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REVIEW

Polymeric micelles: "magic bullets" for cancer treatment

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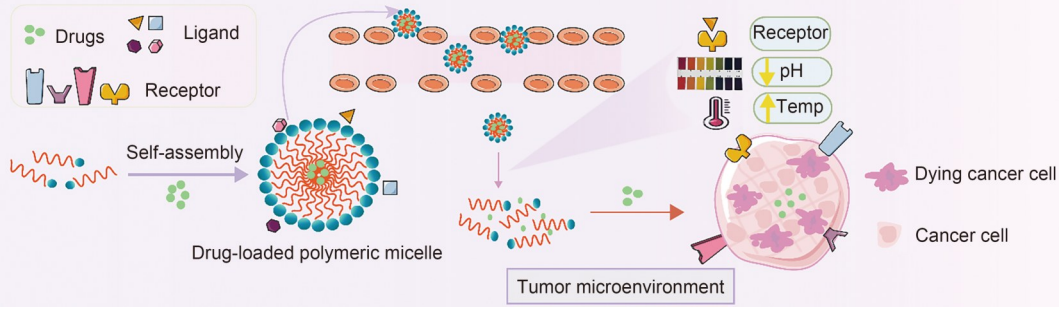
Abstract

Nanocarriers are an efficient drug delivery tool used for cancer treatment. Among various nanocarriers, polymeric micelles (PMs) have garnered attention in recent years due to their excellent properties, including improved solubility of insoluble drugs, enhanced targeting and accumulation of drugs at the cancer site, increased sensitivity of cancer cells to chemotherapeutic drugs, and prolonged circulation time. This review summarizes the preparation methods, characterization, advantages, and classification of PMs as drug delivery systems for oncology therapeutics. In particular, the self-assembly mechanisms of active ingredients into PMs, the anticancer activities of PMs associated with various cell death pathways, and the research cases of PMs as drug delivery vehicles in cancer therapy are described. Finally, this review summarizes the status of the clinical trials and real-world applications of PMs and briefly analyzes the reasons for the unsatisfactory commercialized states. This review supports further research on the role of PMs as nanocarriers in cancer therapy and adds insights for the successful clinical translation of PM-based products.

Graphical abstract



Keywords Cancer therapy · Polymeric micelles · Drug delivery systems · Cell death pathways · Clinical application

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1 Introduction

Cancer remains as one of the leading causes of death worldwide. According to the International Agency for Research on Cancer, there were close to 20 million new cases of cancer diagnoses in 2022 alongside 9.7 million deaths from cancer. It was estimated that the incidence of cancer is approximately 20% for both males and females, whereas the mortality rate from cancer is about 11% for males and 8% for females. Lung cancer caused the most deaths (approximately 1.8 million deaths), followed by colorectal, liver, breast, and stomach cancers [1, 2].

Cancer is mainly caused by the transformation of healthy cells into malignant tumor cells through various triggers. Cancer is marked by its propensity for metastasis and recurrence, along with high morbidity and mortality, making complete cure challenging. Current cancer treatments include surgery, radiotherapy, chemotherapy, chemodynamic therapy (CDT), immunotherapy [3], and various combination therapies. The three main types of clinical treatment commonly used are surgery, radiotherapy, and chemotherapy [4]. However, surgical treatment has a narrow indication and is risky due to increased risks of infection and bleeding [5]. Radiotherapy primarily works by eliminating tumor cells through radiation. However, some tumor cells may develop resistance after exposure, which can diminish treatment efficacy. Additionally, the radiation may further damage other healthy organs or tissues [6]. Chemotherapy uses chemicals to kill tumor cells, but chemotherapy drugs lack tumor-targeting ability, have high toxicity and side effects, and are prone to drug resistance [7], all of which greatly limit the effectiveness of this treatment. Therefore, there is an urgent need for a treatment that can specifically target tumor cells, reduce systemic toxicities, and prevent tumor resistance. To overcome these challenges and improve the efficacy of anticancer drugs, nanomedicines have received widespread attention. Nanomedicines typically rely on a nanocarrier that accommodates the anticancer drugs. Various nanocarriers (e.g., liposomes, polymeric micelles (PMs), dendrimers, metallic/inorganic nanoparticles (NPs), biomimetic NPs, and nanohydrogels) have been explored (Fig. 1) [8].

Among these nanocarriers, PMs have been rapidly developed in recent years. The authors believe that the antitumor effect of PMs exceeds that of other carriers because PMs can enhance the apparent solubility of insoluble drugs, prolong the blood circulation time of drugs, reduce the systemic toxicity of drugs, prevent chemoresistance, control the drug release rate, and enhance the targeting specificity of therapeutic drugs to tumors. PMs can be categorized into three groups based on the type of delivery system: passive targeting PMs, active targeting PMs, and stimuli-responsive PMs. Passive targeting is regulated by the concentration of

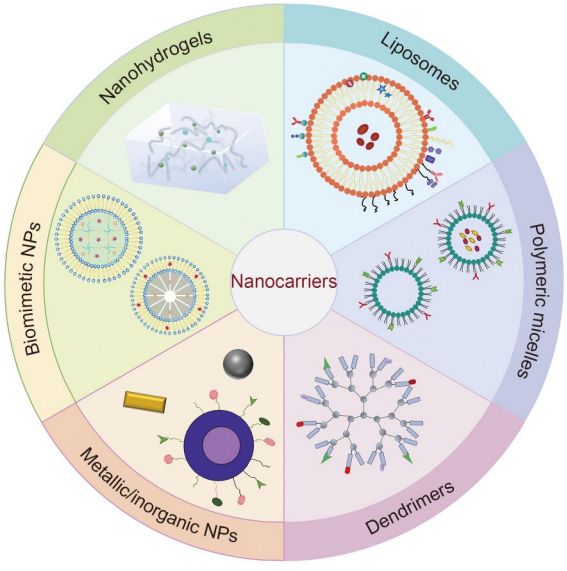

Fig. 1 Different types of nanocarriers

therapeutic agents at the tumor site, relying on the enhanced permeability and retention (EPR) effect. Active targeting is based on specific ligand-receptor binding to enhance the internalization of PMs. Stimuli responsiveness refers to response to a specific stimulus that causes the responsive degradation of drug-loaded PMs, thereby increasing drug accumulation at the tumor site. These types of micelles are described in detail in this review.

This review aims to provide a comprehensive overview of PMs. Specifically, the basic properties of PMs will be introduced, and the classification of PMs as drug delivery systems for oncology therapies will be summarized (located in the supplementary information). In addition, this review focuses on the self-assembly mechanisms of the active ingredients in PMs, the anticancer activities of PMs associated with various cell death pathways, and the application of PMs as drug delivery vehicles in cancer therapy. Finally, this review summarizes the status of the clinical trials and real-world applications of PMs. This review provides new perspectives on the role of PMs as nanocarriers in cancer therapy and insights into the successful clinical translation of PM-based products.

2 Self-assembly of active ingredients into PMs in cancer therapy

Owing to their excellent drug-loading capacity and targeted response performance, PMs have become a prominent area of research. Depending on the method used to encapsulate the drugs, PMs can be categorized into two main types: those that load drugs through chemical linkages and those that use physical encapsulation methods. Specifically, PMs

that incorporate drugs through chemical linkages are self-assembled from amphiphilic copolymers, with the drug or active ingredient chemically embedded within the PM. In contrast, PMs that directly load hydrophobic drugs into hydrophobic cavities are classified as a physical encapsulation method. Notably, recent studies using chemical linkages have revealed a range of specialized types of PMs, including PMs designed for apoptosis, necrosis, autophagy, ferroptosis, and pyroptosis, each targeting specific mechanisms of cell death induced by the active ingredients, as illustrated in Fig. 2.

2.1 PMs for apoptosis

Apoptosis is an autonomous and orderly form of cell death that occurs in the body under specific physiological or pathological conditions to maintain the stability of the internal environment by regulating intracellular genes and products. This process is programmed and involves the activation, regulation, and expression of a series of genes, among which caspase-3 is a key marker of apoptosis [9]. Morphologically, apoptotic cells exhibit chromatin condensation, shrinkage, and the formation of apoptotic bodies. Apoptosis is crucial for preventing tumor development and serves as an effective strategy for cancer treatment [10]. Consequently, PMs that induce apoptosis are essential tools in cancer therapy.

α-Tocopherol succinate (α-TOS) is an effective apoptosis inducer. Studies have shown that α-TOS induces apoptosis by interfering with mitochondrial electron transport and increasing the intracellular levels of reactive oxygen species (ROS) [11]. However, one of the limitations of α-TOS is its poor solubility, which restricts its bioavailability and effectiveness in therapeutic applications. To address the solubility limitations of α-TOS, D-α-tocopherol polyethylene glycol succinate (TPGS) has been used. By combining hydrophobic α-TOS with hydrophilic polyethylene glycol (PEG), TPGS not only preserves the antitumor activity of α-TOS but also enhances its anticancer efficacy by significantly improving its solubility. Building on this mechanism, Dong et al. [12] developed a pH-responsive amphiphilic micelle ($PIAT_{hyd}CA$) by combining the ROS-generating agent cinnamaldehyde (CA) with hydrophilic poly(itaconic acid), while TPGS was the hydrophobic side chain. In the acidic tumor microenvironment (TME), the hydrazone bonds within $PIAT_{hyd}CA$ were cleaved to release CA. As both TPGS and CA induce ROS, they could work synergistically to enhance oxidative stress, promote ROS accumulation, and activate caspase-3, inducing apoptosis. In addition, TPGS could inhibit the function of P-glycoprotein (P-gp), a drug efflux transporter protein, which helps to reduce the resistance of multidrug-resistant tumors to various anticancer drugs. This is exemplified by the synthesis of a TPGS-based paclitaxel (PTX) prodrug (TPGS-SS-PTX) capable of self-assembly, where a disulfide bond links TPGS and the PTX prodrug. Under intracellular reductive conditions, the disulfide bonds in the PMs are cleaved to allow rapid dissociation and drug release in the cancer cells. The in vitro and in vivo results showed that TPGS-SS-PTX significantly reduced the exocytosis of PTX and induced apoptosis [13].

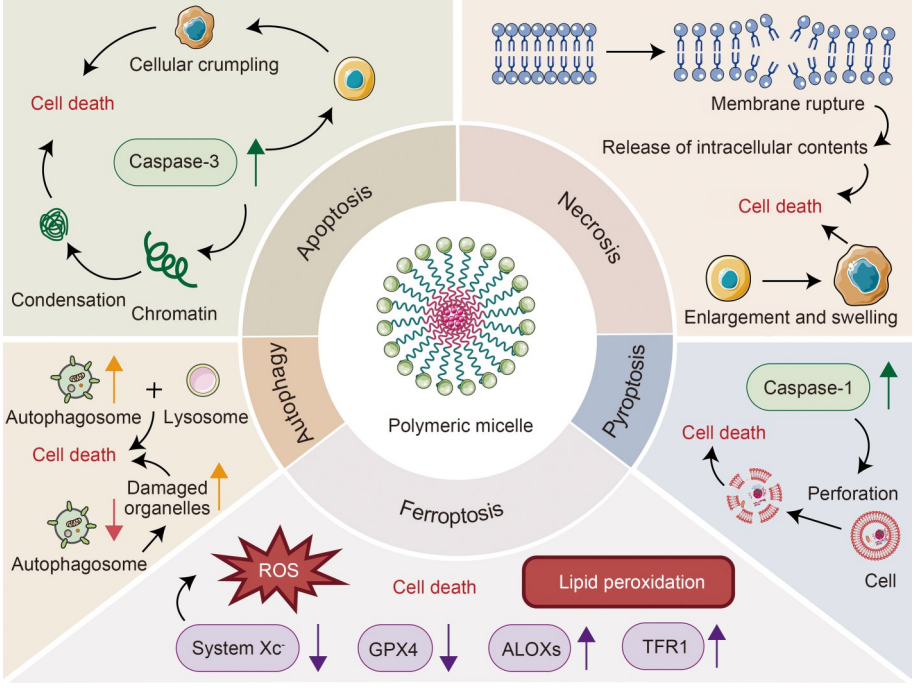

Fig. 2 PMs loaded with drugs through chemical linkages induce apoptosis, necrosis, autophagy, ferroptosis, and pyroptosis for cancer treatment

Likewise, the self-assembled micelles of galactosamine-hyaluronic acid-vitamin E succinate (Gal-HA-VES) designed by Jiang et al. could also act as a P-gp inhibitor and markedly reduce the efflux of norcantharidin, a synthetic anticancer drug. The use of Gal-HA-VES for norcantharidin delivery has been shown to enhance antitumor activity in vivo [14].

