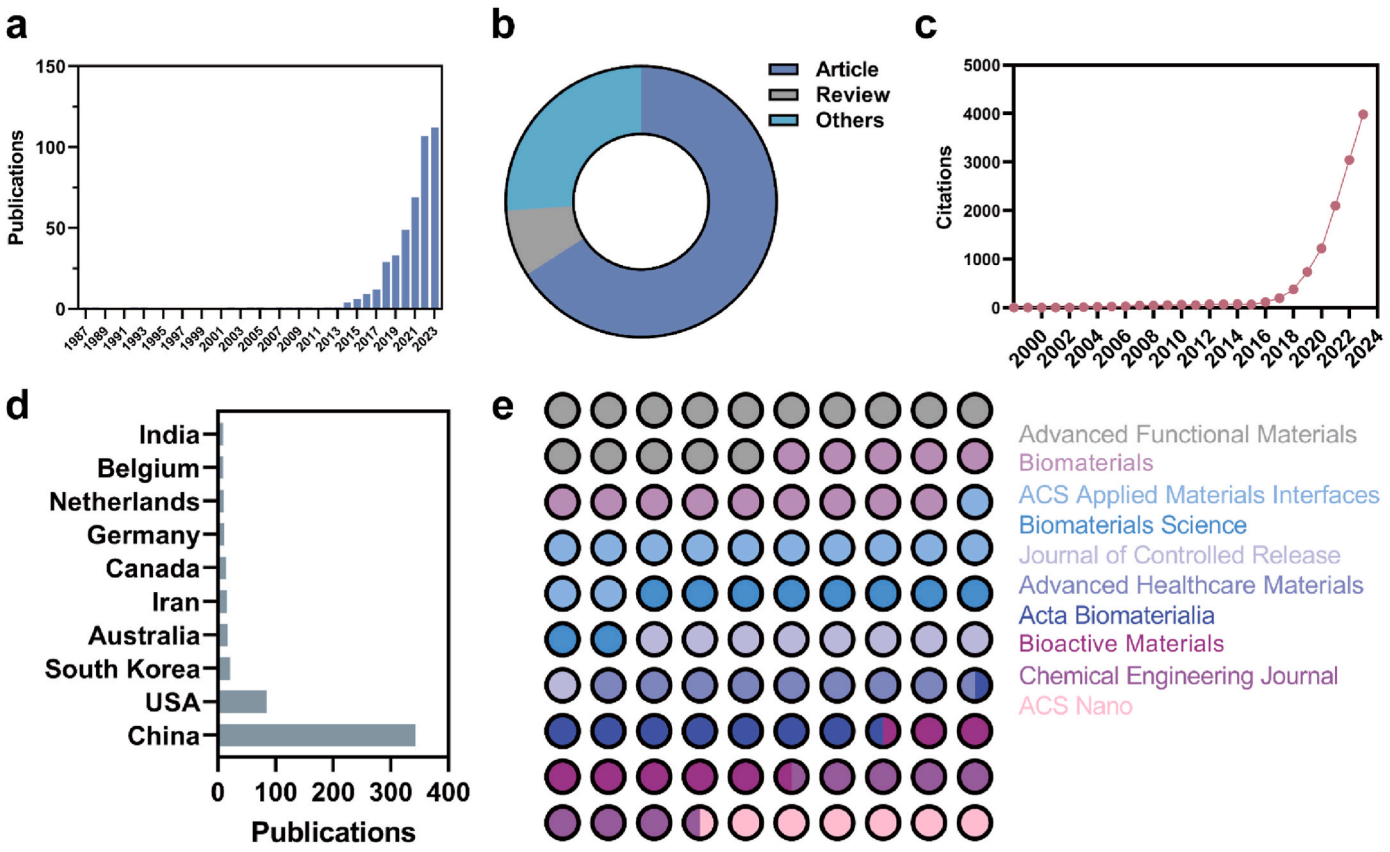


Fig. 2. Bibliometric analysis of HLDDS. (a) Number of publications *versus* year. (b) Types of publications. (c) Citations of these publications. (d) Numbers of publications from top-10 regions. (e) Number of publications in top-10 periodicals.

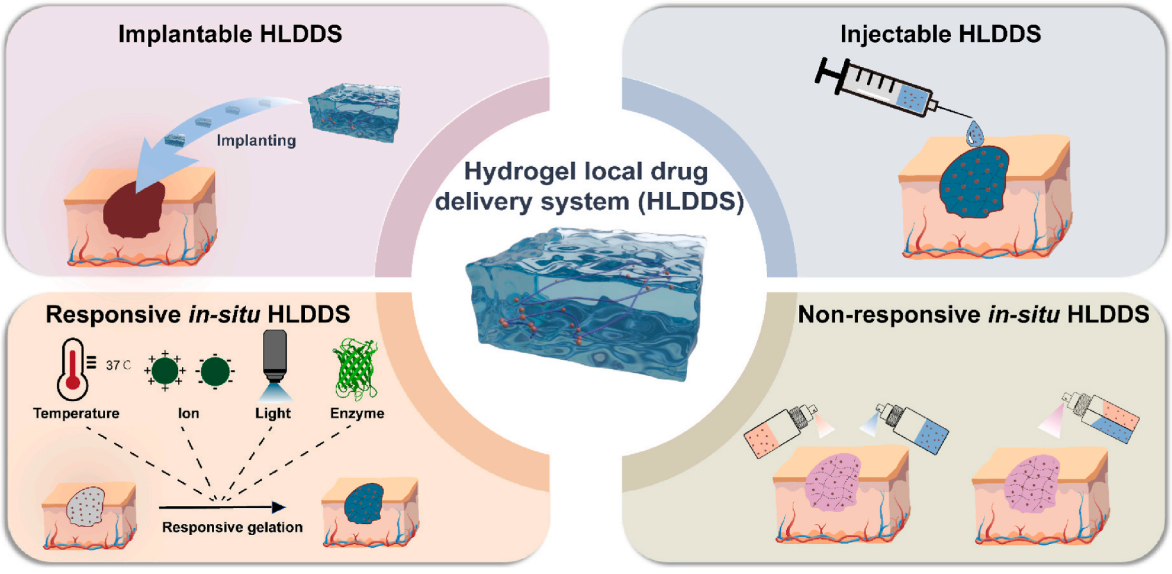


Fig. 3. Various types of HLDDS, including implantable HLDDS, injectable HLDDS, responsive *in-situ* HLDDS and non-responsive *in-situ* HLDDS.

for the postoperative treatment of breast cancer, and co-loaded cyclopamine with anti-CD47 antibodies in the hydrogel for chemo-immunotherapy [24]. The hydrogel exhibited favorable mechanical properties and drug-release kinetics. The results demonstrated that the implanted hydrogel formed a spherical mass in the fourth mammary fat pad, maintaining its shape even under gentle compression, thus meeting the aesthetic requirements of women after mastectomy. However, despite serving as a scaffold, the hydrogel failed to sufficiently occupy the surgical cavity. To solve this issue, Li et al. constructed a regenerative hydrogel scaffold by binding a colony-stimulating factor 1 receptor inhibitor GW2580 onto in situ crosslinked hydroxybutylchitosan/oxidized chondroitin sulfate hydrogel layer covering a 3D printed calcium phosphate scaffold based on electrostatic interaction for the postsurgical treatment of bone tumors (Fig. 4a–b) [25]. This hydrogel scaffold with customized shapes made by 3D printing technology was perfectly adapted to the tumor lesion. The cytotoxicity result demonstrated that

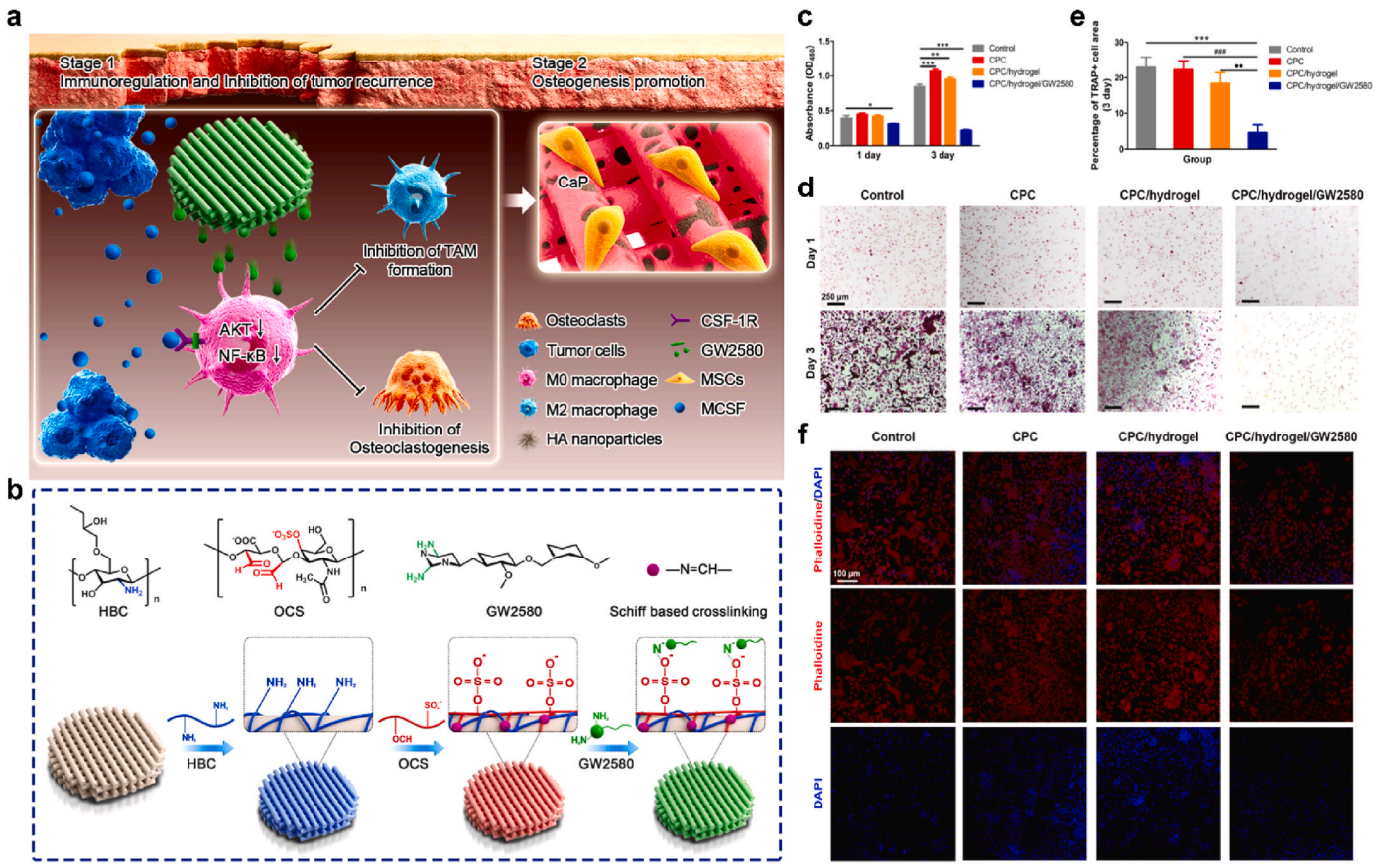


Fig. 4. The design and mechanism of 3D printed hydrogel scaffolds for bone tumor postoperative treatment. (a) The schematic of function process and mechanism of the 3D printed scaffold regulating macrophage immune microenvironment for postoperative treatment of bone tumors. (b) Schematic of preparation process and related mechanism of the inhibitor-loaded scaffold. (c) Effect of released components from scaffolds on BMMs proliferation after 1 and 3 days of culture. (n = 3, *P < 0.05, **P < 0.01, ***P < 0.001 vs. control by one-way ANOVA). (d) TRAP staining images and (e) related quantification results show the effect of released components on BMMs osteoclastogenesis after 1 and 3 days of culture. ($n = 3$, ***P < 0.001 vs. control; $^{\#\#\#}$P < 0.001 vs. CPC group; ··P < 0.01 vs. CPC/hydrogel group by one-way ANOVA). (f) Confocal microscope images show morphology of BMMs in scaffold extract medium after 3 days of culture. Reproduced from Ref. [25] with permission from Elsevier.

the proliferation of bone marrow-derived monocyte (BMMs) cultured in the extract medium of CPC/hydrogel/GW2580 scaffolds was significantly inhibited (Fig. 4c). The effect of scaffold extract medium on osteoclastogenesis of BMMs was then analyzed by a tartrate-resistant phosphatase (TRAP) staining after 1 and 3 days of co-culture (Fig. 4d–e). The results showed that osteoclastogenesis of BMMs was completely inhibited in the CPC/hydrogel/GW2580 extract medium. TRAP-positive osteoclasts were hardly detected after 3 days of co-culture. Additionally, cell morphology observation under a confocal microscope confirmed the TRAP staining results (Fig. 4f). Induced multi-nucleated osteoclasts were found in the control group after 3 days of culture but were not detected in the CPC/hydrogel/GW2580 group. Thus, the results demonstrated that the 3D printed calcium phosphate scaffold was beneficial in blocking the important link in the vicious cycle of tumor recurrence and metastasis. Although this 3D-printed hydrogel scaffold could be customized to the tumor lesion, this approach made the manufacturing process of the hydrogel scaffold more complex, such as the need to obtain the size and depth of the tumor lesion, as well as the limited material selection for preparation.

The traditional implantable HLDDS has several limitations when utilized for local treatment after tumor surgery, with the primary concern being their inability to perfectly conform to the postsurgical wound and cavity [24,25]. In cases where the wound or cavity is irregular or uneven, small cavities and hidden corners may persist even after filling with solid hydrogel, making the complete coverage of drug delivery impossible. As previously discussed, while the implantable HLDDS developed by Chen et al. [24] and Li et al. [25] demonstrated some inhibition of tumor recurrence, it did not achieve the desired efficacy. Consequently, while implantable HLDDS offer significant advantages in terms of support and shaping capabilities, they exhibit evident shortcomings in effectively eradicating residual tumor cells and thereby inhibiting tumor recurrence and metastasis.