In another study, Wan et al. linked PTX to poly(ethylene glycol)-*b*-poly(L-lactide-*co*-2-methyl-2-carboxyl-propylene carbonate) to form a PTX-conjugate copolymer. This was mixed with the folic acid (FA)-carrying copolymer poly(ethylene glycol)-*b*-poly(L-lactide-*co*-2,2-dihydroxylmethyl-propylene carbonate/FA) (PEG-*b*-P(LA-*co*-DHP/FA)) to form FA–PTX micelles [15]. Flow cytometry and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay demonstrated that both PTX and FA–PTX PMs induced apoptosis, with the FA–PTX micelles demonstrating superior performance compared to the PTX micelles. This suggests that folate-mediated active targeting could be leveraged with the use of FA to enhance the anticancer efficacy. The ability of PMs to encapsulate multiple drugs can also enhance tumor therapy. For instance, Jin et al. [16] conjugated the hydrophilic drug floxuridine (FdU) with the hydrophobic polymer polycaprolactone (PCL) via esterification to create FdU-PCL conjugates, which were self-assembled with the nitric oxide (NO) precursor, phenylsulfonyl furoxan (PSF), to form PSF@FdU-PCL PMs. Acidic conditions hydrolyzed the ester bonds, releasing FdU and PSF, with glutathione (GSH) in the tumor microenvironment facilitating NO release. The combination of FdU and NO elicited synergistic antitumor effects in vitro and in vivo, surpassing the efficacy of individual agents. NO also inhibited P-gp expression, enhancing drug sensitivity and antitumor activity.

In summary, the self-assembly of the active ingredients into the PMs holds great potential for apoptosis-mediated cancer therapy. By combining apoptosis-inducing drugs with amphiphilic conjugates capable of self-assembly, PMs can not only trigger apoptosis but also perform specialized tasks. This multimechanism approach enhances the induction of cell death, offering a robust strategy for cancer treatment. Therefore, advancing research and development in this area is of great significance for improving cancer therapies.

2.2 PMs for necrosis

Cell necrosis refers to uncontrolled cellular death caused by severe physical, chemical, or biological stressors [17], a passive pathological process. Key morphological changes include increased membrane permeability, cell swelling, organelle deformation, membrane rupture, and the release of intracellular contents, triggering local inflammation. Tissue healing may also lead to fibrosis and scar formation [18]. Necrosis is frequently utilized in cancer therapy, where pharmaceutical agents induce tumor cell demise [19, 20]. PMs are among the most promising tools to induce necrosis.

Photodynamic therapy (PDT) is a noninvasive therapeutic approach that selectively targets tumor cells with high precision using photosensitizers. Known for its minimal invasiveness, low toxicity, and excellent selectivity, PDT is a strong contender in cancer treatment, offering advantages over traditional methods [21, 22]. To enhance the efficacy of PDT, Zhang et al. [23] synthesized PMs (AIE-M) with aggregation-induced emission (AIE) properties by self-assembly design using a salicylaldazine-based amphiphilic polymer (AIE-1) as the raw material. AIE-M was passively targeted to tumor cells via the EPR effect. In vitro studies have shown that AIE-M accumulates predominantly in the mitochondria of the cancer cells. With light irradiation, the phototoxic AIE can catalyze the production of intracellular ROS, effectively instigating cell necrosis and apoptosis. These findings highlight the potential of these PMs to enhance PDT-mediated cancer therapy. Furthermore, a self-assembled polymeric micellar immunomodulator (SPI), which is derived from cationic amphiphilic polymers, has attracted considerable attention in necrosis-mediated cancer therapy, as demonstrated by Yim et al. [24]. These potent positively charged PMs were formed by the self-assembly of ATRA-$_{Low}$PEI monomers, which were a hybrid conjugate of hydrophilic low-molecular-weight PEI ($_{Low}$PEI, M_n=1.8 kDa) and hydrophobic all-*trans*-retinoic acid (ATRA). The cell death mechanism study revealed that the positive surface charge of SPI generated substantial mechanical disruptive forces, triggering cancer cell necrosis. Furthermore, this induction of necrosis elicited an antitumor immune response, which worked synergistically to enhance tumor eradication.

Similar to the PTX mentioned earlier, docetaxel (DTX), which belongs to the taxane class of drugs, is used to treat various cancers, including breast cancer, nonsmall cell lung cancer, and oral cancer [25]. However, its nonspecific distribution, poor water solubility, and potent adverse effects hinder its clinical application [26]. To address these challenges, Shi et al. [27] conjugated a hydrophilic monomethoxy-poly(ethylene glycol)-*b*-poly(lactide) (mPEG-PLA) polymer block to the DTX molecule via ester bonds to form nanoscale PMs (DTX-PM). Leveraging the EPR effect, DTX-PM achieved passive cellular targeting, effectively addressing the challenges of nonspecific distribution and mitigating the adverse effects commonly associated with DTX. The incorporation of the hydrophilic segment and the formation of PMs imparted hydrophilicity and significantly improved the bioavailability of DTX, enhancing its antitumor activity. Based on hematoxylin and eosin (H&E) staining and TUNEL assays, DTX-PM demonstrated a pronounced capacity to induce cancer cell necrosis in vivo.

According to the findings from the aforementioned experiments, molecules capable of inducing cellular necrosis and self-assembly into PMs harbor considerable potential in cancer therapy. Thus, the development of PMs capable of inducing cell necrosis represents a significant and promising avenue for addressing the limitations of cancer treatments, warranting substantial clinical research and exploration.

2.3 PMs for autophagy

Cellular autophagy is a critical defense mechanism that degrades and removes damaged organelles and macromolecules, thus maintaining cellular homeostasis. Its role in cancer therapy is complex [28]. On the one hand, autophagy can mitigate chronic inflammation and reduce DNA damage, potentially inhibiting cancer progression. However, it can promote tumor growth by providing essential metabolic intermediates and supporting cellular homeostasis within the TME [29]. Consequently, autophagy-mediated cancer therapy presents a dual approach: one strategy involves activating autophagy to induce autophagosome formation and subsequent cellular death through lysosomal degradation [30], while the other focuses on inhibiting autophagy in tumor cells to disrupt cellular homeostasis, leading to the accumulation of damaged macromolecules or organelles, inducing cell death [31, 32]. PM-mediated cellular autophagy holds significant promise in cancer treatment and is capable of disrupting tumor cell homeostasis through either excessive activation or inhibition of autophagy, exerting anticancer effects.

For instance, Cao et al. [33] developed methotrexate-polyethylene glycol (MTX-PEG) modified chitosan/2,3-dimethyl maleic anhydride (CG/DMMA) PMs loaded with doxorubicin (DOX) (DOX@CDPM). MTX-PEG modification significantly enhanced drug accumulation at target sites by passive targeting mediated by EPR effects, reduced cytotoxicity, and prevented protein corona formation. The experiments demonstrated that CG/DMMA induced autophagosome formation in conjunction with DOX, impairing lysosomal function and autophagic flux, thus inducing autophagic death in triple-negative breast cancer cells. In another approach, Mei et al. [34] incorporated a self-inducing autophagic agent, rapamycin, into PEG-DSPE PMs (7pep-M-RAP) modified with 7pep (Histidine-Alanine-Isoleucine-Tyrosine-Proline-Arginine-Histidine). 7pep, with high affinity for transferrin receptor 1 (TFR1), selectively and actively targeted tumor cells with high TFR1 expression. When conjugated with PTX, 7pep-M-RAP PMs (7pep-M-PTX) synergistically increased the levels of the intracellular autophagy-related protein LC-II, significantly increasing autophagic vesicle formation. Subsequent in vivo experiments confirmed that both 7pep-M-RAP and 7pep-M-PTX effectively induced cell death through collaborative induction of autophagy. Furthermore, utilizing trimethyl-chitosan conjugated with DOX and Beclin-1 siRNA, Zhong et al. [35] synthesized PMs with potent autophagic capabilities (Si-Beclin1/DOX-TMC). These PMs demonstrated significant intracellular autophagosome formation in vitro and antitumor efficacy against drug-resistant bladder cancer in vivo.

Excessive suppression of autophagy in tumor cells can also promote cell death. Common autophagy inhibitors include chloroquine, 3-methyladenine, bafilomycin A1, and LY294002. To overcome multidrug resistance and treat oral squamous cell carcinoma, Saiyin et al. [36] devised a formulation encapsulating LY294002 within PMs (LY@HPAH-DOX). These micelles were self-assembled from a combination of pH-responsive hydrophilic hyperbranched polyacylhydrazone and hydrophobic DOX. In the acidic TME, pH-responsive LY@HPAH-DOX effectively released DOX and LY294002. Compared with micelles devoid of LY294002, LY@HPAH-DOX exhibited superior antitumor activity due to the preferential release of LY294002, which significantly inhibited cellular autophagy, rendering the tumor cells more susceptible to DOX.

The manipulation of autophagy in tumor cells, either through activation or inhibition, has implications for cancer therapy. PMs engineered with autophagy modulators can effectively disrupt the autophagic homeostasis maintained by tumor cells, exerting anticancer effects. Notably, although hydrophobic autophagy activators such as DOX are commonly used, research on active agents to inhibit tumor autophagy as polymer block segments for self-assembling PMs remains limited and warrants further investigation.

2.4 PMs for ferroptosis

Ferroptosis, a form of iron-dependent programmed cell death distinct from apoptosis, necrosis, and autophagy, was first characterized by Dixon in 2012 [37]. The principal mechanism of ferroptosis involves the peroxidation of unsaturated fatty acids on the cell membrane catalyzed by lipoxygenases or ferrous iron, leading to membrane damage and subsequent cell death [38]. Morphologically, ferroptotic cells are distinguished by mitochondrial shrinkage and increased membrane density. Concurrently, diminished cellular antioxidant defenses coupled with ongoing redox reactions lead to the accumulation of ROS within the cell, implicating modulation of several proteins and factors, including glutathione peroxidase 4 (GPX4), System Xc^-, arachidonate lipoxygenases (ALOXs), and TFR1 [39]. As additional ferroptosis inducers emerge, more studies will focus on ferroptosis-based cancer therapy. The potential of ferroptosis-inducing molecules capable of self-assembly into PMs is a novel approach for tumor suppression [40, 41].

To address multidrug resistance in cancer cells, Gao et al. [42] harnessed an augmented ferroptosis-based

therapy. They conjugated arachidonic acid, an unsaturated fatty acid, with the amphiphilic copolymer methoxyl poly(ethylene glycol)-poly(lysine) (mPEG-PLys) to generate bioactive PMs, which were loaded with the prototypical ferroptosis inducer RSL3, creating RSL3-loaded PMs (RSL3/PMs). The EPR-based passive targeting ability enhanced the accumulation of RSL3/PMs at the tumor site. The study demonstrated that RSL3/PMs, containing unsaturated fatty acids, undergo rapid peroxidation within the tumor microenvironment, releasing RSL3, which induces ferroptosis by inhibiting GPX4 activity. In addition, peroxidized AA depletes intracellular GPX4 and, in conjunction with intracellular peroxidized lipids, synergistically induces ferroptosis. This dual mechanism enhances the efficacy of cancer therapy while overcoming cellular multidrug resistance.

Research on the mechanisms of ferroptosis continues to evolve. PMs capable of inducing ferroptosis are potent formulations for inhibiting tumor growth and progression. However, direct investigations of the self-assembly of ferroptosis-inducing molecules into PMs are limited. Hence, this area of research requires further exploration.

2.5 PMs for pyroptosis

Pyroptosis, a form of cellular inflammatory necrosis, was first reported by Cookson et al. in 2001. This mode of cell death is primarily mediated by caspases, including caspase-1, as inflammatory vesicles respond to various external stimuli. This activation leads to the cleavage and multimerization of the gasdermin family proteins, resulting in cell membrane perforation and ultimately cell death [43]. In contrast to other modes of cell death, e.g., apoptosis or necrosis, pyroptosis features morphological changes including membrane pore formation, nuclear condensation, and the presence of large air bubbles at the plasma membrane that eventually rupture [9]. As a highly proinflammatory programmed cell death mechanism, pyroptosis is closely related to the development and treatment of many types of cancers [44]. The use of PMs to deliver pyroptosis inducers is a promising approach for cancer treatment.

Jin et al. [45] synthesized mitochondria-targeted PMs for enhanced osteosarcoma immunotherapy (OPDEA-PDCA). These PMs utilized the amphiphilic ionic poly[2-(*N*-oxide-*N*,*N*-diethylamino)ethyl methacrylate] (OPDEA) to rapidly target mitochondria upon internalization. OPDEA, in combination with dichloroacetate, a specific inhibitor of mitochondrial pyruvate dehydrogenase kinase 1, induces excessive oxidative stress and oxidative phosphorylation in mitochondria, triggering pyroptosis in osteosarcoma cells. In vitro studies demonstrated that OPDEA-PDCA-mediated pyroptosis led to a massive release of immunogenic substances like calreticulin and high mobility group box-1 protein, along with altered expression of programmed cell death-ligand 1 (PD-L1). Moreover, OPDEA-PDCA combined with anti-PD-L1 monoclonal antibody significantly suppressed tumor growth in vivo compared with PMs without this combination. This evidence highlights the potential of self-assembling pyroptosis inducers into PMs for cancer therapy. However, few pyroptosis inducers can self-assemble into PMs; thus, further research is needed, especially on additional cell death mechanisms when using this approach.

3 PMs as drug delivery carriers in cancer therapy

In aqueous environments, PMs form through the self-assembly of amphiphilic block copolymers, yielding a hydrophobic core surrounded by a hydrophilic shell. This structure enables PMs to physically encapsulate small hydrophobic drugs within their core and deliver them to within biological systems [46]. Indeed, PMs not only efficiently transport drugs within the body but also enhance their therapeutic efficacy, pharmacokinetic profiles, and safety parameters [47]. Consequently, PMs have emerged as prominent candidates for drug delivery in cancer therapy, particularly for the transportation of poorly water-soluble small molecules. In the context of cancer treatment, PMs can be categorized into 10 distinct modalities: chemotherapy, CDT, PDT, photothermal therapy (PTT), immunotherapy, gene therapy, starvation therapy, sono-dynamic therapy (SDT), magnetic hyperthermia therapy (MHT), and targeted therapy.

3.1 Chemotherapy

Chemotherapy remains a cornerstone of cancer therapy, harnessing potent chemical agents to target and eradicate tumor cells [48]. This therapeutic approach utilizes a range of well-established drugs, including PTX [49, 50], 5-fluorouracil [50, 51], and DOX [52]. To enhance drug localization and minimize adverse effects, PMs could deliver chemotherapeutic payloads with improved efficacy and biocompatibility.

PEG and its derivatives frequently serve as hydrophilic blocks within copolymers, which, when combined with hydrophobic segments like PCL or tetraphenylene (TPE), help form PMs through self-assembly. These PMs can encapsulate chemotherapeutic agents [53]. For instance, Yang et al. [54] utilized PEG-*b*-poly(lactide) (PEG-PLA) to create arenobufagin (ArBu)-loaded PMs (ArBu@PEG-PLA) via thin-film hydration (Fig. 3a). The resulting micelles demonstrated excellent stability, drug-loading capacity, and drug-release kinetics. In vitro and in vivo evaluations revealed that ArBu@PEG-PLA not only induced

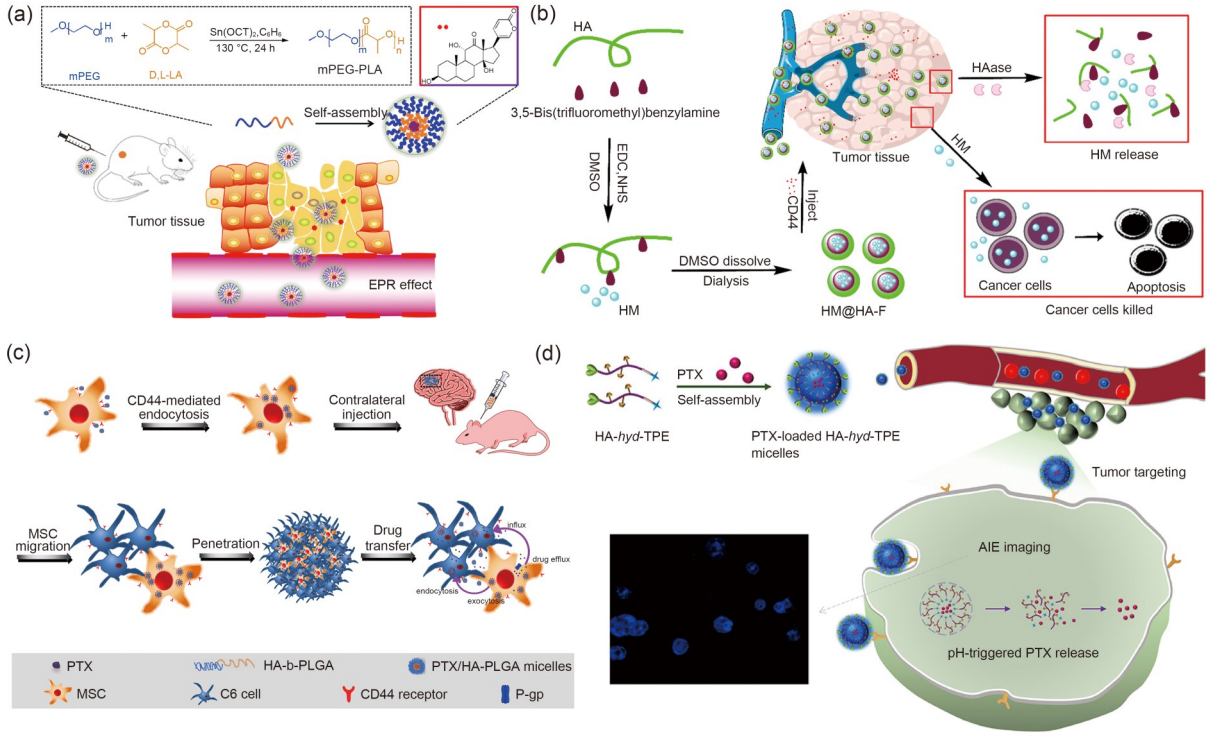

Fig. 3 Chemotherapy-based PMs for cancer therapy. (a) Schematic of the formulation and antitumor mechanism of ArBu@PEG-PLA (reproduced from [54], Copyright 2023, with permission from the authors, licensed under CC BY 4.0). (b) Schematic of the formulation and antitumor mechanism of HM@HA-F (reproduced from [57], Copyright 2023, with permission from the authors, licensed under CC BY-NC-ND). (c) Schematic of the formulation and antitumor mechanism of PTX/HA-PLGA PMs (reproduced from [58], Copyright 2022, with permission from the authors, licensed under CC BY 4.0). (d) Schematic of the formulation and antitumor mechanism of PTX-loaded HA-*hyd*-TPE PMs (reproduced from [59], Copyright 2023, with permission from the American Chemical Society)

apoptosis via mitochondrial apoptotic pathways but also was safer than free ArBu, with an anticancer potency increase of 1.28-fold. Similarly, Wang et al. [55] synthesized PMs using PEG-PCL copolymers to load deguelin and PTX. These nanomicelles effectively inhibited breast cancer cell proliferation by inducing apoptosis.

mPEG, a derivative of PEG, where a methoxy group is substituted at one terminal, is another building block for PMs. Zhao et al. [56] created an amphiphilic copolymer (Bi(mPEG-S-S)-TPE) through disulfide bond coupling between mPEG and TPE. This copolymer self-assembled into PMs with a high hydrophobic drug-loading capacity, effectively encapsulating PTX. The presence of disulfide bonds rendered this PM redox-responsive for rapid degradation in the high GSH environment of tumors. These PMs demonstrated superior antineoplastic efficacy and reduced adverse effects, with TPE also enhancing biological imaging capabilities due to its AIE properties.

Other hydrophilic segments, including hyaluronic acid (HA), have also been used to synthesize PMs. For example, Tang et al. [57] performed an amide reaction-mediated coupling between HA and 3,5-bis(trifluoromethyl)benzylamine, the result of which seamlessly self-assembled with the hydrophobic agent harmine, yielding drug-loaded PMs (HM@HA-F) (Fig. 3b). The surface-grafted HA of HM@HA-F exerted an active targeting effect and bound to CD44 overexpressed on tumor cells, enabling hyaluronidase-mediated hydrolysis to liberate harmine. Flow cytometry assays have shown that HM@HA-F induces apoptosis in breast cancer cells by modulating the cell cycle. Similarly, Wang et al. [58] developed PMs by leveraging the hydrophilicity of HA and the lipophilicity of poly(D, L-lactide-*co*-glycolide) (PLGA), encapsulating the chemotherapeutic agent PTX to produce PTX/HA-PLGA PMs. These micelles exhibited exceptional specificity, eradicating tumors by enhancing drug accumulation in both mesenchymal stem cells and tumor sites as well as drug penetration into deep-seated gliomas (Fig. 3c). Furthermore, Li et al. [59] synthesized a hydrazone linkage-conjugated HA with a TPE derivative (HA-*hyd*-TPE), which self-assembled with PTX to form drug-loaded PMs (PTX-loaded HA-*hyd*-TPE PMs), as illustrated in Fig. 3d, akin to the strategy used by Zhao et al. with their Bi(mPEG-S-S)-TPE PMs. Both HA-*hyd*-TPE and Bi(mPEG-S-S)-TPE micelles displayed remarkable cellular imaging capabilities and anticancer activities.

Block copolymers designed for PMs can release chemotherapeutic agents in response to particular stimuli, e.g.,

changes in pH, hypoxia, or redox conditions. The acidic TME offers the opportunity to design acid-responsive PMs that facilitate site-specific drug release, enhancing therapeutic efficacy while mitigating adverse systemic effects. For example, Chen and Liu [60] developed two distinct functionalized dendritic polyurethanes, Ph-DPUGly-PEG and Ph-DPUTEA-PEG, derived from glycerol and triethanolamine, respectively. Both copolymers demonstrated a strong propensity to self-assemble into micelles in aqueous environments. Furthermore, drug-loading studies with DOX revealed the exceptional drug encapsulation capabilities for both PMs. However, in simulations of the TME, Ph-DPUTEA-PEG demonstrated acid-responsive drug release, a feature not observed in Ph-DPUGly-PEG. This difference was attributed to the protonation of tertiary amines in triethanolamine under weakly acidic conditions. Consequently, Ph-DPUTEA-PEG emerged as a promising candidate for the development of pH-responsive PMs, with potential applications in targeted chemotherapeutic delivery.