4.2. *Injectable HLDDS*

Unlike implantable HLDDS, injectable HLDDS is a self-healing hydrogel with shear-thinning properties that can be injected through a needle to fill irregular areas [69]. It is similar to traditional implantable HLDDS in that it's also cross-linked *in vitro* in a semi-solid or solid state before administration. However, the key distinction is that the shear-thinning property of injectable HLDDS allows it to pass through a needle, making it suitable for minimally invasive delivery to tissues [70]. Typically, injectable HLDDS is formed through dynamic and reversible interactions between polymers or peptides, exhibiting shear-thinning and self-healing properties. These interactions include physical association (such as hydrogen bonds, host-guest interactions, biological recognition sequences, hydrophobicity, electrostatic and metal-ligand coordination) as well as dynamic covalent chemistry (such as Schiff bases, oxime chemistry, disulfide bonds and reversible Diels-Alder) [71]. The shear-thinning properties of injectable HLDDS enable it to exhibit viscous flow under applied stress, presenting the desired potential for injection. Furthermore, its self-healing properties

allow for mechanical properties to recover when stress is reduced [72]. Therefore, injectable HLDDS is highly suitable for the postsurgical treatment of tumors, effectively filling irregular surgical cavities and tissue defects. Additionally, the injectable HLDDS is less susceptible to stress-induced crack formation, thereby extending the lifespan of its tissue engineering structure [73,74]. Huo et al. used silk protein to construct a calcium carbonate biomineralized hydrogel, carrying the membrane proteins of 4T1 cells-dendritic cells (DCs) fusion cells, for the suppression of recurrence of triple-negative breast cancer after surgery [75]. The frequency scanning results and the puncture test results of the rheometer showed that the silk protein hydrogel had good shear-thinning properties. After calcium carbonate biomineralization, the hydrogel had a large number of pores ranging from 100 to 1000 nm, and this special structure was conducive to the transport of substances in the hydrogel. By constructing a model of post-surgical triple-negative breast cancer, the biomineralized hydrogel significantly inhibited tumor recurrence and promoted anti-tumor immune responses *in vivo*.

In recent years, injectable HLDDS have been increasingly utilized in the postoperative treatment of brain tumors, particularly glioblastoma (GBM). The postoperative GBM recurrence is extremely common due to the deep intracranial location of the tumor and the invasive and diffuse nature of residual GBM cells [76]. Furthermore, the effectiveness of current postoperative GBM treatments was hindered by the selective permeability of the blood-brain barrier (BBB) [77]. Injectable HLDDS offer promising prospects for improving postoperative GBM treatment through their ability to locally deliver drugs, minimally invasive injection, high biological safety, and ease of modification. Chen et al. developed a cavity-injectable nanoporter-hydrogel superstructure that creates glioma-stem-cells-specific chimeric antigen receptor macrophages/microglia surrounding the cavity to prevent GBM relapse [26]. Based on the locoregional immunity therapy, the combined treatment with nanoporter-hydrogel superstructure and CD47 antibody increased the frequency of positive immune responding cells and suppressed the negative immune regulating cells, conferring a robust tumoricidal immunity surrounding the postsurgical cavity and inhibiting postoperative GBM relapse. However, the drug release profile of the hydrogel developed by Chen et al. was uncontrolled, resulting in its distribution in non-tumor areas and diminishing its efficacy. To address these challenges, Zhang et al. developed an adenosine triphosphate (ATP)-responsive release immune-activating hydrogel by conjugating CpG ODN with a nucleic acid aptamer and incorporating an ATP-specific aptamer (Apt) into the molecular structure of hyaluronic acid methacryloyl (HAMA) *via* amide bond (Fig. 5a–c) [27]. The ATP-responsive release immune-activating hydrogel undergone degradation upon the release of ATP triggered by pyroptosis, thereby facilitating localized release of CpG ODN (Fig. 5b). And the ATP-responsive hydrogel had excellent rheological properties (Fig. 5d–e). Co-incubation of ATP-responsive hydrogel in artificial cerebrospinal fluid simulating the *in vivo* environment demonstrated that the addition of various ATP concentrations to the solution post gel formation yielded distinct fluorescence intensity variations. Higher concentrations of ATP were found to accelerate the release of CpG ODN, and the degradation rate of the hydrogel was dependent on ATP concentration, with higher concentrations resulting in faster degradation (Fig. 5f–g). The efficacy of the antitumor intervention *in vivo* was evaluated utilizing the GL261 syngeneic orthotopic mouse model. Fluorescence Wheat Germ Agglutinin (WGA) staining of tumor tissues after 30 days of treatment revealed a narrower distribution and increased vacuole formation in the IASNDS@gel group. These changes and the observed softening of the tumor texture seem to correlate with pyroptosis-mediated tumor cell death (Fig. 5h). Further immunohistochemical staining of tumor tissues showed Ki-67 tissue expression of the SDV@gel and IASNDS@gel groups upon gel-based intervention was the lowest (Fig. 5i). These results, including reduced Ki-67 expression, a narrower distribution, and increased vacuole formation in the tumor tissue after treatment, demonstrated the inhibition of the ATP-responsive release immune-activating hydrogel in GBM recurrence.

In *non-in-situ* HLDDS, implantable HLDDS exhibits robust mechanical properties and a certain degree of rigidity, rendering them suitable for postsurgical stents. However, due to the irreversible structure, implantable hydrogel fails to achieve perfect conformity with the tumor's postsurgical cavity and hinders comprehensive drug coverage within the surgical cavity. Compared to implantable HLDDS, injectable HLDDS possesses dynamically reversible chemical covalent bonds, granting them shear-thinning properties and injectability. Therefore, injectable HLDDS facilitates easy administration and superior filling of surgical tumor cavities. However, the presence of numerous microporous cavities and irregular edges within these surgical cavities still pose challenges in meeting drug delivery and treatment requirements. Compared to *non-in-situ* HLDDS, *in-situ* HLDDS are administered in liquid form, exhibiting excellent fluidity that enables precise conformation to the postsurgical tumor cavity and coverage of microcavities [78,79]. They can undergo gelation triggered by microenvironmental factors or external conditions after administration, thereby achieving therapeutic effects.

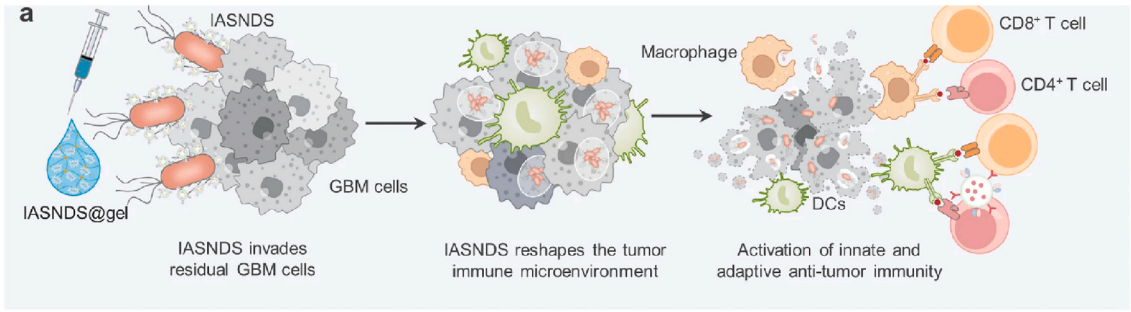
5. *In-situ* HLDDS

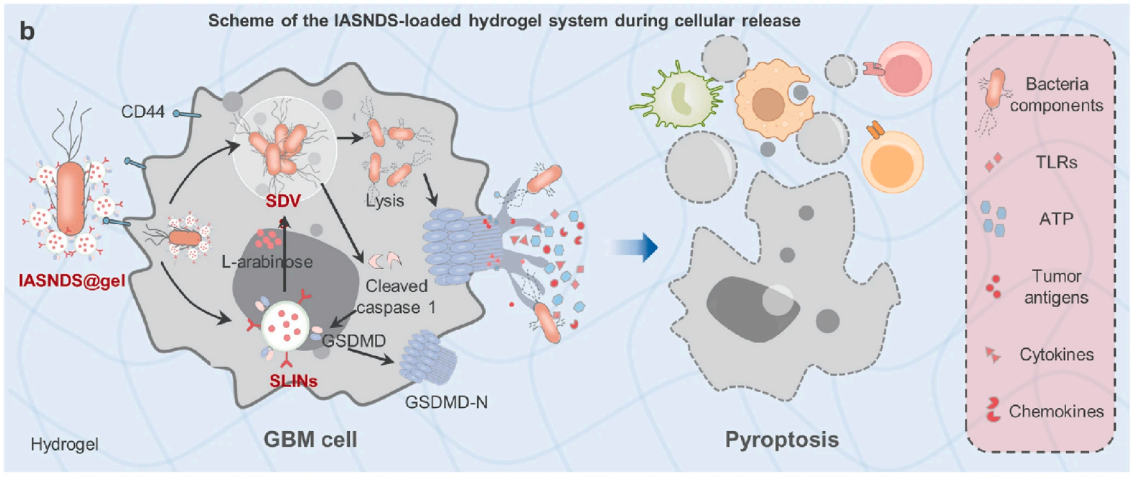
In recent years, the *in-situ* HLDDS has emerged as a prominent area of research, garnering significant attention within the postsurgical management of tumors. The precursor solution of the *in-situ* HLDDS can be delivered to the tumor resection cavity in a minimally invasive manner like injection or spray, and undergo phase transition triggered by external stimuli (such as temperature, ion, light and enzyme) to form a semi-solid hydrogel state drug reservoir [80,81]. Alternatively, the materials solution may be delivered to the excision cavity using a dual syringe or a dual-cartridge sprayer and subsequently chemically cross-linked to produce an *in-situ* hydrogel after filling the cavity. The HLDDS precursor loaded with active drugs can effectively leverage its "adaptability to local conditions" by precisely conforming to diverse irregular surgical cavities [15,82]. Once formed, the *in-situ* HLDDS can persist at the postoperative site for an extended period, releasing drugs and providing mechanical support with optimal efficacy, achieving eradication of residual tumor cells or reversal of immunosuppressive microenvironment, reducing the likelihood of local recurrence and distant metastasis [83].

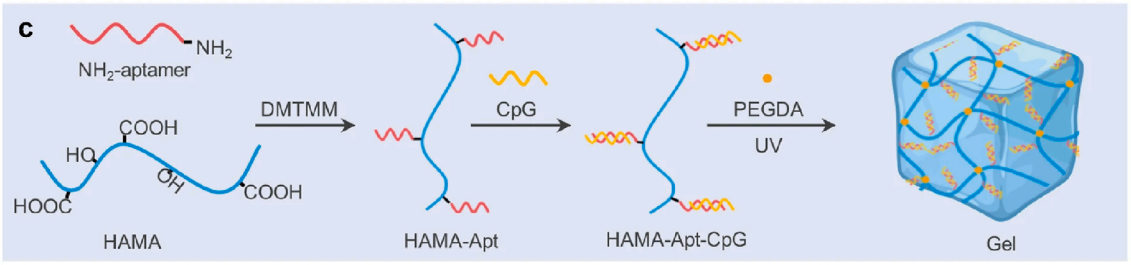
In the field of postsurgical management of tumors, *in-situ* HLDDS has gained widespread utilization for localized drug delivery owing to its exceptional biocompatibility, degradability, sustained and controlled release, spatial controllability and superb filling. Here, we conducted a comprehensive analysis of *in-situ* HLDDS in the field. We categorized these HLDDS into non-responsive, thermo-sensitive, ion-sensitive, photocuring, and other types of HLDDS based on the stimuli triggering their phase transitions. Furthermore, we summarized their gelling mechanism, hydrogel matrices, and applications for tumor postsurgical management.

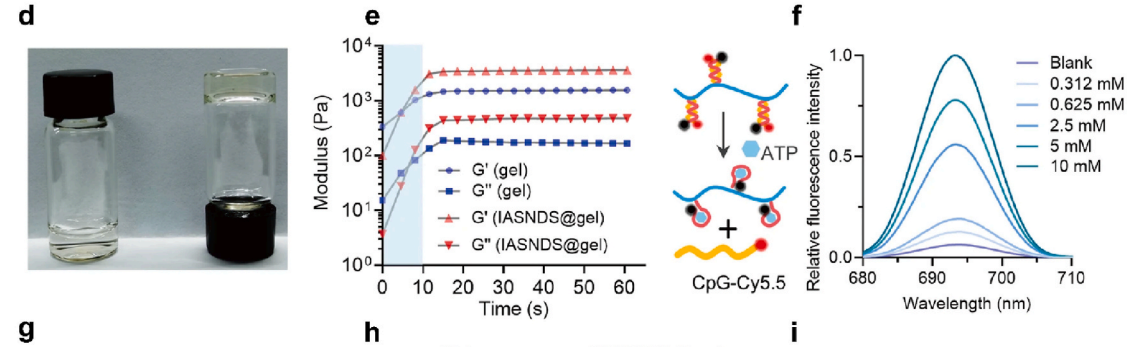
5.1. *Non-responsive in-situ HLDDS*

Gels formed at the administration site through crosslinking agents or chemical crosslinking between different matrix materials are considered *in-situ* HLDDS. "A + B″ two-component hydrogels are specifically engineered to rapidly blend into a hydrogel matrix, allowing for simultaneous delivery and *in-situ* cross-linking facilitated by dual syringes or a dual-cartridge sprayer. For instance, when gelatin and chondroitin sulfate (OCS) are co-injected into the postoperative site of osteosarcoma using a dual syringe, the aldehyde group in OCS can rapidly react with the amino group of gelatins to form a hydrogel *via* Schiff base reaction [84]. The drug-loaded gel has a gelling time of approximately 3 min, allowing for complete filling of the tumor cavity. Furthermore, the hydrogel exhibits pH and GSH dual-responsive drug release behavior in a TME-mimicking environment (pH = 5.5, 10 mM GSH), resulting in a