The rapid proliferation of tumors often increases expression of hydrogen peroxide (H_2O_2) and hypoxia within tumor cells, which have been exploited to create PMs responsive to oxidative stress and hypoxia. Shi et al. [61] designed a novel fluorinated Gemini amphiphilic PM (FnH12DiTeFnH12), which incorporates ditelluride bonds for redox responsiveness and encapsulates the poorly soluble drug camptothecin (CPT), as depicted in Fig. S11a (supplementary information). In the presence of both H_2O_2 and GSH in the tumor microenvironment, the redox-responsive CPT@FnH12DiTeFnH12 PMs underwent mild degradation of the ditelluride bonds, facilitating the liberation of CPT. Notably, in vitro studies revealed that increasing the fluorocarbon chain length of these PMs enhanced uptake by HeLa cells, amplifying their antitumor efficacy.

Hypoxia-responsive PMs also play a pivotal role in chemotherapy. Li et al. [62] synthesized a hypoxia-responsive polymer, Fuc-azo-LA, using hydrophobic linoleic acid and hydrophilic fucoidan. The integration of the antitumor drug DOX with the polymer produced FAL@DOX PMs, as shown in Fig. S11b (supplementary information). Under hypoxic conditions, cleavage of the azobenzene linker within FAL@DOX depleted the intracellular nicotinamide adenine dinucleotide phosphate (NADPH) and GSH, concomitantly releasing DOX. This enhancement of oxidative stress significantly improved the anticancer activity of DOX, making FAL@DOX a promising candidate for further oncological research. Additionally, Wang et al. [63] developed hypoxia-responsive PMs capable of selectively depleting NADPH and GSH, as illustrated in Fig. S11c (supplementary information). These PMs, constructed from methoxyl poly(ethylene glycol)-*co*-poly(aspartate-nitroimidazole) (mPEG-P(Asp-NI)), carried dual payloads of the NOQ1 inhibitor dicoumarol and the anticancer drug sorafenib. Cellular assays confirmed that these pH-responsive dual-drug PMs had superior anticancer efficacy compared with monotherapy.

In conclusion, PMs harbor vast potential for enhancing chemotherapy. However, most research to date has centered on delivering conventional chemotherapeutic agents, e.g., DOX and PTX. Relatively few studies have explored the use of novel chemotherapeutic agents within these systems, and this direction warrants further study to enhance therapeutic outcomes.

3.2 CDT

CDT emerged in 2016 as a promising modality for cancer treatment, utilizing endogenous chemical entities present within tumors. Specifically, the overexpression of H_2O_2 and the mildly acidic tumor microenvironment serve as effective substrates for initiating intracellular Fenton reactions [64, 65]. These reactions generate abundant ROS that damage tumor cells and exert anticancer effects [66, 67]. CDT has attracted widespread attention for its remarkable anticancer potential, and PMs have enhanced CDT-mediated tumor therapy.

Zhang and colleagues fabricated a novel multimeric superstructure, Hb@GOx NPs through sophisticated assembly and cross-linking techniques for the targeted delivery of potent catalytic agents for CDT, namely glucose oxidase (GOx) and hemoglobin (Hb) [68]. To combat glioblastoma multiforme, they encapsulated these agents within a layer of the erythrocyte membrane, obtaining the highly biocompatible RBC@Hb@GOx NPs (Fig. 4a). The incorporation of the erythrocyte membrane not only significantly reduced the immunogenicity of RBC@Hb@GOx NPs but also facilitated their efficient passage across the blood–brain barrier, allowing them to accumulate at specific tumor sites. RBC@Hb@GOx NPs have been shown to generate robust levels of ROS both in vitro and in vivo, inducing mitochondria-mediated apoptosis and markedly suppressing tumor cell proliferation.

While singular CDT may demonstrate commendable anticancer efficacy, it is not without its limitations. Factors including insufficient intracellular substrate H_2O_2 curtail its antitumor effects. To address this, a synergistic approach combining CDT with chemotherapy has been explored. Zhang et al. [41] proposed the codelivery of α-TOS and Fe^{2+} using pH-responsive polyethylene glycol-*b*-polyamino acid block copolymers (PPA), thereby synthesizing PPA/TF PMs, as illustrated in Fig. 4b. In vitro assays showed that α-TOS induced apoptosis, while Fe^{2+} interacted with intracellular H_2O_2 to trigger Fenton reactions, generating copious ROS while depleting intracellular GSH, exerting CDT effects. In vivo studies revealed that the chemotherapy/CDT combination therapy mediated by PPA/TF elicited potent anticancer effects. Furthermore, in pursuit of integrated

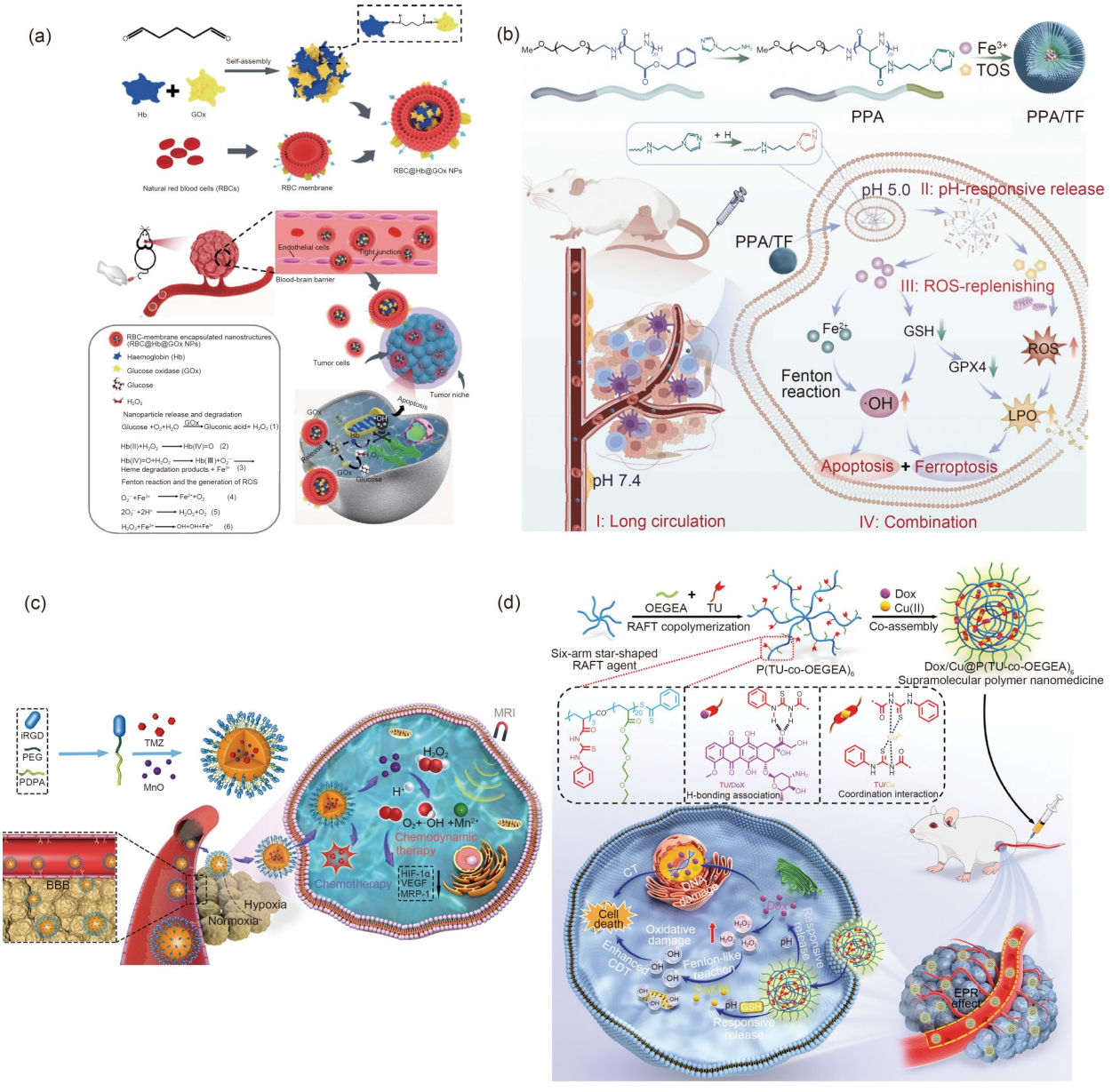

Fig. 4 CDT-based PMs for cancer therapy. (a) Schematic of the formulation and antitumor mechanism of RBC@Hb@GOx NPs (reproduced from [68], Copyright 2020, with permission from the authors, licensed under CC BY 4.0). (b) Schematic of the formulation and antitumor mechanism of PPA/TF (reproduced from [41], Copyright 2024, with permission from Elsevier B.V.). (c) Schematic of the formulation and antitumor mechanism of iRPPA@TMZ/MnO (reproduced from [69], Copyright 2020, with permission from the authors, licensed under CC BY). (d) Schematic of the formulation and antitumor mechanism of DOX/Cu@P(TU-*co*-OEGEA)$_6$ (reproduced from [70], Copyright 2024, with permission from Wiley-VCH GmbH)

diagnosis and therapy for glioblastoma, Tan et al. [69] developed therapeutic diagnostic PMs (iRPPA@TMZ/MnO) by loading temozolomide (TMZ) and oleic acid-modified manganese dioxide (MnO) NPs onto polyethylene glycol-poly(2-(diisopropylamino)ethyl methacrylate)-based PMs decorated with internalizing arginine-glycine-aspartic acid (iRGD), as depicted in Fig. 4c. The iRGD manifested distinct active targeting properties to tumor sites, where TMZ, Mn^{2+}, and O_2 were released in the acidic TME. TMZ-induced apoptosis and Mn^{2+}-mediated Fenton reaction synergistically inhibited tumor growth while significantly alleviating intratumoral hypoxia in vivo and in vitro. Mn^{2+} also served as a contrast agent for imaging, to monitor tumor response to therapy.

Interestingly, the dual noncovalent interactions of thiourea (TU) motifs have shown unexpected synergy in combining chemotherapy and CDT. Li et al. [70] exploited the hydrogen bonding and metal coordination of TU motifs to synthesize supramolecular PMs loaded with DOX and Copper (II), coined as DOX/Cu@P(TU-*co*-OEGEA)$_6$, based on

poly(acylthiourea-*co*-oligo(ethylene glycol) ethyl acrylate)$_6$ (Fig. 4d). Upon internalization into the tumor cells, DOX/Cu@P(TU-*co*-OEGEA)$_6$ released DOX and reduced Cu(II) in response to pH and GSH. This process generated H_2O_2, which reacted with Cu(I) in a Fenton-like reaction, generating a plethora of ROS and exerting CDT effects. In vitro and in vivo studies demonstrated that the combined chemotherapy and CDT approach using DOX/Cu@P(TU-*co*-OEGEA)$_6$ significantly inhibited tumor growth. TU motif-responsive supramolecular nanocarriers are therefore a promising drug delivery system.

In summary, PMs have proven to be highly effective in oxidative stress-mediated CDT for cancer treatment. As versatile delivery vehicles, PMs can encapsulate multiple drugs, enabling synergistic therapy with various agents. Notably, the combination of chemotherapy and CDT has shown remarkable efficacy in cancer treatment. One future direction involves linking amphiphilic segments with molecules capable of specific drug binding, imparting PMs with targeted drug delivery capabilities, as exemplified by the design of DOX/Cu@P(TU-*co*-OEGEA)$_6$ [70]. Given the substantial antitumor effects observed with CDT, future investigations may explore its combination with other modalities, e.g., immunotherapy or thermotherapy, to further enhance outcomes in cancer treatment.

3.3 PDT

PDT, an established cancer treatment modality, involves the localized activation of photosensitizers at tumor sites using light, inducing the generation of ROS and consequently causing tumor cell death [21]. Compared with traditional chemotherapy and radiation therapy, PDT is more selective and therefore effective for treating localized lesions. PDT is currently used for various cancers, including superficial skin cancers, esophageal cancer, and lung cancer [71]. Common photosensitizers include chlorin e6 (Ce6) [72], IR780 iodide (IR780) [73], hypericin [73], and aluminum chloride phthalocyanine (AlClPc) [74]. Given that most photosensitizers are lipophilic compounds, PMs with hydrophobic cores have emerged as effective delivery vehicles for PDT-mediated cancer therapy.

Huntošová and colleagues investigated the efficacy of poly(2-oxazoline)-based gradient copolymers for delivering the photosensitizer hypericin, aiming to evaluate the potential of such PMs in PDT [75]. Their study revealed that PMs self-assembled from three distinct gradient copolymers, (EtOx)$_{88}$-*grad*-(MeOPhOx)$_{12}$, (EtOx)$_{88}$-*grad*-(EtOPhOx)$_{12}$, and (EtOx)$_{88}$-*grad*-(HexOPhOx)$_{12}$, were all capable of delivering hypericin to tumor cells. However, (EtOx)$_{88}$-*grad*-(HexOPhOx)$_{12}$ prolonged the release of hypericin at the tumor site, highlighting its potential as an effective carrier for photosensitizers.

To enhance drug specificity, researchers have explored pH-responsive micelles for PDT applications. Taillefer and colleagues synthesized three polymers, poly(N-isopropylacrylamide$_{93}$-*co*-methacrylic acid$_5$-*co*-octadecyl acrylate$_2$), poly(N-isopropylacrylamide$_{95}$-*co*-methacrylic acid$_3$-*co*-octadecyl acrylate$_2$), and DODA-poly(N-isopropylacrylamide$_{96}$-*co*-methyl acrylic acid$_3$), which self-assembled with the second-generation photosensitizer AlClPc into pH-sensitive PMs [76]. Both in vitro and in vivo assessments revealed that these pH-sensitive PMs exhibited significantly enhanced PDT efficacy. Thus, these responsive PMs offer a promising alternative for hydrophobic drug delivery.

As singular PDT has limitations in combating tumors, there is increasing interest in the synergistic effects of multiple drugs. The current research focuses on the codelivery of chemotherapeutic agents and photosensitizers via PMs to achieve a synergistic antitumor effect through the integration of chemotherapy and PDT. Li et al. [77] developed redox-responsive core-cross-linked PEG-polyphosphoester PMs (PEG-PBYP PMs). By incorporating both the hydrophobic drug DOX and Ce6 via a thioketal-containing linker into the hydrophobic core of the PMs, they created stable DOX- and Ce6-*co*-loaded ROS-responsive core-cross-linked PEG-PBYP PMs (RCCL-DC), as illustrated in Fig. 5a. Investigations revealed that upon light activation, RCCL-DC generated abundant ROS, triggering responsive cleavage of the thioketal chains and subsequent disruption of the PM structure. This disruption accelerated the release of DOX, inducing apoptosis. Similarly, Yang et al. [78] sought to address the drawbacks of conventional single-mode therapies by developing an amphiphilic FA-HA-SS-vitamin E succinate (FHSV) that self-assembles into PMs. Following dialysis, the photosensitizer IR780 was co-loaded with the chemotherapeutic agent PTX into FHSV PMs, yielding redox-responsive dual-receptor-targeted drug-loaded PMs (IR780/PTX/FHSV PMs), as depicted in Fig. 5b. The dual active targeting of FA and HA facilitated drug accumulation at the tumor sites. In the TME, characterized by high GSH levels, the IR780/PTX/FHSV PMs rapidly degraded, releasing IR780 and PTX. Under near-infrared laser irradiation, IR780 generated many ROS, inducing localized PTT. The ROS, coupled with the apoptotic effects of PTX, synergistically eradicated the tumor cells. The results highlighted the antitumor efficacy of IR780/PTX/FHSV PMs-mediated chemotherapy/PDT synergy.

In conclusion, PMs are excellent carriers for hydrophobic photosensitizers and play a crucial role in PDT-mediated tumor therapy. As highly effective delivery vehicles, PMs have widespread applications in the synergistic application of PDT with other therapeutic modalities. Furthermore, some responsive PMs have been included in PDT-mediated tumor therapy for site-specific drug release at tumor sites,

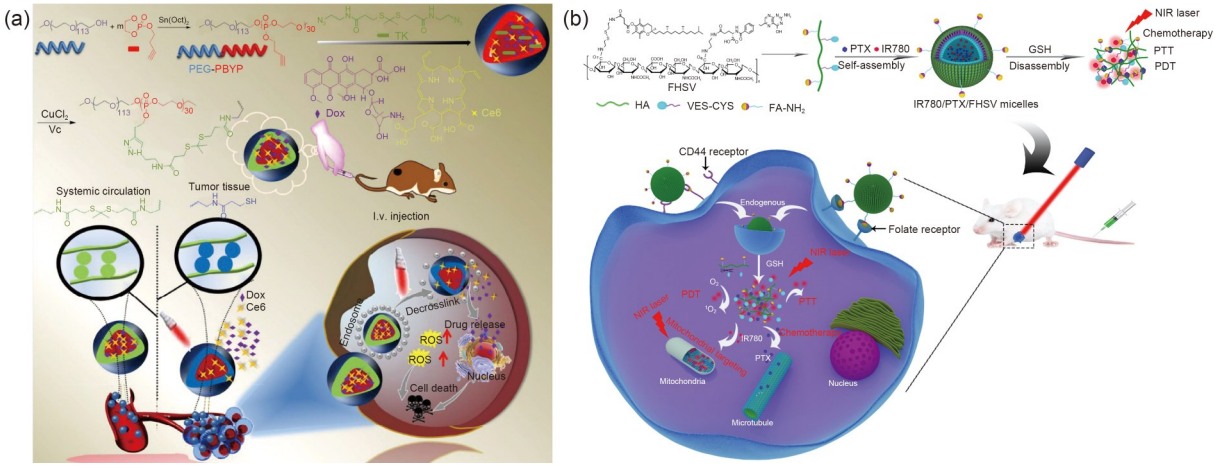

Fig. 5 PDT-based PMs for cancer therapy. (a) Schematic of the formulation and antitumor mechanism of RCCL-DC (reproduced from [77], Copyright 2019, with permission from the authors, licensed under CC BY 4.0). (b) Schematic of the formulation and antitumor mechanism of IR780/PTX/FHSV PMs (reproduced from [78], Copyright 2021, with permission from Elsevier B.V.)

thus mitigating the adverse effects of drugs. Notable examples are the ROS-responsive RCCL-DC and GSH-responsive IR780/PTX/FHSV PMs. The design of these multimodal formulations offers numerous avenues and strategies for advancing tumor therapy.

3.4 PTT

PTT, a type of phototherapy, harnesses the photothermal conversion properties of specific agents to generate localized heat in tumors upon irradiation, damaging tumor cells [79]. Unlike PDT, which generates ROS, PTT primarily produces heat. An advantage of PTT is its independence from tumor hypoxia, making it particularly useful in cancer treatment [80]. Common photothermal agents include metal NPs (e.g., gold and palladium NPs) and small molecule dyes (e.g., indocyanine green (ICG), phthalocyanine (PC), naphthalocyanine (NC), and IR780) [80–82]. To enhance the in vivo stability of these agents or to provide additional functionalities such as targeting, PMs are effective delivery vehicles. Furthermore, the excellent drug-loading capacity of PMs supports the development of synergistic anticancer therapies involving PTT and other modalities.

To explore the efficacy of PM-mediated PTT against tumors, researchers have developed various active formulations. Shao et al. [83] synthesized amphiphilic polymers (CMCh-BAPE) from 4-hydroxymethyl-pinacol phenylborate (BAPE) and carboxymethyl chitosan. These polymers self-assembled into PMs and encapsulated the hydrophobic drug ICG. Subsequently, RGD was introduced to enhance active targeting capabilities, resulting in smart PMs (CMCh-BAPE-RGD@ICG). The borate ester bonds in BAPE exhibited redox-responsive hydrolysis in the TME, promoting the release of ICG. In vitro and in vivo studies demonstrated that ICG-mediated PTT effectively induced tumor cell apoptosis and necrosis, and ICG was used as a near-infrared imaging agent for tumor diagnosis.

While ICG exhibits excellent PTT capability, its rapid clearance has motivated the development of alternative agents, e.g., PC and NC derivatives. For example, Tian et al. [84] synthesized 40 different NC and PC dyes and loaded them into PEG-PCL PMs. Cu(II)5,9,14,18,23,27,32,36-octabutoxy-2,3-naphthalocyanine (CuNC(Octa)) demonstrated superior photothermal conversion efficiency and photostability, capable of eradicating highly invasive tumors. However, CuNC(Octa)@PEG-PCL PMs did not produce ROS under irradiation. Similarly, Abad et al. [85] synthesized PMs (PEG-*b*-PDAP PMs) using polymethacrylate containing the nucleobase analog 2, 6-diacylaminopyridine (DAP) and PEG as starting materials. Within the core of these PMs, the palladium precursors were spontaneously converted into palladium nanosheets using microfluidic techniques, yielding Pd-loaded PMs (PEG-*b*-PDAP/Pd PMs) that accumulated at the tumor via EPR effect-mediated passive targeting. PEG-*b*-PDAP/Pd PMs effectively induced cellular damage through PTT.

In the realm of synergistic cancer therapies, PMs are extensively applied alongside PTT and other modalities, e.g., chemotherapy and PDT. Wu et al. [38] engineered amphiphilic ABA triblock copolymers, comprising poly(oligo(ethylene glycol) ethyl acrylate) (POEGEA)-*b*-poly(diaminopyridine acrylamide-*co*-2,2,2-trifluoroethyl acrylate) (P(DAPA-*co*-TFEA))-*b*-POEGEA, which self-assembled into PMs. DAP was present in the hydrophobic core of these PMs, which could encapsulate the chemotherapy agent carmofur via specific triple hydrogen bonding interactions. Concurrently, the photothermal agent IR780 was encapsulated within the core of the PMs, as illustrated in Fig. 6a. Upon exposure to 808-nm laser irradiation, IR780's photothermal conversion triggered the dissociation of hydrogen bonds