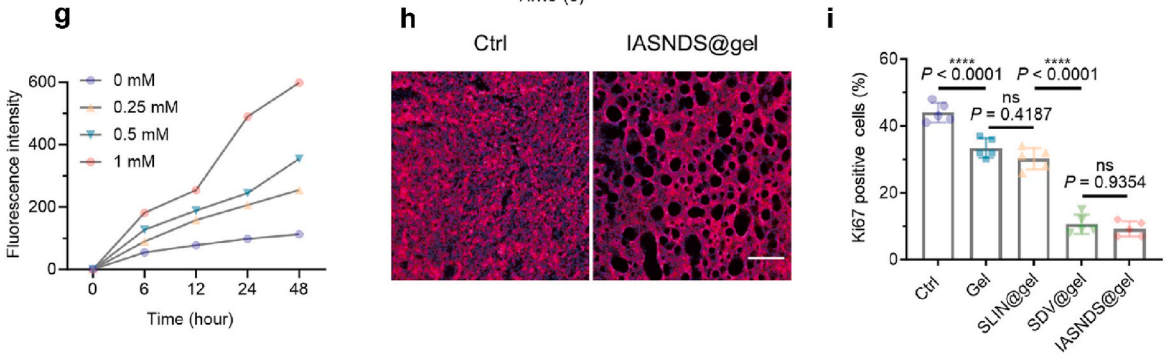


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Fig. 5. Mechanism of immunogenic cell death (ICD) induced by the autolysing Salmonella delivery vehicle (SDV), and ATP-responsive hydrogel design and characterization. (a) Illustration depicting the immunostimulatory autolyzing Salmonella-nanocapsule delivery system (IASNDS) invading GBM cells, triggering cell death, activating antigen-presenting cells, and eliciting an immune response. (b) IASNDS cellular entry, intracellular autocleavage initiation, and tumor cell pyroptosis induction mechanism. (c) Schematic of the ATP-responsive hydrogel used to encapsulate the IASNDS. (d) Representative photographs of hydrogels before and after gel formation. (e) Variation in the hydrogel modulus with time, measured at an angular frequency of 1 rad s^{-1} ($n = 3$). (f) Schematic of ATP-induced dehybridization of double-stranded Black-Hole-Quencher 3-modified Apt and Cy5.5-modified CpG structures, with fluorescence spectra showing the fluorescence recovery of Cy5.5 under ATP induction. ($n = 3$). (g) Cumulative amount of CpG ODN released from the hydrogel under different concentrations of ATP. ($n = 3$). (h) Visualization of alterations in mouse brain tissues was achieved by applying WGA staining (red), enabling observation of tumor cell dynamics across the different treatment groups in mice ($n = 3$). (i) The percentage of positive cells was tallied following immunohistochemical staining for Ki-67 in tumor tissues originating from various mouse groups ($n = 5$). Data are presented as the mean ± S.D. Reproduced from Ref. [27] with permission from Springer Nature.

drug release efficiency of up to 40 %. Zhang et al. developed a crosslinked hydrogel using biological orthogonal reactions. The azide groups-modified chimeric exosomes from bone marrow-derived Cells and GL261 tumor cells can undergo bioorthogonal reactions with the alkynyl-modified alginate polymer to form exosome crosslinked gels [85]. The hydrogel can function as an artificial lymph node, significantly enhancing the proliferation and activation response of T cells while effectively reversing T cell depletion. Furthermore, it can greatly inhibit the proliferation and invasion of mouse intracranial tumor cells, almost eliminating intracranial lesions in a postoperative model of in-situ glioblastoma mice. In addition, the gel matrix can be pre-mixed, administered as a solution into the surgical cavity, and subsequently molded in situ to form a hydrogel. Chen et al. developed an *in-situ* hydrogel using Schiff base. They initially combined two gel matrices, including oxidized starch solution and gelatin solution, and injected the precursor solution through a single syringe into the edge of the liver cavity [86]. It took approximately 60 s for the adhesive hemostatic hydrogel to form *in-situ*. The residual aldehyde group in the gel can covalently react with the amino group on the surface of fresh tissue, thereby producing a certain hemostatic function. The addition of mesoporous bioactive glass nanoparticles and NETs lyase combined with natural killing cell infusion has been shown to effectively prevent hepatocellular carcinoma (HCC) recurrence after resection.

Among non-responsive *in-situ* hydrogels, it is crucial to effectively control the phase transition time of the gel. If the phase transition time is too short, there may be inadequate filling of the surgical cavity; conversely, if it is excessively prolonged, there exists a potential risk of drug infiltration into surrounding tissues, thereby resulting in undesired side effects.

5.2. Thermo-sensitive in-situ HLDDS

In addition to non-responsive *in-situ* HLDDS, there are many *in-situ* gelatination HLDDS triggered by external factors. Thermo-sensitive HLDDS refers to a formulation capable of undergoing phase transition in response to external temperature stimuli. The conformation of its matrix structure is temperature-dependent, thereby influencing its solubility and giving rise to two distinct types of thermosensitive hydrogels. One type exhibits reverse thermosensitivity, undergoing sol-gel transition above the low critical solution temperature (LCST), while another type displays positive thermosensitivity properties, with gel-sol phase transition occurring beyond the high critical solution temperature (UCST) [87,88]. To meet the clinical requirements for rapid and thorough filling of irregular surgical cavities, the LCST of most thermosensitive hydrogels used for tumor postoperative treatment is set close to or slightly below 37 °C to achieve sol-gel transition. Below the LCST, the thermo-sensitive hydrogel assumes a liquid state characterized by high fluidity, which endows its ability to completely cover the cavity. Upon exposure to body temperature, hydrophobic segments within the thermo-sensitive hydrogel aggregate to form clusters and expel water molecules, resulting in the expansion of the solution into a semi-solid state for sustained and controlled release of drugs over an extended period [89]. Currently, a wide range of thermo-sensitive materials, such as natural polymers and primarily synthetic polymers consisting of macromolecular chains, hydrophilic groups, and hydrophobic groups, are utilized to prepare thermo-sensitive hydrogels for preventing postsurgical tumor recurrence. As the temperature increases above LCST, their solubility decreases, leading to phase separation and turbidity, which impact the network structure within the hydrogel. In this context, chitosan, poloxamer, PEG/polyester, poly (N-isopropylacrylamide)-based *in-situ* hydrogels are introduced and reviewed (Fig. 6 and **Table 1**).

5.2.1. Chitosan-based HLDDS

Chitosan, a naturally cationic polymer, exhibits intrinsically superior biocompatibility and biodegradability compared to synthetic polymers. Comprised of (1–4)-linked glucosamine and N-acetylglucosamine units, chitosan is derived from chitin through chemical or enzymatic deacetylation(Fig. 6a) [90]. As the only alkaline polysaccharide found in nature, it possesses the ability to be absorbed by the human body and demonstrates good biocompatibility by enzymes within the body and converting it into non-toxic chitooligosaccharide and glucosamine [91,92]. The positively charged free amino group of chitosan can undergo electrostatic adsorption with groups containing negative charge, thereby conferring upon it strong adhesion [93], bacteriostatic [94,95], hemostatic [96] and other properties. However, the positive charge within the molecular chain of chitosan results in its limited solubility, only allowing for dissolution in dilute acid. Once the pH value surpasses 6.2, it will result in the development of a hydrated gel-like precipitate. Furthermore, it lacks thermo-sensitive properties on its own. To address this limitation, the addition of negatively charged polymers such as alginate and pectin, or the basic salt β-disodium glycerophosphate (β-GP), to facilitate ion crosslinking with chitosan. Through these modifications, chitosan can acquire thermo-sensitive phase transition properties, making it suitable for various biomedical applications [97,98].

For instance, in a study by Wang et al., a multifunctional thermosensitive hydrogel was developed with tumor suppression, hemostasis, and antibacterial properties [21]. At 37 °C, chitosan and a substantial amount of negatively charged black phosphorus nanosheets (BPNS) form a hydrogel through electrostatic interaction, which is conducive to maintaining a moist environment for wound healing. Additionally, the cationic groups within chitosan molecules are capable of interacting with anions on red blood cells, thereby inducing platelet aggregation and exerting a hemostatic effect. Furthermore, copper nanoparticles loaded in the hydrogel can generate ROS through Oxidation-Reduction (REDOX) reactions, effectively inhibiting the proliferation of *Escherichia coli* and *Staphylococcus aureus* while also promoting fibrinogen formation to accelerate postoperative wound scabbing and healing. Lastly, leveraging the exceptional photothermal effect of BPNS, near-infrared (NIR) irradiation can facilitate the biodegradation of the gel into hydrogel fragments that traverse the blood tumor barrier, ultimately inducing chemodynamic therapy (CDT) effects leading to brain cancer cell death.

β-GP is commonly utilized as a proton acceptor for chitosan, facilitating the transformation of pH-gelated cationic polysaccharide solution into a thermo-dependent gelated aqueous solution. Chen et al. developed a thermosensitive hydrogel using chitosan, gelatin and β-GP as a proton acceptor [99]. At physiological temperature and near neutral pH, the mixture remains in a liquid state. However, gelation occurs upon injection into the resection cavity of GBM within approximately 2 min.

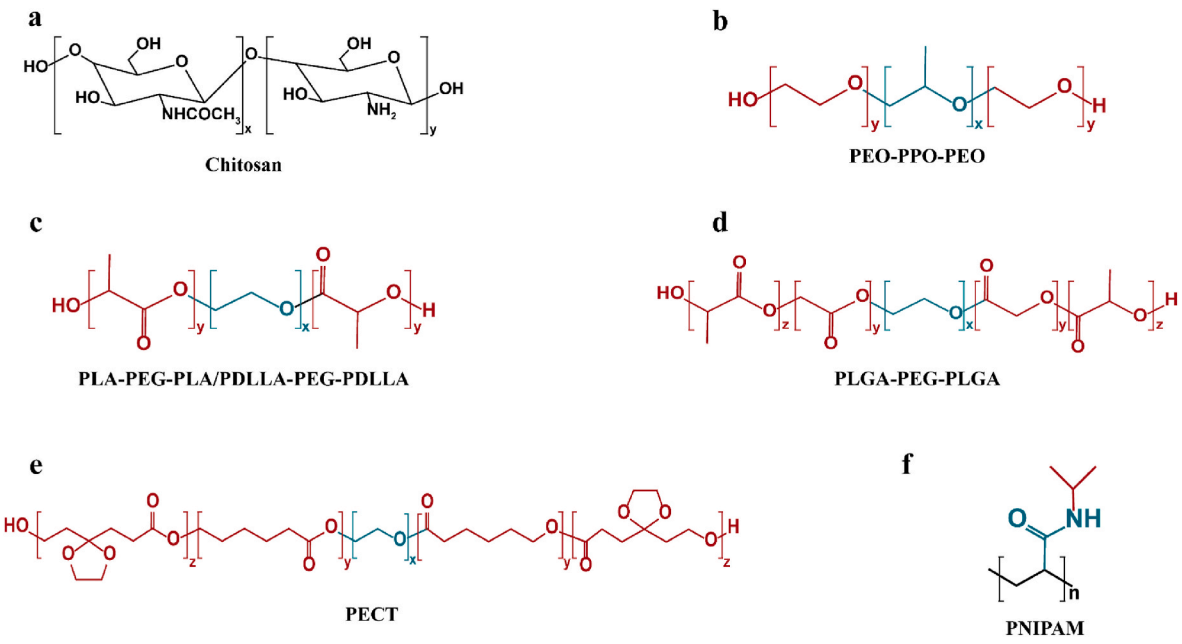

Fig. 6. The structural formula of (a) chitosan, (b) poloxamer, (c) PLA-PEG-PLA, PDLLA-PEG-PDLLA, (d) PLGA-PEG-PLGA, (e) PECT and (f) PNIPAM.

Table 1
Temperature-sensitive materials and their applications.

Types		LCST	Applications	References
Chitosan	Chitosan	37 °C	PPT; CDT; Immunotherapy; Hemostasis; Antibacterial; Wound healing.	[21]
	Chitosan/gelatin/β-GP	26.5 °C	Chemotherapy	[99]
	Chitosan/β-GP	37 °C	Immunotherapy; PPT	[28]
	CSSH/HNTs-SH	37 °C	Chemotherapy	[101]
Poloxamer	F127	25 °C	Immunotherapy; PPT	[111]
	P407/P188/carbomer 974P	33.1 °C	Chemotherapy	[119]
	F127/HA	25 °C	Immunotherapy	[120]
	F127-g-Gelatin	37 °C	Immunotherapy	[124]
PEG/ polyester	PLA-PEG-PLA	35.07–35.88 °C	Chemotherapy	[141].
	PLA-PEG-PLA	32 °C	Magnetic hyperthermia; Chemotherapy	[131]
	PLGA-PEG-PLGA	15 °C	Chemotherapy	[142]
	Two PLGA-PEG-PLGA with different PEG/PLGA ratios	23 °C; 31 °C	Immunotherapy	[144]
	Two PLGA-PEG-PLGA with different PEG/PLGA ratios	39 °C	Immunotherapy	[145]
	PDLLA-PEG-PDLLA	37 °C	Chemotherapy	[146]
	PDLLA-PEG-PDLLA	34 °C	Chemotherapy Immunotherapy	[136]
	PDLLA-PEG-PDLLA	37 °C	PPT; Immunotherapy	[147]
	PECT	37 °C	Chemotherapy	[152]
	PECT-Cur NPs	35 °C	Immunotherapy	[153]
PNIPAM	PNIPAM	32.3 °C	Immunotherapy	[157]
	pNIPAAm-co-AAc	39 °C	Starvation therapy	[158].

The mechanism of gelation involves electrostatic attraction between ammonium ions and phosphate groups, hydrophobic interaction between chitosan molecules facilitated by glycerol, and enhanced hydrogen bond formation between chitosan chains in the presence of salt solution [100]. Similarly, Meng et al. prepared a formulation by mixing R837 nanocrystals coated with polydopamine (PDA) with chitosan and β-GP, which was then administered *via* injection into mouse melanoma [28]. The combination with PTT led to the transformation of the tumor into an *in-situ* vaccine, effectively promoting DCs maturation. Ultimately, the proposed hydrogel achieved a remarkable tumor inhibition rate of 90.8 %.

Functional groups within the chitosan molecule, such as -NH2 and -OH, have the potential for chemical modification, enabling them to respond and release substances according to specific requirements. Li et al. developed a hydrogel (DOX@CSSH/HNTs-SH Gel) through the formation of disulfide bonding and electrostatic interaction at 37 °C [101](Fig. 7a). This was accomplished by blending thiolated chitosan with doxorubicin (DOX)-loaded thiolated halloysite nanotubes (HNTs-SH) for approximately 117 s, resulting in a gelation time lower than that of DOX@CSSH hydrogel (151s)(Fig. 7b). The crosslinking with HNTs-SH effectively enhances the mechanical properties of the hydrogel (Fig. 7c). To mimic the acidic tumor microenvironment, the DOX@CSSH/HNTs-SH gel demonstrated complete release of DOX after 120 h at a pH of 5.5. This effectively suppresses the proliferation of MCF-7 cells, recurrence of breast cancer, and lung metastasis. Chitosan-based thermo-sensitive materials have been extensively employed in the postoperative treatment of cancer due to their ability to promote wound healing, hemostasis, and antibacterial effects. In addition to chitosan, methyl cellulose [102], chitin [103], agarose [104] and other natural thermo-sensitive materials are frequently employed in HLDDS aimed at preventing tumor recurrence. Natural polymers not only exhibit biodegradability, biocompatibility, biomolecular recognition, and low cost, but also demonstrate diverse molecular weights, and various structural reaction groups, amenable to chemical modification.

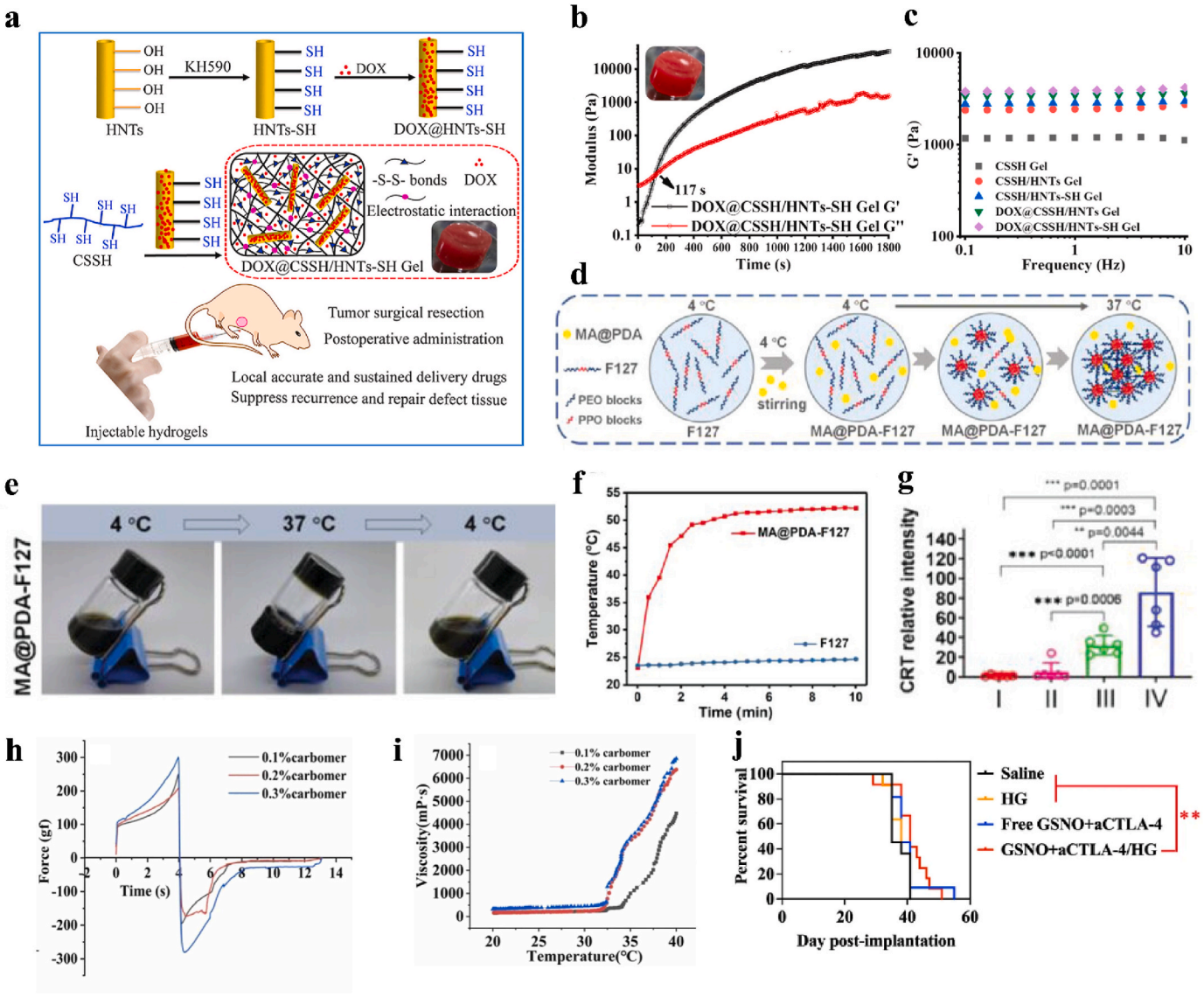

Fig. 7. Chitosan and Poloxamer-based *in-situ* HLDDS prevent tumor recurrence. (a) Schematic illustration of the synthesis procedure for DOX@CSSH/HNTs-SH Gel and its application in inhibiting tumor recurrence. (b) The gelation time of DOX@CSSH/HNTs-SH Gel. (c) The G′ values of different hydrogels varied with frequency in frequency sweep mode. (d) Illustration of the preparation process of MA@PDA-F127. (e) Optical photograph depicting the sol-gel transition of MA@PDA-F127 hydrogels in response to temperature changes. (f) Photothermal heating curves of MA@PDA-F127 hydrogels under irradiation by an 808 nm laser with a power density of 1.5 W cm^{-2}. (g) Quantification of Calreticulin (CRT) expression in 4T1 cells following various treatments. (h) Texture curve of PTX-NCS-gel prepared with 0.1 %, 0.2 %, and 0.3 % carbomer, and the area under the curve is expressed as adhesion. (i) Temperature viscosity curves of PTX-NCS-gel prepared with 0.1 %, 0.2 %, and 0.3 % carbomer. (j) Kaplan–Meier survival curves of 4T1 tumor models after different treatments. Reproduced from Refs. [101,111,119,124] with permission from Elsevier, Wiley and Springer Nature.

However, the majority of natural materials are composed of polysaccharide compounds. While they excel in water absorption and retention, their mechanical properties are poor, making them prone to rupture or deformation. Consequently, there have been numerous reports on amphiphilic synthetic polymers-based HLDDS.

5.2.2. *Poloxamer-based HLDDS*

Poloxamer belongs to the class of poly (ethylene oxide) -poly (propylene oxide) -poly (ethylene oxide) (PEO-PPO-PEO) amphiphilic triblock copolymer, with the molecular formula $HO{\cdot}(C_2H_4O)m{\cdot}(C_3H_6O)_n{\cdot}H$, which is synthesized through ring-opening polymerization of ethylene oxide and propylene oxide(Fig. 6b) [105]. Currently, Pluronics®, Kolliphor® (BASF), Synperonics® (Croda) and various other brands are available in the market [106]. Serving as a widely utilized thermosensitive HLDDS matrix, poloxamer undergoes hydrogel formation *via* two processes, micellar and gelation, both of which are influenced by temperature or concentration variations [106–110]. At critical micelle temperature (CMC), the polymer is capable of forming core-shell micelles in aqueous solution. The non-polar PPO forms a hydrophobic core through van der Waals force, while the polar PEO segments form hydrophilic shell structures through hydrogen bonding with solvents. As the temperature continued to increase and surpassed the LCST, the polymer concentration reached the critical gel concentration (CGC), and the PEO surface underwent dehydration, leading to the organized accumulation of micelles into a cubic hydrogel structure [107,108]. Different poloxamers exhibit unique properties attributed to different PEO and PPO block ratios or molecular weights. Among them, Pluronics F68 or Pluronics 188 (EO80-PO30-EO80), F127 or P407 (EO100-PO65-EO100) have been approved by the U.S. Food and Drug Administration (FDA) for biomedical applications. Their exceptional biocompatibility and thermosensitive hydrogel formation capability render them highly promising for the development of HLDDS for

anti-cancer and anti-recurrence therapies. For instance, Meng et al. demonstrated successful loading of PDA-coated *Microcystis aerugiosa* into Pluronics F-127 hydrogel and activation of systemic anti-tumor immunity through PTT and immunotherapy [111]. The precursor solution is capable of being easily administered into the cavity *via* a syringe or a sprayer. Upon exposure to body temperature, the 25 % W/V F127 solution rapidly transitions into a semi-solid state and can be reverted to a liquid state at low temperatures, facilitating localized drug release while minimizing biological toxicity to normal tissues (Fig. 7d–e). Upon 808 nm laser irradiation and microcystin induction, tumor cells underwent ICD, thereby enhancing DCs maturation, T cell activation, and eliciting a systemic immune response (Fig. 7f–g).

However, the HLDDS consisted of only one type of poloxamer that exhibits inherent limitations. Upon contact with bodily fluids, the concentration may be diluted below the CGC, leading to an inability to maintain its three-dimensional structure. This phenomenon might result in poor mechanical strength, burst release and weak adhesion, which make it unsuitable for most applications [112–114]. Various methods have been investigated to develop a more robust and controlled release HLDDS, including physical mixing and chemical modification. The combination of two varieties of poloxamer to strengthen the gel network, commonly blending P188 with F127 [112,115], as well as blending poloxamer with other excipients or conjugating it with other polymers [116,117] are frequently investigated. For instance, carbomer has been commonly utilized as a hydrogel thickener and adhesive in these formulations [118]. Fan et al. incorporated carbomer 974P into the mixed solution of F127 and F68 to modulate adhesion and gelation temperature [119]. It was observed that as the concentration of carbomer 974P increased from 0.1 % m/v to 0.3 % m/v, the adhesion of the hydrogel to mouse tissue increased from 436.35gf * s to 770.55gf * s, while the gelation temperature decreased from 34 °C to 32.3 °C (Fig. 7h–i). This thermosensitive hydrogel, when loaded with paclitaxel (PTX) nanocrystals, effectively prevents PTX leakage and significantly inhibits post-surgery breast cancer recurrence. An additional example involves the development of a thermosensitive hydrogel through the physical combination of HA with F127, which demonstrates an improvement in mechanical strength and gel stability [120]. With the assistance of $CaCO_3$ NP, the hydrogel-encapsulated membranomycin and catalase-loaded therapeutic nanoplatform (TCCaN), along with granulocyte-macrophage colony-stimulating factor, serve to enhance macrophage-mediated phagocytosis. This formulation up-regulates the expression of pro-phagocytosis signals, effectively inhibiting tumor development and recurrence. Additionally, poloxamer can be combined with chitosan [121], xanthan gum [122], alginate [115,123]and other adhesive compounds to enhance the mechanical strength of pure poloxamer hydrogel.

In addition to physical mixing, poloxamer can also undergo chemical modification and covalent linkage to other compounds. For instance, Kim et al. covalently linked F127 to gelatin to design a thermo-sensitive gel capable of delivering S-nitroso glutathione and aCTLA-4 [124]. The CGC of the grafted F127-G-gelatin polymer (4.0–7.0 wt%) was proved to be much lower than that of F-127 hydrogel alone (20 wt%) [125]. Furthermore, it effectively suppresses the proliferation and distal metastasis of melanoma (Fig. 7j). Additionally, linoleic acid also presents as a favorable option to prolong hydrogel retention time at the tumor site for extended drug release [126].

It is worth noting that when selecting the adhesive or conjugate type and concentration, several key considerations should be taken into account: (1) ensuring biocompatibility and biodegradability; (2) ensuring appropriate viscosity of the mixed hydrogel at low temperatures to enable delivery to the lesion site through a narrow needle; and (3) regulating gelation time and temperature to ensure complete filling of the surgical cavity before gelation. However, despite its excellent physical and chemical properties following adhesive addition, poloxamer HLDDS's biomedical application remains limited due to its non-degradability and potential for accumulation in the body, leading to an increase in triglyceride levels following the operation [105, 127–129]. Therefore, the temperature-sensitive biodegradable polymers have been investigated extensively in recent years.

5.2.3. PEG/polyester triblock polymer-based HLDDS

Similar to poloxamer, polyethylene glycol (PEG) triblock copolymers have also been extensively studied. These thermo-sensitive biodegradable polymers are composed of PEG and biodegradable polyester. PEG and PEO share a similar structure with comparable carbon chain skeletons, although PEO terminated by a methyl group whereas PEG terminated by a hydroxyl group. Both of them exhibit high solubility in water [130]. Cross-linking PEG with degradable polyesters such as polylactic acid (PLA) [131], poly-(lactate-glycolic acid) (PLGA) [132–134], poly-DL-lactic acid (PDLLA) [135,136] *etc.,* results in the formation of amphiphilic polyblock copolymers, denoted as PEG-X-PEG or X-PEG-X (where X represents polyester). And akin to poloxamer, these copolymers have the potential to self-assemble into micelles and undergo gelation in response to changes in concentration and temperature [127,137–140].