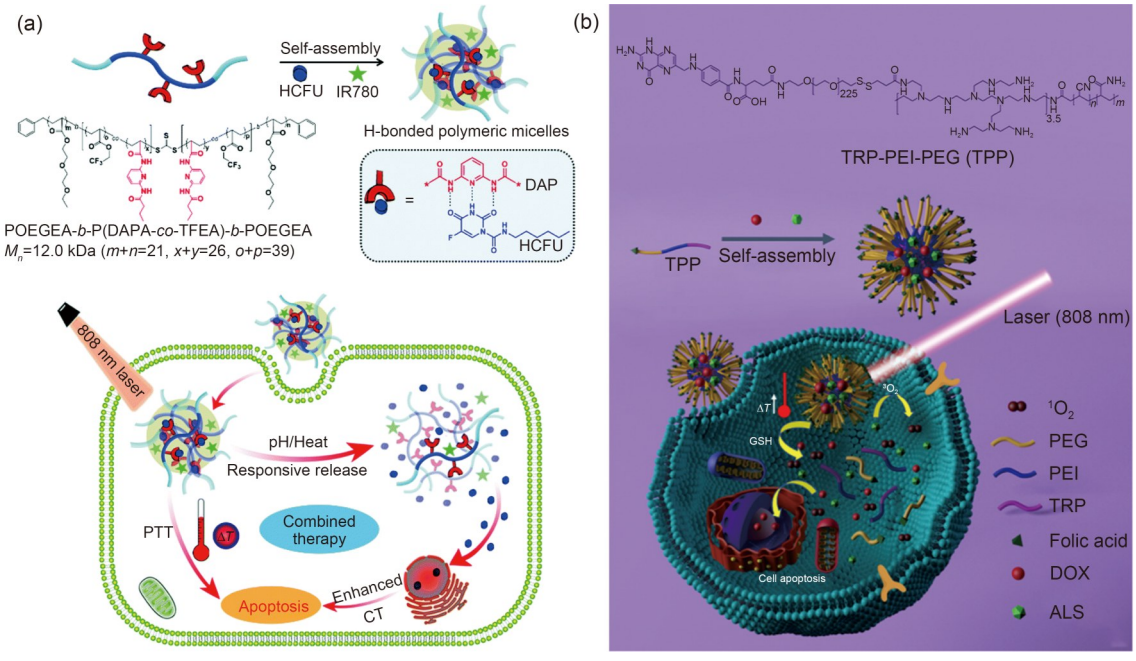

Fig. 6 PTT-based PMs for cancer therapy. (a) Schematic of the formulation and antitumor mechanism of H-bonded PMs (reproduced from [38], Copyright 2022, with permission from The Royal Society of Chemistry). (b) Schematic of the formulation and antitumor mechanism of DOX&ALS@MFM (reproduced from [86], Copyright 2022, with permission from the American Chemical Society)

and expedited the release of carmofur. This combination of chemotherapy and PTT enhanced anticancer efficacy compared with monotherapy. Ji and collaborators synthesized multifunctional PMs (DOX&ALS@MFM) that integrated chemotherapy, PDT, and PTT [86]. These PMs, composed of DOX and the photosensitizer ALS within the hydrophobic core of an amphiphilic block copolymer P(AAm-*co*-AN)-*b*-PEI-ss-PEG-FA, targeted the tumor sites (Fig. 6b). The active targeting effect of FA facilitated the accumulation of DOX&ALS@MFM at the tumor site. In the GSH-rich TME, near-infrared illumination accelerated the decomposition of PMs, facilitating the release of ALS and DOX. ALS not only exerted cell-killing effects via photothermal conversion but also generated singlet oxygen, whereas DOX exerted chemotherapeutic effects. The synergistic effects of ALS-mediated PTT and PDT, along with DOX chemotherapy, significantly impeded tumor growth both in vitro and in vivo.

In summary, PMs help enhance the solubility and stability of hydrophobic photothermal agents and enable targeted delivery and controlled release, thus minimizing the side effects. Moreover, PMs facilitate the integration of various therapeutic modalities, such as DOX&ALS@MFM, to help create synergistic PTT-mediated cancer treatments.

3.5 Immunotherapy

Immunotherapy involves harnessing, augmenting, or modulating the body's innate immune system to control or eradicate tumor cells [87, 88]. Common immunomodulators include NLG919 [89], 1-methyl-L-tryptophan (1-MT) [90], IL-2, IL-15 [89], and chemokine (C-X-C motif) ligand 9 (CXCL9) [91], among others. Despite their potential, many of these immunomodulators face challenges, e.g., instability or poor solubility, which warrant delivery vehicles like PMs for tumor immunotherapy.

A significant target in cancer immunotherapy is indoleamine 2,3-dioxygenase (IDO), which depletes intracellular tryptophan, thereby reducing the activity of T lymphocytes. Hence, small molecules with selective IDO inhibitory properties, e.g., NLG919 and 1-MT, have emerged as crucial therapeutics in cancer immunotherapy to bolster intracellular immune responses. However, the hydrophobic nature of these IDO inhibitors limits their clinical effectiveness. To address these solubility issues and improve drug delivery, Park and colleagues developed an IDO enzyme-responsive PEG-polytryptophan amphiphilic block copolymer [89]. This polymer self-assembled into PMs that encapsulated hydrophobic IDO inhibitors and were delivered to tumor cells through passive targeting. The NLG919@PEG-PW PMs exhibited enhanced antitumor efficacy, suppressing IDO expression and promoting the recruitment of effector T cells within tumors. Using another approach, Shao and colleagues conjugated IL-2 and IL-15 to a PEG-hydrophobic polymer known as polytrimethylene carbonate to form PMs (IL15/2-PEG-PTMC) [92], which enriched tumors due to passive targeting (Fig. 7a). This design aimed to extend the circulation time and activation efficacy of both cytokines.

Compared with free IL-15 and IL-2, IL15/2-PEG-PTMC significantly enhanced the proliferation and activation of natural killer cells, amplifying intracellular immune responses and demonstrating substantial antitumor efficacy.

However, conventional PMs suffer from the challenges related to conformational changes during protein delivery. Hence, the concept of nanochaperone (nChap) based on mixed-shell PMs (MSPM) emerged. This platform consists of poly(ε-caprolactone)-*b*-poly(β-amino ester) (PCL-*b*-PAE), carboxyl-modified PEG-*b*-PCL (COOH-PEG-*b*-PCL), and poly(ethylene glycol)-*b*-poly(ε-caprolactone) (PEG-*b*-PCL) amphiphilic segments, which were synthesized under acidic conditions. Two immunomodulators, BRD4-PROTAC (dBET6) and CXCL9, were encapsulated in nChaps to synergistically modulate tumor immunotherapy [91] (Fig. 7b). Ultimately, nChap significantly reduced drug clearance, extended the half-life of the drugs, and passively targeted tumor cells in vitro and in vivo. dBET6@nano-CXCL9 released CXCL9 and dBET6, inducing $CD8^+$ T cell recruitment to the tumor site and immunogenic cell death (ICD). This combination of chemokines and PROTACs is a novel strategy for tumor immunotherapy.

Chemotherapy, with its ability to promote the antitumor immune cycle and induce ICD, can complement tumor immunotherapy. The design of rational delivery carriers for chemoimmunotherapy has become a critical focus. Song et al. [90] developed redox-responsive PMs composed of an oxidation-sensitive phenyl peroxalate ester, an enzyme-cleavable 1-MT ester, and a hydrophilic PEG. By encapsulating an ICD inducer within the core, they created PTX@PoxMTP NPs, as depicted in Fig. 8a. The presence of ROS at the tumor site triggered the decomposition of these PMs, leading to the release of PTX. PTX then promoted intracellular immune activation by inducing ICD, while the enzyme-responsive cleavage of 1-MT enhanced $CD8^+$ T cell accumulation and immune responses by

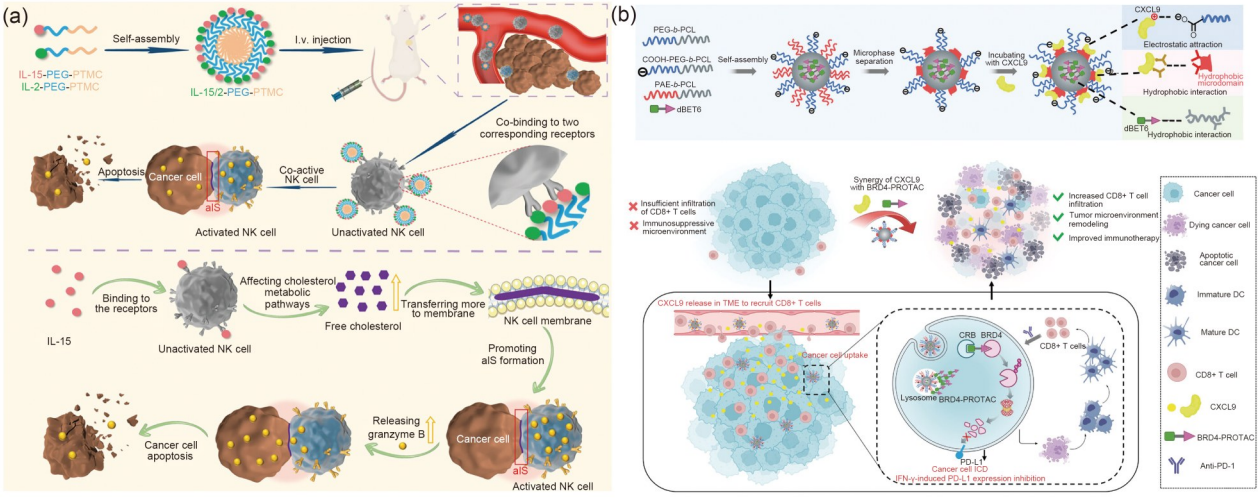

Fig. 7 Immunotherapy-based PMs for cancer therapy. (a) Schematic of the formulation and antitumor mechanism of IL15/2-PEG-PTMC (reproduced from [92], Copyright 2023, with permission from Wiley-VCH GmbH). (b) Schematic of the formulation and antitumor mechanism of dBET6@nano-CXCL9 (reproduced from [91], Copyright 2024, with permission from Wiley-VCH GmbH)

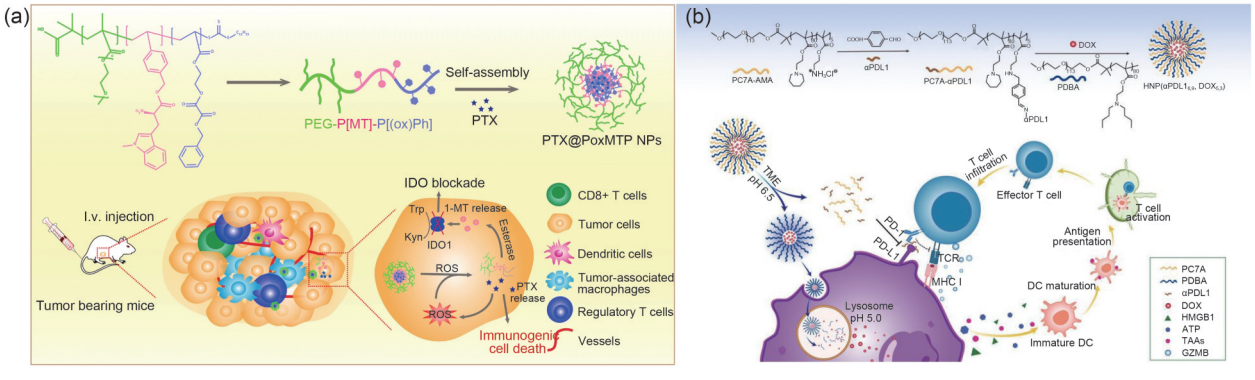

Fig. 8 PMs in combined chemoimmunotherapy for cancer therapy. (a) Schematic of the formulation and antitumor mechanism of PTX@PoxMTP NPs (reproduced from [90], Copyright 2023, with permission from the authors, licensed under CC BY 4.0). (b) Schematic of the formulation and antitumor mechanism of HNP(αPDL1$_{6.9}$, DOX$_{5.3}$) (reproduced from [93], Copyright 2024, with permission from Wiley-VCH GmbH)

inhibiting IDO. The synergistic effect of PTX's chemotherapy with the aforementioned immunotherapy yielded the greatest therapeutic efficacy in vitro and in vivo, significantly inhibiting primary tumors and reducing pulmonary metastasis.

Despite these advances, the spatial separation between the sites of action for chemotherapy and immunotherapy poses a challenge. To address this, Wang and colleagues developed sequential dual-pH-responsive hybrid PMs [93]. This PM, comprising PC7A-α programmed cell death-ligand 1 (PC7A-αPDL1) and poly(ethylene oxide)-*b*-poly(2-(dibutylamino) ethyl methacrylate) (PEO-*b*-PDBA), encapsulates DOX, as shown in Fig. 8b. The hybrid PMs prevented premature leakage of DOX and enabled sequential release of αPDL1 and DOX, enhancing antitumor efficacy.

In summary, functional PMs will catalyze cancer immunotherapy. However, more intelligent PMs are needed to optimize therapeutic outcomes.

3.6 Gene therapy

Gene therapy involves introducing exogenous target genes into specific target cells via vectors to compensate for defective genes or correct overactive ones, thus exhibiting antitumor effects [94, 95]. Given the susceptibility of genetic materials, e.g., mRNA and siRNA, to enzymatic degradation in vivo, effective carriers are indispensable for successful gene therapy [96]. PMs, known for their high biocompatibility and encapsulation efficiency, are effective delivery vehicles for these insoluble gene therapeutic agents, playing a crucial role in gene therapy.

Garg and colleagues have synthesized novel poly(ethylene oxide)-block-poly(ϵ-caprolactone-grafted-spermine) (PEO-*b*-P(CL-g-SP)) PMs, surface-modified with RGD4C peptide, to deliver MCL-1 siRNA specifically to breast cancer cells [97]. RGD4C exhibited significant active targeting potency, enhancing the higher levels of accumulation of PMs at the tumor sites. Both in vitro and in vivo findings demonstrated the enhanced transfection efficiency of MCL-1 siRNA. This led to the effective silencing of the *MCL-1* gene, exerting potent antitumor effects. Similarly, Yang and colleagues devised a novel approach for efficient mRNA delivery using a self-assembling polyelectrolyte complex composed of *cis*-aconitic anhydride-modified poly(ethylene glycol)-poly(L-lysine) (PEG-pLL(CAA)) block copolymers [98]. This system embedded mRNA within its hydrophobic core, resulting in stable PMs with pH-responsive functionality. The evaluation demonstrated effective mRNA delivery and successful transfection, positioning these engineered PMs as promising carriers for mRNA delivery and tumor gene therapy.

Furthermore, PMs play an indispensable role in the synergistic interplay between gene therapy and other modalities, particularly chemotherapy. Liu et al. [99] pioneered the preparation of mPEG-azo compound (AZO)-poly-L-lysine (PLL) PMs co-loaded with DOX and short hairpin hypoxia-inducible factor 1 (shHIF-1α), termed AZO-PMs/DOX+shHIF-1α, as illustrated in Fig. S12 (supplementary information). In the hypoxic tumor microenvironment, the AZO moiety underwent cleavage, facilitating the release of both DOX and shHIF-1α. The transfection of shHIF-1α effectively silenced the hypoxia-activated HIF-1α pathway, suppressing tumor growth, while DOX provided chemotherapeutic activity. Both in vitro and in vivo studies demonstrated that AZO-PMs/DOX+shHIF-1α maximized tumor growth inhibition and metastasis suppression through the synergistic combination of chemotherapy and gene therapy. To combat the emergence of cellular resistance associated with chemotherapy, antimicrobial siRNA has emerged as a promising candidate for cancer therapy, targeting survivin, a key antiapoptotic protein. Salzano et al. [100] incorporated siRNA-S-S-phosphothioethanol (siRNA-S-S-PE) into PEG_{2000}-phosphatidyl ethanolamine (PEG_{2000}-PE) PMs, alongside PTX, creating anti-survivin siRNA/PTX PMs. Passive targeting via the EPR effect facilitated substantial tumor enrichment of the PMs. This formulation effectively downregulated survivin expression through siRNA transfection, reducing cellular anti-apoptotic activity and enhancing PTX-mediated tumor apoptosis.

Based on existing experimental findings, PMs have emerged as effective carriers for gene therapy drugs. In single-gene therapy applications, PMs enhance drug stability and solubility, thus improving gene transfection efficiency. Moreover, their remarkable loading capacity amplifies the potential for combined therapies, thus bolstering the application of gene therapy in cancer treatment.

3.7 Starvation therapy

Due to the heightened nutritional and energy demands of tumor tissues, disrupting their metabolic processes and impeding their access to essential nutrients and energy sources can effectively inhibit tumor growth. This therapeutic approach, known as "starvation therapy," represents a promising new frontier in cancer treatment [101–103]. Despite its potential, research on PMs employed in tumor starvation therapy remains limited.

Dong and colleagues have innovatively developed a GOx nanogel immobilized within polyion complex PMs, which demonstrated potent toxicity against 4T1 cells [104]. The pH- and redox-responsive PMs were self-assembled from tert-butyloxycarbonyl (Boc)-l-methionine-(2-methacryloylethyl)ester (Boc-METMA) copolymers. Simultaneously, these PMs encapsulated curcumin and adsorbed GOx, as depicted in Fig. S13 (supplementary information). GOx-mediated starvation therapy expedited the conversion of glucose to

gluconic acid and toxic H_2O_2, whereas curcumin-mediated chemotherapy further suppressed tumor growth. Cellular toxicity assessments revealed the significant synergistic cytotoxicity of this combined approach.

Currently, research focusing on the development of antitumor PMs mediated by starvation therapy is sparse. However, as a novel adjunct to cancer treatment, starvation therapy holds considerable promise. It is crucial for researchers to invest more effort and resources into advancing this field to unlock its full potential.

3.8 SDT

Blending the principles of optics and acoustics, SDT represents a tumor treatment method wherein specific sonosensitizers are activated by sound waves to induce apoptosis or necrosis. Activation of these sonosensitizers facilitates the generation of toxic ROS within cells, stimulating oxidative stress and causing damage to the tumor cell membrane structures, mitochondria, and DNA, thus achieving the therapeutic goal of tumor treatment [105]. In SDT, the challenge lies in selecting appropriate sonosensitizers and delivering them to the tumor site [106, 107]. Currently, commonly used sonosensitizers include metal complexes and dyes such as purpurin 18 [106, 108, 109]. Given the issues with most sonosensitizers being insoluble and the relatively weak antitumor effects of single-agent therapy, PMs with hydrophobic cores emerge as potential carriers in tumor SDT.

Harnessing the potent sonosensitivity of aggregation-induced emission luminogens (AIEgens), Deng et al. [106] have ingeniously crafted AIE PMs (AIE/Biotin-M) by orchestrating 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly (ethylene glycol)-Biotin (DSPE-PEG-Biotin) and AIE-1. Biotin-mediated active tumor-targeting of PMs was achieved by binding to overexpressed biotin receptors on tumor cells. Overall, AIE/Biotin-M generated abundant singlet oxygen under ultrasound irradiation, effectively inducing cell death. Interestingly, salicylaldazine within AIE/Biotin-M engaged in redox reactions with intracellular Fe^{3+}, Zn^{2+}, and Cu^{2+}, impeding neovascularization in the TME.

Achieving drug-specific release remains a challenge in nanomedicine. Shi and colleagues developed an ultrasound/redox-responsive core-shell structure (NGR@DDP) loaded with DOX and the sonosensitizer purpurin 18 [109] (Fig. S14 in the supplementary information). Specifically, its core architecture comprised ultrasound/H_2O_2-responsive bottlebrush-like unimolecular dextran-poly(oligo(ethylene glycol) methyl ether methacrylate)-*b*-poly(2-(methylthio) ethyl methacrylate) PMs, while the shell structure was based on an NGR (Asn-Gly-Arg)-modified red blood cell (RBC) membrane derived from CRISPR-engineered mice. This red blood cell membrane coating of NGR@DDP facilitated active targeted binding to CD13 receptors on the surface of tumor cells, promoting drug accumulation at the tumor site. The combined action of chemotherapy and SDT mediated by NGR@DDP significantly enhanced drug delivery to the tumor site with the most potent antitumor effect. Likewise, Maghsoudian and colleagues have designed AuS-PM-DOX, coloading AuSNPs and DOX [110]. These PMs, fashioned from PCL-SS-PCL-phosphorylcholine (PCL-SS-PCL-MPC) polymers, self-assembled and possessed pH- and redox-responsive degradation capabilities. Compared with its nonultrasound-treated counterparts, AuS-PM-DOX generated more ROS under ultrasound irradiation with enhanced cytotoxicity.

Thanks to its noninvasiveness, excellent selectivity, and minimal trauma, SDT is a promising treatment modality. Often used synergistically with chemotherapy, it emphasizes the need for suitable delivery vehicles. Indeed, smart PMs in SDT-mediated cancer therapy can enhance drug solubility, synergistic antitumor mechanisms, and anticancer efficacy. Hence, the design and synthesis of multifunctional PMs is one of the most promising strategies to bolster SDT-mediated cancer treatment.

3.9 MHT

MHT is a therapeutic approach that exploits the thermal effects generated within tumor tissues under the influence of an external magnetic field. This localized treatment modality involves introducing magnetic NPs or other magnetic materials into the tumor and activating them with an external magnetic field to generate localized heat, which helps treat tumors [111, 112]. To stabilize magnetic materials (e.g., metallic particles) and achieve tumor-specific delivery, PMs are employed in tumor MHT [113]. The integration of PMs with magnetic materials not only preserves the magnetic-to-thermal conversion capabilities of the magnetic materials but also leverages the multiple binding sites, excellent biocompatibility, and outstanding stability inherent to PMs. These attributes collectively improve antitumor efficacy, stability, and specificity of the therapeutic agents in vivo [114, 115].

In the context of MHT, magnetic imaging technologies such as magnetic particle imaging and magnetic resonance imaging (MRI) are common. This dual functionality enables both therapeutic magnetic heat conversion and diagnostic imaging. Therefore, drug-loaded PMs in MHT can help integrate diagnosis and treatment of tumors. Benassai et al. [111] encapsulated iron oxide magnetite nanoflowers (IONFs) using the classic amphiphilic block copolymer poly(styrene)-block-poly(acrylic acid) (PS-*b*-PAA). Compared to pure IONFs, IONFs@PS-*b*-PAA did not alter the magnetic-to-thermal conversion capability or the photothermal responsiveness of the magnetic particles. Moreover, encapsulation of IONFs by PMs enhanced their

biocompatibility and mitigated the effect of the negative contrast agent on MRI signals. Thus, magnetic PMs are an ideal platform for both therapeutic and diagnostic applications in tumor treatment.

However, few PMs are designed solely for MHT, and most formulations leverage PMs as a delivery platform to synergize MHT with other therapies. The combination of MHT with chemotherapy is a novel strategy in nanotechnology with notable efficacy in cancer treatment. Kim et al. [114] synthesized PEG-PLA PMs containing magnetic NPs (MNPs), termed MNP-PMs, which were loaded with the chemotherapeutic agent DOX. The PMs demonstrated preferential tumor localization via passive targeting, leveraging the EPR mechanism. Under alternating magnetic fields, DOX/MNP-PMs elevated temperatures at tumor sites in vitro, exerting therapeutic effects against tumors. Furthermore, magnetic field irradiation enhanced DOX release, inducing apoptosis in cancer cells. The combined chemotherapy/MHT strategy using DOX/MNP-PMs outperformed individual therapies.

To advance combined chemotherapy and magnetotherapy formulations for tumor treatment, researchers are developing PMs with extensive drug-loading capabilities. For instance, TPGS-PLGA PMs have been engineered to encapsulate superparamagnetic iron oxide NPs (SPIONs) and dual drugs (nitrendipine and curcumin) simultaneously [115]. Under alternating magnetic fields, these PMs generated more magnetic heat compared to bare SPIONs and showed antitumor efficacy in vivo. The exceptional encapsulation efficiency and capability of TPGS-PLGA PMs offer promising avenues for the development of advanced multimodal tumor treatment formulations.

Current research focuses on the synergy between MHT and chemotherapy, leading to a myriad of antitumor formulations. An intriguing avenue for future investigation is the combination of MHT with other therapeutic modalities, e.g., gene therapy and immunotherapy, which may enhance cancer treatment.