PLA, also known as polylactide, is among the earliest reported biodegradable polyester polymers (Fig. 6c). It can undergo hydrolysis to lactic acid monomer and ultimately degrade into CO_2 and H_2O *in vivo*, which can be excreted through normal metabolic pathways without causing evident physiological toxicity. Triblock copolymers synthesized from PLA and PEG exhibit favorable biocompatibility and hold promising potential in the construction of postsurgical HLDDS. Huang et al. developed an ozone-loaded perfluorotributylamine nanoemulsion (O_3/PFTBA@LIP) with a perfluorobutylamine core and lipid monolayer, encapsulated in PLA-PEG-PLA thermo-sensitive hydrogel [141]. With a sol-gel transition temperature range of 35.07–35.88 °C, the hydrogel precursor solution is administered into the surgical cavity using a sprayer, allowing for phase transition induced by body temperature (Fig. 8a–b). The findings revealed that this strategy can induce ferroptosis and apoptosis by modulating the expression of relevant genes (GPX4, ACSL4, CDKN1A, *etc.*) (Fig. 8c). Subsequently, a subcutaneous HuH-7 xenograft-bearing mice model was established and one-week post-surgical resection, the ozone gel group demonstrated significant inhibition of tumor recurrence, prolonging the survival time of mice bearing tumors. Similarly, Choi et al. proposed a PLA-PEG-PLA hydrogel incorporating DOX-loaded micelles and water-dispersible ferrimagnetic iron oxide nanocubes into the resected GBM tumor cavity [131]. The sol-gel transition at 32 °C occurs within approximately 40 s. Fluorescence imaging further demonstrates immediate gelation of the nanocomposite solution upon injection into the artificial brain parenchyma, forming a seamless interface. This approach significantly suppressed tumor growth and enhanced survival in an orthotopic mouse GBM model. However, significant efforts have been devoted to the pursuit of polymers with enhanced hydrogel properties (such as, reduced CGC, slower drug release rate, and improved mechanical strength), and address the limitations of PLA, which is excessively hydrophobic and prone to crystallization and precipitation. As a result, polyester polyether block polymers such as PLGA-PEG-PLGA and PDLLA-PEG-PDLLA have been successfully synthesized.

PLGA, a copolymer of PLA and polyglycolic acid (PGA), has emerged as the predominant polymer in the biomedical field since 1970 due to its complete biodegradability (Fig. 6d). Micromed company has developed a PLGA-PEG-PLGA hydrogel formulation (OncoGel) specifically for the local delivery of PTX to treat esophageal cancer and brain tumors. In one study, Gao et al. employed this formulation along with microspheres to construct a dual-controlled local release system (OL-M/Gel), with a gelation time of approximately 80 s at the LCST of 37 °C [142](Fig. 8d). And this HLDDS enabled slow local release of oleandrin (OL) within the microsphere/gel matrix, resulting in only 5.38 % cumulative release within 24 h (Fig. 8e). This strategy effectively mitigates potential cardiac side effects associated with rapid OL release from microspheres alone. However, due to the composition window of PLGA-PEG-PLGA

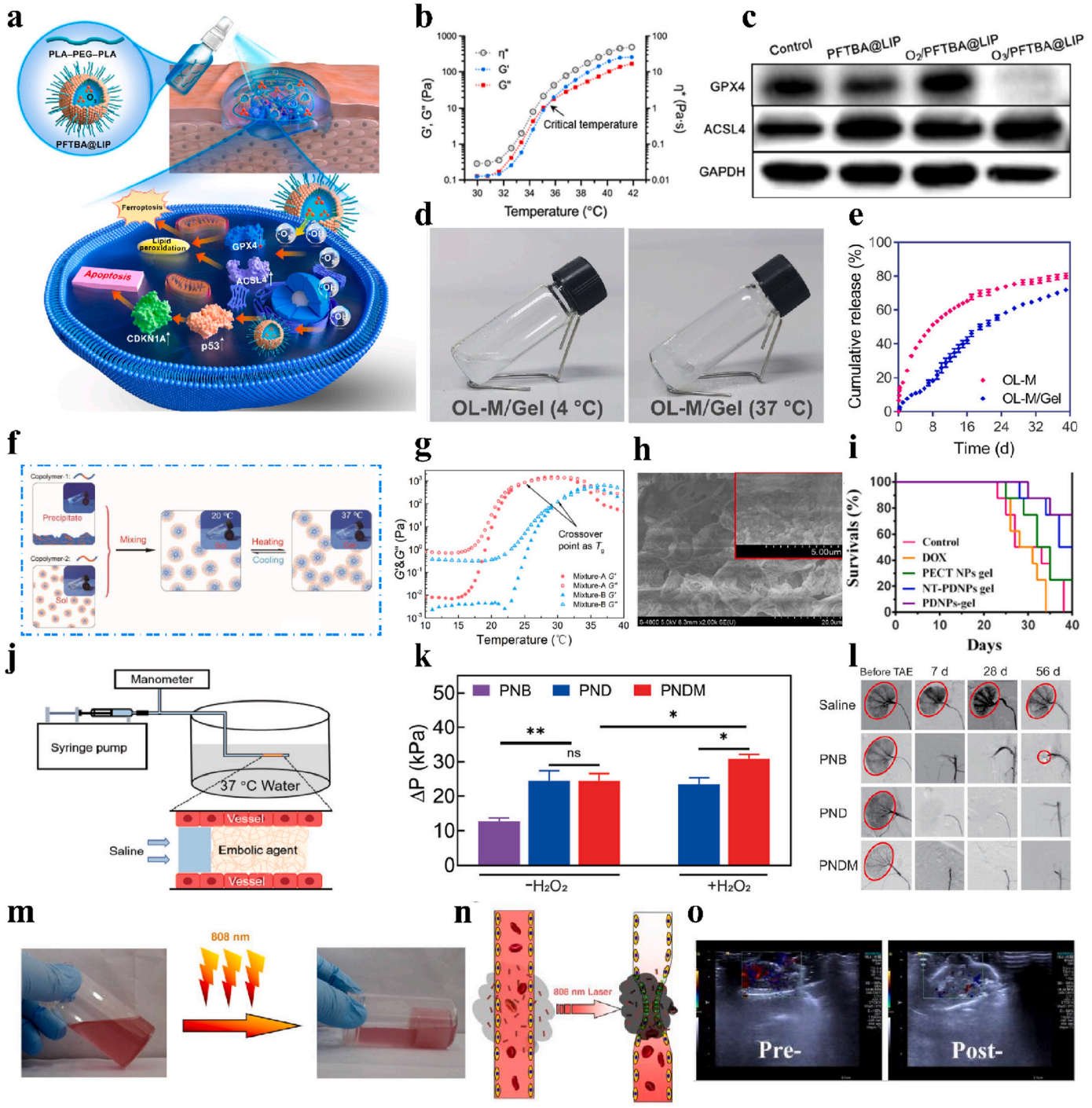

Fig. 8. PEG/polyester triblock polymer and PNIPAM-based *in-situ* HLDDS for preventing tumor recurrence. (a) Schematic illustration of O_3/PFTBA@LIP Gel for the Postsurgical Treatment of HCC. (b) Variations in the complex viscosity (η*), G′ and G″ of PFTBA@LIP@Gel were plotted as a function of temperature (30–42 °C). (c) Western blot analysis of the expression of GPX4 and ACSL4 in HuH-7 cells 12 h after indicated treatments. (d) Sol–gel transition images of OL-M/Gel, sol at 4 °C and gel at 37 °C. (e) The drug release of OL-M and OL-M/Gel. (f) Schematic illustration of the synthesis procedure for PLGA-PEG-PLGA hydrogel by mixing two PLGA-PEG-PLGA triblock copolymers with different PEG/PLGA proportion. (g) The G′ and G″ of the two copolymer mixtures as a function of temperature. (h) SEM images of the PDNPs-gel. (i) Survival rates of mice treated with different formulations after resection of tumor. (j) Schematic diagram of the device for simulating an embolized vessel with different materials flushed by a blood flow *in vitro*. (k) Minimum pressure required to push the various plug forward by normal saline (control) or normal saline containing H_2O_2 at 37 °C. (l) DSA images of kidneys of all five experimental rabbits in each group. (m) The gelation of hydrogel–GNR by 808 nm irradiation. (n) Schematic representation of *in vivo* extravascular gelation shrinkage-induced internal stress to constrict blood vessels upon exposure to an 808 nm laser. (o) CDFI images of the PANC-1 tumor and its periphery before and after the special treatment. Reproduced from Refs. [141,142,144,152,157,158] with permission from American Chemical Society, American Chemical Society, Ivyspring International, American Chemical Society, Wiley, and Springer Nature.

triblock copolymers to achieve a thermosensitive hydrogel being very narrow [143], two triblock copolymers with different PEG/PLGA ratios were mixed to construct a thermo-sensitive hydrogel by Ding et al. [144]. This mixture achieved thermoresponsive gelation at physiological temperature and encapsulate Herceptin for targeted delivery to HER2+ breast tumor cells. Interestingly, neither polymer individually forms a thermo-sensitive gel in water; however, when the two are combined, a thermo-sensitive gel is designed successfully (Fig. 8f). By adjusting the mixture ratio from 7:3 to 5:5, the LCST can be easily controlled within the range of 23 to 31 °C (Fig. 8g). The engineered mixed gel system demonstrated sustained drug release over 80 days, effectively mitigating cardiotoxic side effects associated with the therapeutic agent. Furthermore, the biodegradable nature of the gel matrix facilitated complete *in vitro* and *in vivo* degradation within 2 months. Additionally, the incorporation of calcium sources ($CaCl_2$ and $CaCO_3$) along with the immunoadjuvant R837 into the mixed hydrogel resulted in a prophylactic therapeutic vaccine gel, which exhibited direct eradication of residual breast cancer cells post-surgery through induction of ICD and activation of systemic immune response [145]. By adjusting the block length or composition ratio, appropriate PLGA/PEG copolymers can be designed, showing promising potential for application in HLDDS.

PDLLA-PEG-PDLLA triblock copolymer, synthesized through ring-opening copolymerization of PEG with D, L-lactic, a kind of racemic lactic acid, is also a hydrogel matrix with thermo-sensitive properties (PLEL hydrogel) (Fig. 6c). The polymer can be utilized for targeted delivery of chemotherapy drugs 5-fluorouracil (5-FU) and cisplatin (DDP) to the resection cavity of gastric tumors [146]. The precursor solution underwent rapid *in-situ* gelation using a 24G syringe, resulting in continuous release of 5-FU and DDP in the abdominal cavity over one week, effectively suppressing local tumor recurrence. The relative inhibition rate of tumor growth was approximately 88.04 %, with approximately 20 % of the mice surviving for 60 days. Additionally, PLEL hydrogels have the capability to deliver immune adjuvants as well. Qian et al. developed a combined immunotherapy strategy utilizing PLEL hydrogel [136]. Initially, the hydrogel containing cyclophosphamide (CTX) was intratumorally injected into CT26 tumor-bearing mice to induce tumor cell death and release tumor antigens, thereby initiating an anti-tumor immune response. Subsequently, 3 days later, a PLEL hydrogel vaccine containing the adjuvant cytosine-phosphate-guanine oligonucleotide (CpG-ODN) and tumor lysate was subcutaneously injected into the bilateral groin to generate a cancer vaccine, which facilitated the maturation and activation of immune cells and promoted anti-tumor immunity. Similarly, the group has also developed another local injection treatment platform utilizing PPT. This platform incorporates the photothermal agent indocyanine green and triggers the release of immune adjuvants CPG ODN and resiquimod through NIR to prevent post-surgical recurrence of breast cancer [147]. Qian and colleagues have demonstrated that the LCST of PLEL gel can be adjusted within a physiological temperature range by manipulating molecular weight, segment length, and polymer concentration [148]. This versatile hydrogel not only shows promise in reducing postoperative adhesion but also holds potential for combination with various treatment approaches aimed at preventing postoperative recurrence.

The PECT copolymer, poly (ε-Caprolactone-co-1,4,8-trioxa [4.6] spiro-9-undecanone)-B-poly-(ethylene glycol)-B-poly (ε-caprolactone)-co-1,4,8-trioxa[4.6]-spiro-9-undecanone), is derived from the modification of poly(ε-caprolactone) (PCL) with cyclic ether pendant groups (Fig. 6e). It also exhibits the ability to self-assemble into micelles and hydrogels at elevated temperatures [149,150]. The PECT, developed by Wang et al., represents a novel PEG-type triblock copolymer that addresses some of the limitations associated with previous PEG/polyester compounds [151]. For instance, unlike PEG/PCL, which requires dissolution at higher temperatures, and PLGA/PEG, which forms a thick semi-solid at room temperature, posing inconveniences in weight and transference. PECT exists in a particulate state at room temperature and can be rapidly dispersed in water. Upon injection *in vivo*, it undergoes gelation *in-situ*, offering convenience for preparation storage and clinical application. Liu et al. developed a thermo-sensitive and novel tumor-specific prodrug NP self-aggregated hydrogel (PDNPs-gel) comprising PECT as hydrogel matrix, doxorubicin (DOX)-PECT-DOX as drugs, and CRGDK-PEG-PCL as targeted modules (Fig. 8h) [152]. The aqueous solution exhibits good fluidity at room temperature with a viscosity of approximately 100 Pa s and undergoes spontaneous gelation at 37 °C, effectively inhibiting tumor recurrence (Fig. 8i). Similarly, curcumin (Cur) can be encapsulated in PECT nanoparticles *via* hydrophobic interaction with PECT and integrated with nanovaccines to construct a hydrogel drug library [153]. Upon reaching 30 °C, the G′ value exhibits a sharp increase, subsequently surpassing the G ″, indicating the initiation of hydrogel formation. A single administration of the hydrogel formulation at the surgical cavity demonstrated markedly improved suppression of local tumor recurrence and metastasis to the lung.

To sum up, PEG-polyester triblock polymers with biodegradability exhibit an advantage over poloxamer in terms of biocompatibility. However, it is important to note that not all PEG-polyester triblock copolymers demonstrate temperature sensitivity, and their gelling behavior is intricately linked to the composition of polyester blocks, as well as the MW and molecular weight distribution of the copolymers. Achieving an optimal balance between hydrophilicity and hydrophobicity is crucial for developing gels that meet specific requirements.

5.2.4. PNIPAM-based HLDDS

Polyn-isopropylacrylamide (PNIPAM) is a thermo-sensitive polymer material that can be dispersed in aqueous solution and respond to changes in ambient temperature. Its structure includes a hydrophilic amide (-CONH-) and a hydrophobic isopropyl (-CH $(CH_3)_2$), with an LCST of approximately 32 °C [154,155]. Below the LCST temperature, the amide group of the polymer chain forms hydrogen bonds with surrounding water molecules, resulting in good affinity with the solvent and presenting a liquid state with robust fluidity. As the temperature increases, the partial hydrogen bond between PNIPAM and water is disrupted, enhancing the effect of the hydrophobic isopropyl group. Consequently, this leads to a transition from a loose coil structure to a tight colloidal structure, thereby demonstrating its temperature sensitivity [156]. Due to its LCST being close to body temperature, PNIPAM has been extensively studied for its potential to serve as *in-situ* HLDDS for anti-cancer and anti-recurrence with embolization treatment. For example, the novel liquid embolic agent Pepsin™, a world-first thermo-sensitive liquid embolic agent developed in China, is primarily utilized in the embolization treatment of hemodynamic malignancy. Zhang et al. have successfully synthesized an embolization material using PNIPAM [157]. The experimental results have demonstrated that the hydrogel is capable of withstanding about 25 kPa pressure without loosening in rabbit abdominal blood vessels, which is approximately 1.5 times the physiological pressure (about 16 kPa) (Fig. 8j–k). Due to its strong adhesion, the hydrogel has been able to effectively embolize renal vessels for up to 84 days, leading to significant kidney necrosis and atrophy (Fig. 8l).

However, similar to poloxamer, the use of PNIPAM as HLDDS matrix alone exhibits poor biodegradability, weak mechanical strength, and easy drug release. Therefore, PNIPAM is frequently combined with other compounds or subjected to chemical modification to enhance the physical and chemical characteristics. Zhang et al. developed a composite hydrogel containing PEG-SH-modified gold nanorods (GNR-PEG-SH) and a composite hydrogel matrix (CS/mPEG-Mal/pNIPAAm-co-AAc) for starvation therapy [158]. The introduction of acrylic acid (AAc) resulted in an increase in the LCST of the gel from 32 °C to 38.7 °C, and the sol-gel phase transition was induced under light and heat conversion by an 808 nm laser (Fig. 8m). This starvation strategy has the potential to suppress tumor metastasis and recurrence by decreasing blood vessel density and blood supply, offering a promising approach for the comprehensive treatment of tumors (Fig. 8n–o).

PNIPAM is commonly utilized in embolization therapy. To more effectively prevent tumor recurrence, scientists are exploring the potential of combining embolization with other modalities including immunotherapy, PTT, radiotherapy, and chemotherapy to activate systemic immunity. Nevertheless, the drug loading capacity of hydrophobic chemotherapy agents like PTX and DOX supported by PNIPAM hydrogel remains suboptimal due to a lack of hydrophobic binding sites. Therefore, further modifications or the incorporation of additional compounds are necessary to prepare mixed hydrogels with desired properties.

Among all the factors influencing hydrogel formation, temperature stands out as the most easily controllable factor. And it is noteworthy that the LCST of thermosensitive hydrogels can be easily modulated by adjusting the type and proportion of thermosensitive materials. Consequently, among various *in-situ* HLDDS, thermosensitive gels have garnered the most attention and research.

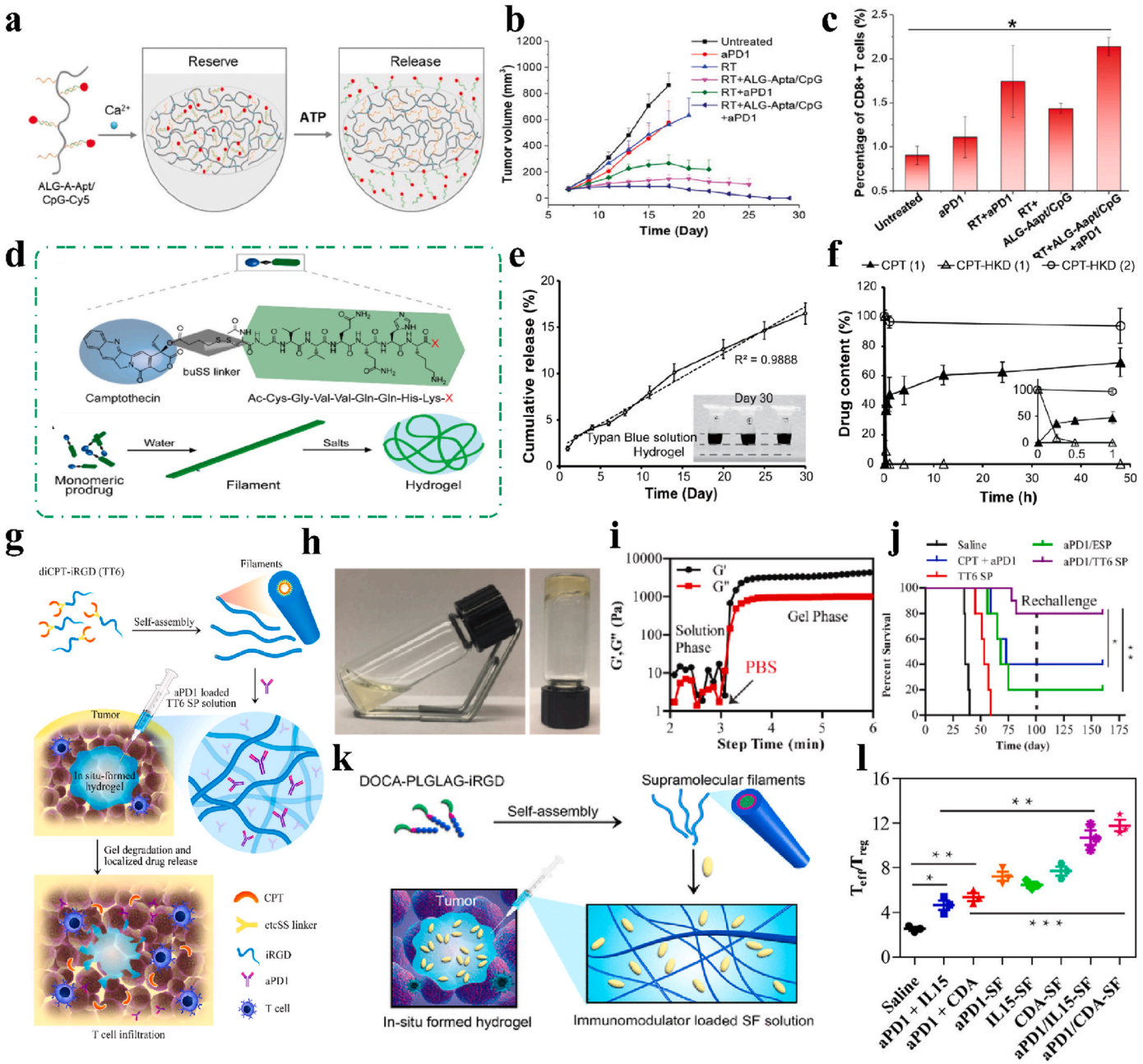

Fig. 9. Ion sensitive *in-situ* HLDDS prevents tumor recurrence. (a) Schematic diagram to show the construction of ALG-Aapt/CpG hydrogel and the release of CpG from the hydrogel in response to ATP. (b) Distal tumor growth curves and (c) percentage of CD8+T cells in distal tumors under various treatment modalities. (d) Chemical structures of the designed CPT prodrug, subsequently self-assembling into supramolecular filaments which upon addition of counterions form a hydrogel. (e) Cumulative release profile of CPT prodrugs from their composed hydrogel in DPBS at 37 °C over 30 days. (f) Effective conversion of CPT-HKD prodrug into active free CPT in DPBS. (g) Schematic illustration of TT6 SP hydrogel for local delivery of aPD1 against malignant tumors. (h) Pictures of the aPD1/TT6 SP solution before and after the addition of PBS. (i) G′ and G″ of TT6 solution from time sweep rheology measurements at 37 °C. The addition of PBS to TT6 solution at 180 s resulted in a rapid increase in G′, indicating the formation of a supramolecular hydrogel. (j) Kaplan-Meier survival curves for rechallenged mice corresponding to the indicated treatments. (k) Schematic illustration of DOCA-PLGLAG-iRGD supramolecular hydrogel. (l) Ratios of the $CD8^+$ T cells to regulatory T cells in tumors corresponding to different treatment groups. Reproduced from Refs. [161,168–170] with permission from Wiley, Elsevier and ACS Publications.

5.3. Ion-sensitive in-situ HLDDS

As a crucial mediator in the regulation of diverse cellular physiological processes, the tumor microenvironment is characterized by high levels of Ca^{2+} [159] and K^{+} [160]. Certain HLDDS are capable of undergoing *in-situ* sol-gel phase transition in response to the presence of ions within the tumor microenvironment or from an external source, leading to the formation of three-dimensional structures known as ion-sensitive *in-situ* hydrogels. One prominent example of ion-sensitive *in-situ* hydrogels is composed of sodium alginate (SA) and Ca^{2+}. For instance, Luan et al. designed an injectable tumor lysate **(O-TL)**-based hydrogel. The oxidized sodium alginate (OSA)-modified tumor lysates were designed as the matrix [22]. Upon subcutaneous injection into C57BL/6 mice, the drug-loaded precursor solution can rapidly form a hydrogel in the Ca^{2+}-rich tumor microenvironment and degrade within 12 days, serving as an antigen reservoir to provide immune stimulation signals. This led to significantly improved tumor invasion and killing function of T cells. Additionally, SA was combined with ATP-specific aptamer(Aapt)and hybridized with immune adjuvant CpG-ODN to form smart SA-based hydrogels(ALG-Aapt/CpG hydrogel) *in-situ* upon injection into the tumor [161]. This innovative design enables the intelligent hydrogel to react to the ATP released as a result of ICD of tumor cells during chemotherapy or radiotherapy (Fig. 9a). As a result, it releases the immune adjuvant CpG ONDs, effectively enhancing the anti-tumor immune response and delaying the growth of distant tumors (Fig. 9b–c).

In addition, supramolecular peptide hydrogels (SPH) can also undergo gelation in response to ions present in tumor tissue fluid. Peptide compounds are capable of self-assembly through hydrogen bonding, hydrophobic interaction, chelation effect and π-π stacking under physiological conditions [162–164], subsequently, the three-dimensional structure formed by self-assembly has found widespread applications in drug delivery, gene delivery, biologics delivery and cell culture. They can form stable network structures *in vivo* with controllable physical and chemical properties [165]. Peptides containing functional side chain amino acids (such as lysine, glutamic acid, cysteine, and serine) can be conjugated with drug molecules to produce prodrugs that enhance the solubility of hydrophobic drugs thereby increasing bioavailability and efficacy [166,167]. When a hydrophilic peptide, such as a cell-penetrating peptide, iRGD, is covalently linked to an anticancer drug, it can lead to the formation of a self-assembled prodrug with a filamentous nanostructure. Upon exposure to the ion-rich interstitial fluid in the tumor environment, these prodrugs have the potential to further coil and form a supramolecular hydrogel. This hydrogel not only facilitates the gradual release of its drug components at the treatment site but also serves as a reservoir for other bioactive drugs. For instance, dithiobutyrate (buSS) is utilized to conjugate camptothecin (CPT) with amphiphilic peptides to produce self-assembling prodrugs, which spontaneously form supramolecular fibers when dispersed in aqueous solution containing ions [168]. The resulting fibers can form a hydrogel with a three-dimensional structure, and subsequently release CPT in a steady manner (Fig. 9d). Approximately 17 % of the prodrug is released at a near-linear rate after 30 days of release in DPBS (Fig. 9e). Following this, when GSH is present, the prodrug can be converted into CPT (Fig. 9f), effectively treating GBM in situ in excised and relapsed mouse models. Cui et al. have developed a supramolecular tubulin (TT) hydrogel with dual functionality as both a therapeutic agent and a carrier for aPD1 [169]. The prodrug TT6, formed by chemically coupling two CPT molecules to iRGD peptide *via* disulfonyl ethyl carbonate (etcSS) linker, spontaneously assembles into a supramolecular hydrogel (TT6 SP hydrogel) in PBS. (Fig. 9g–i). *In vivo*, the results demonstrate that this chemical-immunotherapeutic hydrogel is capable of inducing a long-term systemic anticancer T cell immune response, leading to tumor regression and simultaneous inhibition of tumor recurrence (Fig. 9j). Similarly, the group has synthesized an amphiphilic molecule, DOCA-PLGLAG-iRGD, comprised of deoxycholic acid (DOCA), hydrophilic iRGD peptide, and matrix metalloproteinase 2, which self-assembles into filamentous nanostructures in aqueous solution to form a three-dimensional gel for immunotherapy(Fig. 9k–l) [170].

Ionic cross-linked hydrogels have been extensively developed due to the stimulation by internal tumor site ions and tissue fluid. However, in addition to the endogenous ion-triggered crosslinking provided by the tumor microenvironment, a dual drug dosing device is utilized to introduce exogenous ions for triggering in situ gel formation. For instance, Chen et al. loaded SA solution and $CaCl_2$ solution into each channel of dual-cartridge sprayer and simultaneously sprayed the wound after melanoma surgery, resulting in gel formation at the cavity. This approach not only enables localized drug release to prevent tumor recurrence and metastasis but also facilitates wound healing, demonstrating significant potential for postoperative cancer treatment [171].

5.4. Photocuring in-situ HLDDS

Light can also serve as a stimulant for the phase transition of HLDDS, offering spatiotemporal controllable characteristics. Photosensitive groups within photoresponsive materials can capture light signals and subsequently undergo processes such as photoisomerization, photocracking, addition, and the generation of photoinduced free radicals and other photoreactions. These processes enable the conversion of light irradiation into chemical signals, ultimately leading to alterations in the physical and chemical properties of the precursor solution, resulting in gel formation [172,173]. The combination of methylacrylylation or acrylylation polymers, including functional groups with double bonds, and initiators is commonly utilized for the preparation of photocuring-formation HLDDS intended for biological applications. After the subcutaneous injection, a highly fluid precursor solution rapidly fills the surgical cavity and subsequently undergoes photoinitiated free radical polymerization to form a hydrogel. Under the illumination of a light source, the photoinitiator absorbs photons and undergoes a process of cracking into free radicals [174]. These free radicals then proceed to react with the vinyl bonds present in the polymer, leading to chemical cross-linking between polymer chains and ultimately resulting in the formation of hydrogels [175,176]. Currently utilized photocuring polymers include gelatin methacryloyl (GELMA) [13,177], poly (ethylene glycol) dimethacrylate (PEG-DMA), fibroin protein methacryloyl (SilMA), hyaluronic acid methacryloyl (HAMA), polyether F127 methacryloyl (F127MA) [178]. For instance, in the presence of polycitrate-dopamine (PCD) and Fe^{3+} ions, a double network hydrogel was fabricated through GELMA photo-crosslinking under I 2959 photoinitiator, and the precursor solution could transform into a semi-solid state(GPDF hydrogel) within 60 s of ultraviolet irradiation (Fig. 10a–c) [179]. The incorporation of dopamine and Fe^{3+} conferred the gel with antioxidative properties, outstanding photothermal characteristics, and the capacity to stimulate angiogenesis, thereby effectively suppressing melanoma recurrence and promoting wound healing (Fig. 10d–g). Zhao et al. prepared a hydrogel using PEG-DMA with the photoinitiator LUCIRIN TPO [23]. Following 400 nm light irradiation, the precursor solution underwent rapid photocuring within 15 s, exhibiting low swelling capacity to avoid compression of intracranial tissue and an increase in intracranial pressure. To achieve a hydrogel with mechanical properties compatible with breast tissue, methylacrylyl sericin is integrated into PEG-DMA, allowing for comprehensive breast reconstruction and reducing the risk of tumor recurrence following surgical resection(Fig. 10h) [180]. The fibroin protein, a natural biodegradable biomaterial derived from proteins, has been shown to enhance re-epithelialization, wound closure, angiogenesis and overall wound healing. SilMA, obtained through acrylylation of fibroin protein, has been extensively researched in various studies. SilMA can be photo-crosslinked with I 2959 photoinitiator to form an in-situ gel under the induction of 365 nm UV light [181]. SilMA has demonstrated the ability to promote the healing of staphylococcus aureus infected wounds by hemostasis and promoting hair follicle

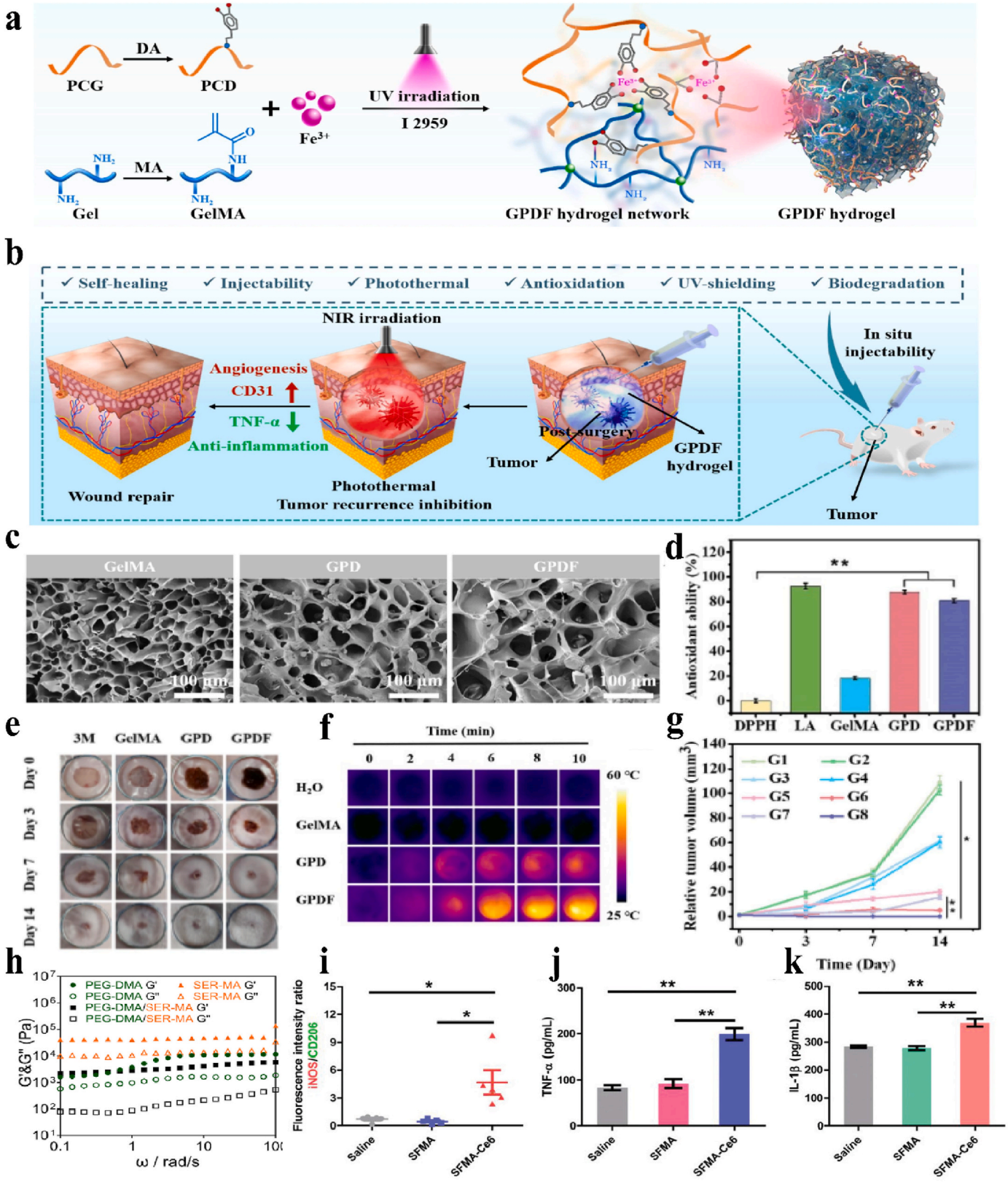

Fig. 10. Photocuring *in-situ* HLDDS prevents tumor recurrence. (a) Schematic diagram illustrating the fabrication process of GPDF hydrogel and (b) its potential application in inhibiting tumor recurrence with various properties. (c) SEM images of GelMA, GPD, and GPDF hydrogels. (d) The antioxidant ability of the various hydrogels. (e) Photographs of the wounds treated with various hydrogels on day 3, 7, and 14. (f) Photothermal images of different samples at various time points under 808 nm laser (1 W/cm$_2$, 10 min). (g) Relative tumor volume in various treatments after resection of tumor. (h) G′ and G″ of the three hydrogels. (i) The proportion of iNOS (M1) and CD206 (M2) and levels of (j)TNF-α and (k) IL-1β in sera of mice bearing B16F10 tumor after 2 days post PDT. Reproduced from Refs. [179–181] with permission from Elsevier and Wiley.

regeneration. Furthermore, the combination of SilMA gel and photodynamic therapy has been shown to effectively recruit macrophages and polarize them into M1 phenotypes, which secrete anti-tumor cytokines and inhibit melanoma recurrence (Fig. 10i–k).

A variety of factors should be taken into consideration during the selection of polymers and photoinitiators, which are the key factors in designing fine photocuring hydrogels. While ensuring biodegradability and biocompatibility, it is crucial to carefully select polymers that can meet specific requirements. For example, hyaluronic acid can enhance viscoelasticity and space-filling, but its compressibility and mechanics are subpar. On the other hand, fibroin protein exhibits excellent tensile properties. Additionally, it is important to consider the appropriate degree of acrylyl substitution, as a higher degree can result in a denser network structure with stronger mechanical properties [182]. Furthermore, careful consideration of the selection of an appropriate photosensitizer and light source is crucial. It should be noted that the use of ultraviolet light poses significant challenges and limitations in the clinical conversion process due to biosafety concerns and free radical generation [183]. Exposure to short and medium-wavelength ultraviolet light (200–320 nm) can result in skin damage, making it generally inappropriate for photocuring. Furthermore, studies have indicated that even UVA at 337 nm can cause DNA damage, highlighting the importance of exploring visible light and its related initiators [184]. Lastly, it is worth noting that the free radicals produced during PDT can be utilized to trigger the polymerization of hydrogels, thereby achieving a dual purpose. For instance upon injection of poly(ethylene glycol) double acrylate (PEGDA) into the tumor site, ROS generated by the photoinitiator CE6 not only initiated polymerization of PEGDA but also induced photodynamic destruction of tumor cells under 660 nm LED light irradiation [185]. This strategy may have significant value for clinical translation.

5.5. Other responsive in-situ HLDDS

In addition to the aforementioned irritant factors, the tumor surgical cavity also presents other unique microenvironmental factors, including the presence of enzymes and an acidic environment. It is important to note that the presence of tissue fluid itself in the surgical cavity can also lead to the gelation of the hydrogel.

In the application of tumor postsurgical management, enzyme-responsive gel-forming HLDDS has been reported. For example, fibrinogen can be decomposed into fibrin by thrombin and polymerized into insoluble fibrin polymers, ultimately leading to the formation of a three-dimensional structure [186]. Gu et al. developed a spray-type fibrin hydrogel by using a double-barrel nebulizer to simultaneously spray the fibrin solution containing aCD47@$CaCO_3$ and thrombin solution into the tumor cavity, resulting in the formation of fibrin hydrogel. In the mouse model of incomplete tumor resection, aCD47 was evenly distributed in the tissue after spray hydrogel treatment, effectively blocking the 'don't eat me' signal. The addition of $CaCO_3$ not only

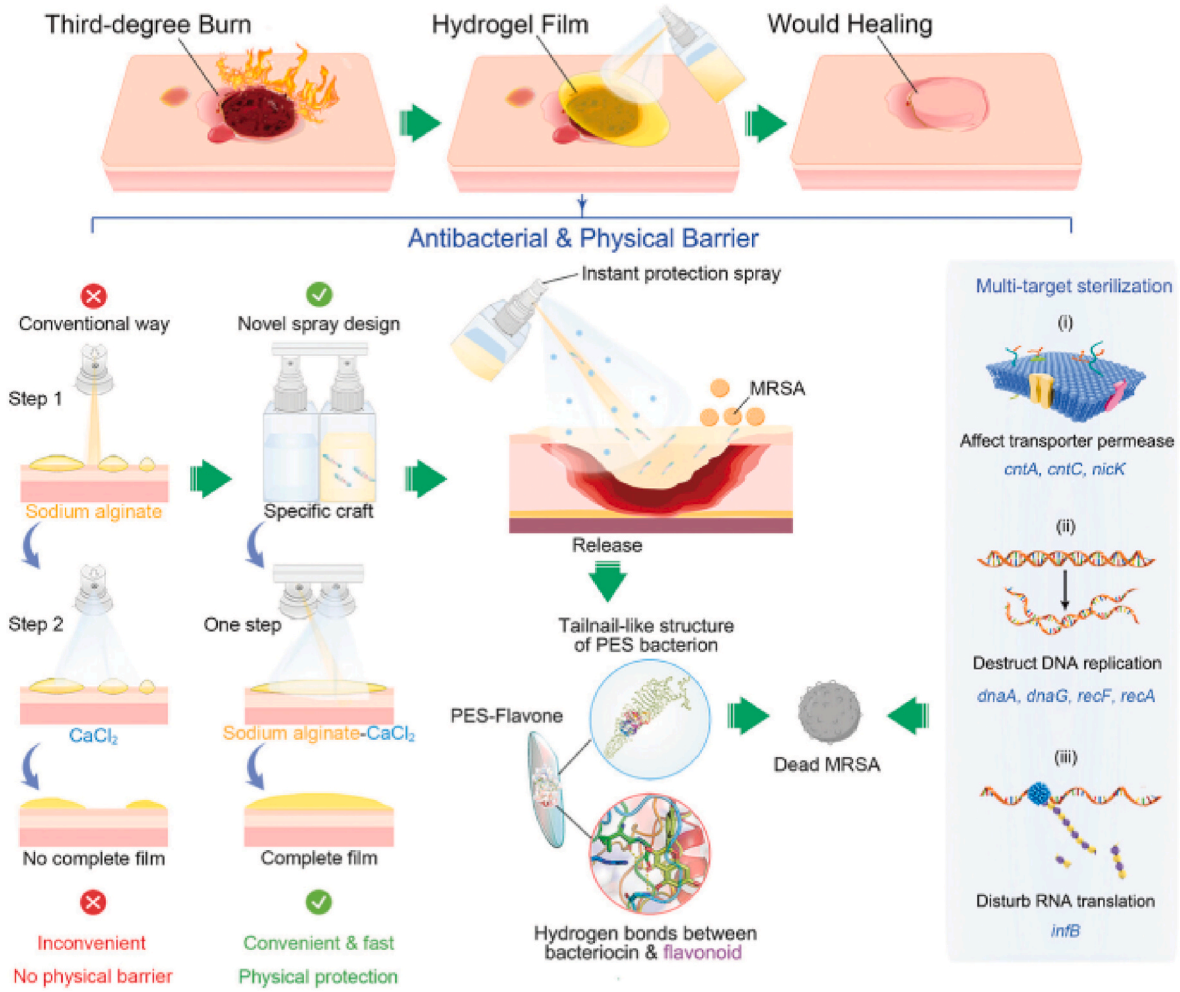

Fig. 11. The design of an instant protection spray (IPS), provides burn with an antibacterial and physical barrier. IPS was designed based on a novel crossed-angle layout. Unlike the conventional step-by-step spray, IPS owned a faster and more convenient one-step use mode and can form a complete hydrogel film instantly within 30 s to provide a physical barrier for burn. Reproduced from Ref. [189] with permission from Wiley.

promotes the formation of fibrin hydrogel but also reduces the acidity of TME, thereby enhancing immune function. As a result, 50 % of the mice survived for at least 60 days, and both local tumor recurrence and distant tumor cell growth were effectively inhibited [187]. Similarly, Huang et al. utilized two sprayers to apply fibrinogen and thrombin separately into tumor incisions, forming a hydrogel. They then employed starvation/chemokinetic therapy to target residual IDH1 (R132H) tumor cells post-surgery, exhibiting an outstanding anti-tumor recurrence effect [188]. Besides, the impact of varying cross angles on the formation of hydrogel films has also been investigated. For example, Guan et al. developed a rapid gelation spray with a novel cross-angle layout to form an instant protection spray and provide a physical and anti-infectious barrier for burns within 30 s (Fig. 11) [189]. They demonstrated that the various cross angles of the nozzle exerted a significant influence on the characteristics of the hydrogel. Specifically, they discovered that an optimal hydrogel film with appropriate area and thickness was formed when the cross angle was 10°–10°.

pH-sensitive-formation hydrogels in external factor-responsive hydrogels are widely used in the field of biomedicine. However, it is because of the typically acidic conditions of the tumor microenvironment [190], that normal chemical bonds (such as Schiff base bonds) are sensitive to acid, resulting in bond breakage, hydrogel dissolution, and drug release. In the context of HLDDS for tumor postsurgical management, there is a growing preference for the use of pH-responsive release hydrogels rather than pH-sensitive-formation hydrogels [86]. Interestingly, there have been reports of the phase transformation of tissue fluid-induced precursor solution into *in-situ* hydrogels. The addition of a solvent with low solubility to the polymer solution can initiate the transformation of the polymer chain from a loose to an aggregated state. In this process, similar to the "extraction" process, the polymer is "extracted" through solvent exchange to facilitate hydrogen bond formation and hydrophobic aggregation within and between polymers. This ultimately leads to the formation of hydrogels *in-situ* [191]. Peng et al. developed a highly adhesive hydrogel through solvent exchange, which has the potential to be utilized in the treatment of solid tumors through simultaneous ethanol ablation and local chemotherapy [192]. Initially, they synthesized polygallic acid-lipoic acid (PGL) ethanol gel *in vitro*. This gel exhibited weak interaction and could be injected into water using a 16-gauge syringe needle. Upon transformation, it formed PGL hydrogels with denser cross-linked networks and increased cohesion. The resulting gel was capable of treating Hepa 1–6 tumors by locally sustaining the release of chemotherapy drugs DOX and ethanol ablation. In addition, the solute liquid crystal gel, which is created through the self-assembly of amphiphilic molecules and solvents, can form a long-range ordered phase structure. Its precursor solution can also spontaneously form a unique three-dimensional structure upon contact with water [193,194]. While neither of these gels has been reported for use in HLDDS for postsurgical management, it appears that the tissue fluid-induced gelation may offer a simpler method and holds great potential for applications.

In conclusion, through the above analysis, the advantages and disadvantages of various types of HLDDS for postsurgical management of tumors were outlined in **Table 2**.

6. Conclusion and perspectives

Surgery is one of the most commonly utilized approaches for treating solid tumors. However, postsurgical tumor recurrence significantly diminishes patient survival ratio and adversely impacts their quality of life. Research has indicated that residual tumor cells within the surgical cavity, often referred to as "seeds," exhibit heightened invasiveness and metastatic potential compared to other tumor cells. Furthermore, the immunosuppressive microenvironment at the tumor site provides a fertile “soil” for these "seeds" to proliferate. In addition to these challenges, postsurgical tumor management encompasses various requirements such as hemostasis, inflammation control, wound healing promotion and antimicrobial effects. Consequently, there is a pressing need to develop novel drug delivery systems tailored to meet the diverse demands of postsurgical tumor management.

HLDDS offers unique advantages in this context compared to systemic drug delivery systems. Specifically, local drug delivery can mitigate systemic side effects while responsive hydrogel materials enable precise adherence within the surgical cavity and efficient drug distribution even in concealed corners. Moreover, hydrogels can confine drugs specifically at lesion sites where high local concentrations are conducive to implementing novel therapeutic approaches. Based on the gelatinization site, hydrogels can be divided into *non-in-situ* HLDDS (including implantable HLDDS and injectable HLDDS) and *in-situ* HLDDS (such as responsive *in-situ* HLDDS and non-responsive *in-situ* HLDDS). These versatile properties make them promising for addressing diverse needs in postsurgical tumor management. For instance, implantable HLDDS with rigid structures can function as breast cancer postoperative support catering to aesthetic concerns following mastectomy procedures among female patients. Injectable HLDDS enhance ease of use during application. Furthermore, responsive *in-situ* HLDDS possess condition-induced gelatinization capabilities that facilitate better adhesion within microscopic pores present in surgical cavities. They can also carry various chemotherapeutic drugs or functional substances combined with novel therapies aimed at meeting multifaceted needs associated with postsurgical tumor management. Consequently, the application of HLDDS in postsurgical tumor management has received significant attention (Fig. 12a).

However, despite the abundance of publications on the utilization of HLDDS in postsurgical tumor management, their practical application in the clinical application following tumor surgery is exceedingly limited. In this part, we provided a comprehensive analysis of the underlying factors of this issue (Fig. 12b). (1) Primarily, challenges arise from the construction of postsurgical tumor models. Predominantly utilizing rats or mice to construct postsurgical tumor models makes it hard to accurately represent human physiological conditions. The construction of postsurgical tumor models demands a high level of technical proficiency. For instance, surgical resection techniques vary significantly

Table 2
HLDDS for postsurgical management of tumors.

Types		Advantages	Disadvantages	References
Non-in-situ HLDDS	Implantable HLDDS	Certain rigidity; Serve as postsurgical scaffold	Difficult to degrade; Need a larger wound to implant; Hard to completely conform postsurgical wounds and cavity	[24,25]
	Injectable HLDDS	Shear thinning; Injectable; Minimally invasive	Poor mechanical strength; High requirements on materials	[26,27,75]
In-situ HLDDS	Thermo-sensitive *in-situ* HLDDS	Easy to adjust, control and implement; Convenient retrieval of thermo-sensitive materials	Natural biomaterials: Poor plasticity; Insufficient mechanical strength Synthetic material: Suboptimal biocompatibility	[105, 127–129]
	Ion-sensitive *in-situ* HLDDS	Rapid response and excellent biocompatibility	Low mechanical strength; Insufficient ions in tumor tissue fluid	[171]
	Photocuring *in-situ* HLDDS	Remote control; Being able to combine with PDT or PTT	Biosafety concerns like skin damage and chemical toxicity of photosensitizers	[183,185]
	Non-responsive *in-situ* HLDDS	Suitable for chemical cross-linked hydrogels with good mechanical strength	Require a dual syringe or a dual-cartridge sprayer	[85]

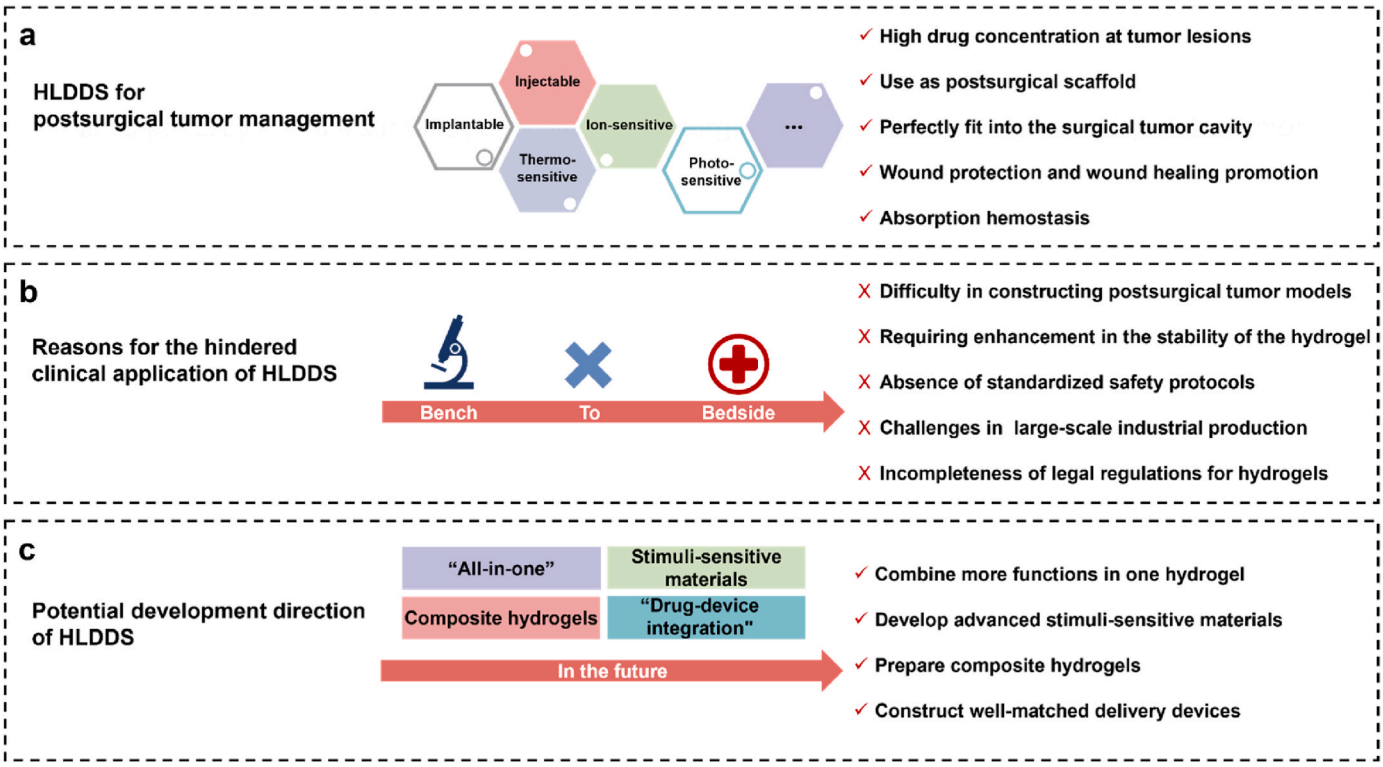

Fig. 12. Conclusion and perspectives of HLDDS in postsurgical tumor management. (a)The advantages of HLDDS for postsurgical tumor management. (b)The reasons for the hindered clinical application of HLDDS. (c) The development direction and potential of HLDDS in postsurgical tumor management.

across different anatomical sites and necessitate boffins with specialized surgical expertise. Besides, many boffins opt for subcutaneous xenograft tumor models over orthotopic tumor models. Stringent environmental requirements including humidity control, temperature regulation and sterility further complicate experimental procedures. (2) Secondly, improvements in the stability of the hydrogel formed at the surgical site have not garnered adequate attention. The unique environment following tumor surgery, characterized by exposed wounds, moist tissue fluids, mechanical friction, and so on, presents significant challenges to the stability of HLDDS. Enhancing the stability of HLDDS is crucial for advancing its clinical application. For instance, materials exhibiting high viscosity and friction resistance are beneficial for the stabilization of the hydrogel at the wound site and preserving the integrity of the wound microenvironment, thereby promoting wound closure [195]. (3) Thirdly, there is currently an absence of standardized safety protocols for hydrogel applications in postsurgical tumor management and no well-established recognized evaluation systems. Hydrogel materials are derived from diverse sources encompassing natural, semi-synthetic and synthetic origins. However, only a handful have obtained FDA approval for medical use, such as alginate, polyvinyl alcohol, chitosan, PEG and HA. (4) Fourthly, the preparation of HLDDS for tumor postsurgical management is currently limited to the laboratory stage, posing challenges for large-scale industrial production. This can be ascribed to several factors, including the intricate preparation process of hydrogel products, low repeatability and yield rates, difficulties in producing multifunctional hydrogel materials, as well as the nascent state of hydrogel drug delivery instruments. (5) Lastly, existing legal regulations for hydrogels lack comprehensiveness. The design, construction, industrial production, transportation, and clinical application of HLDDS for postoperative tumor management all require legal regulations to govern and constrain them. Accelerating the development and improvement of relevant laws and regulations is crucial.

In the above content, the application prospects of HLDDS for postsurgical tumor management and the problems existing in the clinical transformation of HLDDS are analyzed and discussed. Then, the future development direction and potential of hydrogels in postsurgical tumor management are provided (Fig. 12c). (1) Firstly, the tumor lesion after surgery has a large wound and cavity, which may face many problems, such as infection, inflammation and pain. Therefore, the demand for postsurgical tumor management is diverse, and in the future, hydrogels should combine more functions in one (namely "all-in-one"), including but not limited to hemostasis, antibacterial, anti-inflammatory, analgesic, and wound healing functions. Specifically, the organic integration of multiple functions through material development or drug loading to construct multifunctional hydrogels may become the focus of future studies. (2) Secondly, *in-situ* HLDDS are more advantageous than none *in-situ* HLDDS in postsurgical tumor management, and the key to the product and preparation of *in-situ* HLDDS lies in the development of stimuli-sensitive materials. In the future, the development of hydrogel materials for postsurgical tumor management should be more focused on being compatible with the tumor microenvironment, and the tumor microenvironment-sensitive gelatinization of the material is conducive to the perfect adhesion of the hydrogels with the tumor surgical cavity, providing potential for the realization of new therapies. Besides, extracellular matrix hydrogel has shown excellent application perspectives in the treatments of various diseases due to its desired biocompatibility and unique biological functions. Up to now, its extracellular matrix can come from adipocytes [196], cardiac muscle tissue [197] and tumor cell lysate [198]. In the future, more materials of extracellular matrix hydrogel should be developed. (3) Thirdly, composite HLDDS combining the advantages of hydrogel and other formulations are expected to be a key focus of future research. For example, nanoparticles offer a range of advantages including the reduction of drug side effects, enhancement of drug bioavailability and controlled drug release profile. Furthermore, nanoparticle modification can provide them with additional functionalities such as responsive drug release to the tumor microenvironment and targeted delivery to specific cells or cellular organelles. Thus, HLDDS loading nanoparticles show significant potential for advancing

tumor treatment. (4) Finally, in practical applications, the utilization of delivery devices alongside hydrogels is indispensable. In line with the "drug-device integration" concept, future emphasis should also be placed on the development of hydrogel devices. And the delivery device should be customized to match the specific type of hydrogels, disease type and drug characteristics. The approach described in this review involves simultaneous injection of two solutions into the lesion site using a double-tube syringe or a double-barrel nebulizer with the "drug-device integration" concept [44,189,199]. Consequently, there exists promising potential for advancing the application of hydrogels through the development and optimization of drug-delivery devices.

CRediT authorship contribution statement

Ziqiao Zhong: Writing – original draft, Visualization, Formal analysis. **Lu Gan:** Writing – original draft. **Ziyi Feng:** Visualization, Formal analysis. **Wenhao Wang:** Writing – review & editing. **Xin Pan:** Investigation, Funding acquisition. **Chuanbin Wu:** Funding acquisition. **Ying Huang:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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