3.10 Targeted therapy

As described in the previous content and supplementary information, targeted therapy is divided into two mechanisms: passive targeting and active targeting [116], the difference being the presence or absence of specific targeting receptors and ligands. Nanoscale PMs could all be passively targeted to tumor cells via the EPR effect, thus accumulating at the tumor site more efficiently than pristine agents [117]. For instance, in the recent studies mentioned above, DTX-PM [27], RSL3/PMs [42], PEG-*b*-PDAP/Pd PMs [85], siRNA/PTX PMs [100], and MNP-PMs [114] all belonged to the category of delivery to tumor cells through passive targeting function. However, the efficacy of passive targeting remains relatively modest. Consequently, most research concentrates on active targeting therapies for tumors [118].

The surface customization of PMs with specific targeting molecules enables them to target tumors precisely. Common tumor-targeting molecules include vitamins (e.g., FA), natural products (e.g., HA), peptide-based agents (e.g., RGD peptide), and monoclonal antibodies (e.g., nimotuzumab) [119]. Specifically, both FA–PTX micelles [15] and DOX&ALS@MFM [86] described above have been included in surface modification with FA to achieve active targeting, directing the drug to FA receptors that are abundantly expressed on tumor cells. In addition, HA, a widely used tumor-targeting ligand, binds to CD44 receptors overexpressed on cancer cells, thereby enhancing drug accumulation at the tumor site. Gal-HA-VES [14], HM@HA-F [57], PTX/HA-PLGA PMs [58], and PTX-loaded HA-*hyd*-TPE PMs [59] mentioned above adopt this approach. Furthermore, RGD peptides, which specifically bind to integrin receptors on tumor cells, enhance delivery and active targeting potential, e.g., iRGD-based iRPPA@TMZ/MnO [69] and CMCh-BAPE-RGD@ICG [83]. Monoclonal antibodies, which are also highly specific, can recognize and bind to specific antigen molecules. Yu et al. [120] have harnessed the targeting precision of therapeutic agents using surface-modifying maleimide polyethylene glycol-Ce6 (Mal-PEG-Ce6) and polymer-doxorubicin prodrug (PEG-b-P(GMA-ss-DOX)) hybrid micelles (DCMMs) with NTZ. Among them, the NTZ on the surface of NTZ-DCMs can specifically bind to the overexpressed epidermal growth factor receptor (EGFR) on the surface of liver cancer cells and therefore be taken up by tumor cells.

In summary, the application of targeted PMs in cancer therapeutics has boosted the efficacy of antitumor treatments. Nevertheless, the pool of specific targeting molecules remains limited. Hence, there is a need to develop new targeting molecules and formulations with enhanced targeting capabilities for anticancer agents.

4 Clinical application of PMs

Based on current marketing and clinical data, only a few PMs have been approved for commercial use, while most remain in the clinical trial or research and development stages. Moreover, the number of PMs approved for global distribution is limited, with most products approved only in specific regions. Based on the review of relevant information, the antitumor PMs are categorized into two groups: those that are already listed and commercially available (listed PMs) and those that are still in the clinical phase of development (PMs still in the clinical phase).

4.1 Listed PMs

Statistical data reveal that only a few PMs for cancer treatment have been approved in various countries. These include Genexol® PM, PTX PMs for injection, and Nanoxel® M. Detailed information on these clinical trials is summarized in Table S4 (supplementary information) [121].

Genexol® PM, developed by the Korean biopharmaceutical company Samyang Biopharmaceuticals Co., is the first PM clinically approved for cancer treatment in humans. It is a polyoxyethylene castor oil-free PTX PM encapsulated with mPEG-*b*-poly(D, L-lactide) as the block copolymer and is indicated for the treatment of nonsmall cell lung cancer, metastatic breast cancer, and ovarian cancer [122]. Genexol® PM was initially approved in the Republic of Korea in 2007 following Phase I and Phase II studies that evaluated its safety and efficacy, respectively. This formulation demonstrated superior tolerability and efficacy compared with PTX injection (Taxol) and PTX albumin NPs (Abraxane) [123, 124]. The product has since been approved in Serbia, the Philippines, Vietnam, and India. Efforts to expand its market presence in the US under the 505(b)(2) pathway are ongoing, although no data have been published to date [122].

In October 2021, Shanghai Yizhong Pharmaceutical Co., Ltd. received approval for another type of PTX formulation known as PTX PMs for injection in China. The PMs are cross-linked with $mPEG_{2000}$-poly(D, L-lactic acid) as a copolymer and can be used in combination with platinum-based drugs for the first-line treatment of patients with non-small cell lung cancer harboring mutation-negative epidermal growth factor receptor and anaplastic lymphoma kinase-negative tumors, which are locally advanced or metastatic and not amenable to surgical resection [125].

In addition, Nanoxel® M, developed by Samyang Biopharmaceuticals Co., was launched in the Republic of Korea in 2012. This formulation, which uses mPEG-*b*-poly(D, L-lactide) similar to Genexol® PM, is loaded with DTX [126]. Nanoxel® M has shown an excellent biosafety profile due to the absence of polysorbate 80, compared to traditional DTX injections (Taxotere). It is currently used for treating recurrent or metastatic squamous cell carcinoma of the head and neck [127]. Moreover, Nanoxel® M is undergoing a Phase II clinical study (NCT03585673) in combination with oxaliplatin for the treatment of metastatic esophageal squamous cell carcinoma.

4.2 PMs in the clinical phase

Unsurprisingly, most antitumor PMs are still undergoing clinical trials and are not yet available on the market. The PMs currently in clinical development include NK-105, CPC634, NC-6004, NC-4016, NK911, NC-6300, SN-38, and NK012 (Table S5 in the supplementary information) [121].

NK-105, developed by Nanocarrier/Nippon Kayaku in Japan in 1990, is a PTX PM utilizing PEG-*b*-poly(aspartate) as the block copolymer. Currently, NK-105 has completed Phase III trials (NCT01644890) with results indicating similar efficacy to PTX alone [125]. In addition to PTX, an anti-platinum-resistant ovarian cancer study of DTX PMs (CPC634) polymerized from mPEG-*b*-p(HPMAm-Lacn) was completed in December 2020 [128], although the results have not yet been published (NCT03742713).

Platinum-based drugs, e.g., cisplatin and oxaliplatin, are classical cancer therapies. Cisplatin-encapsulated PMs (NC-6004), jointly developed by NanoCarrier Co., Ltd. and Orient Europharma Co., Ltd., use PEG-*b*-poly(glutamic acid) as the block copolymer. A Phase I/II study of NC-6004 combined with gemcitabine demonstrated excellent safety and tolerability (NCT02240238) [129]. The Phase III trial for the treatment of locally advanced or metastatic pancreatic cancer was completed in 2019, but the results have not been released yet (NCT02043288). Oxaliplatin PMs (NC-4016), also developed by NanoCarrier Co., Ltd., utilize PEG-*b*-poly(glutamic acid) as well and completed a Phase I trial for advanced solid tumors or lymphoma in 2018, with results pending (NCT03168035).

DOX and its derivative, epirubicin, are widely used in cancer therapy. NK911, a DOX-loaded PM with PEG-*b*-poly(aspartate), was evaluated in a Phase I trial in Japan in 2004. The study reported a minimum toxic dose of 67 mg/m^2 and a recommended dose of 50 mg/m^2 with favorable tolerability and pharmacokinetic data compared to single agents [128]. Despite these findings, there have been no further updates on the progress of NK911. Similarly, NC-6300, an epirubicin PM developed by NanoCarrier Co., Ltd. using PEG-*b*-poly(aspartate) as the polymer block, is undergoing a dose-escalation and extension Phase I/II trial in patients with advanced solid tumors or soft tissue sarcomas in the United States, with recruitment ongoing (NCT03168061).

SN-38 (7-ethyl 10-hydroxy camptothecin) is a biologically active metabolite of irinotecan hydrochloride (CPT-11). It has significant antitumor activity but suffers from poor water-solubility [130]. NK012, a PM based on PEG-*b*-poly(glutamate) with a chemically conjugated SN-38 payload, targets rectal, breast, and gastric cancers. This PM shows slow clearance and targets tumor aggregation. Phase I trials in the United States and Japan demonstrated significant inhibition of tumor activity [131]. Currently, Phase II trials of NK012 for nonsmall cell lung cancer and triple-negative breast cancer have been completed and revealed excellent inhibition of nonsmall cell lung cancer and high tolerability, although results for triple-negative breast cancer are still pending [132]. Additionally, NK012

has been tested in a Phase I trial in combination with 5-fluorouracil/formyltetrahydrofolate, showing good tolerability (NCT01238939). Nevertheless, further pharmacodynamic studies are needed to explore this combination therapy's potential.

4.3 Reflections on the clinical status of PMs

Despite extensive research into PMs, their clinical translation remains limited, with very few products approved for market use. This mirrors the broader trend observed in the clinical advancement of NP formulations. The primary reasons behind this disparity can be attributed to the following factors: (1) There is a significant gap in understanding the intricate yet complex interactions between NP structures and the diverse physiological environments within the human body. The current in vivo detection methods for NPs cannot fully capture these interactions [133]. (2) Clinical translation is hindered by the absence of versatile and widely applicable screening platforms, thus impeding the rapid assessment of NP efficacy and toxicity. This gap hinders the establishment of strong correlations between preclinical and clinical outcomes [133]. (3) Often, NP formulations are characterized under conditions that do not accurately replicate the complexity of physiological environments. This limitation results in the failure to accurately and fully capture the interactions between NP formulations and biological tissues [134]. (4) Although there are a plethora of animal models for preclinical investigations, there is a significant gap between the outcomes observed in these models and those seen in clinical trials. This discrepancy stems from the inability of single-animal tumor models to fully mimic the complexity of human cancers, making them inadequate for predicting clinical outcomes [135]. (5) The sophisticated design of NP formulations necessitates a thorough reevaluation of the chemistry, manufacturing, and controls and stringent adherence to good manufacturing practices. The development of novel manufacturing processes is imperative, especially for NP formulations with high complexity, which pose considerable challenges for large-scale and reproducible production [136].

5 Conclusions and future perspectives

PMs are formed through the self-assembly of amphiphilic block copolymers, which consist of a hydrophilic "outer shell" and a hydrophobic "inner core." Alternatively, the "shell" and "core" can also be composed of natural polymers with excellent safety and environmental friendliness, resulting in multifunctional PMs. Their excellent drug-loading capacity, good biocompatibility, and strong targeting abilities have made them a promising new type of nanomedicine carrier in recent years. The rational design of PMs to incorporate various stimulus-responsive drug delivery systems according to the needs can achieve precise drug release at the tumor site while minimizing systemic toxicity. The ability of PMs to encapsulate hydrophobic drugs in their cores contributes to their role in various cancer therapies, including chemotherapy, CDT, and immunotherapy. These properties underscore the potential of PMs in cancer treatment.

However, the poor stability of PMs in the human body limits their clinical application because the micelles degrade in the blood circulatory system, leading to premature drug release, loss of tumor-targeting, and potential damage to healthy organs or tissues. The stability of PMs can be classified into kinetic stability and thermodynamic stability. Thermodynamic stability, often characterized by the critical micelle concentration (CMC), indicates the stability of the micelles under equilibrium conditions. The lower the CMC, the greater the micelle stability. Kinetic stability pertains to the micelle–micelle and micelle–environment interactions, which are influenced by factors such as the length of the hydrophobic chain segments and temperature. More hydrophobic drugs tend to bind more tightly to the hydrophobic core of the micelle. In addition, the stability of PMs is affected by the blood environment, including pH, salt content, and the presence of blood cells and proteins, which can adsorb onto the micelle surface and destabilize them.

To address these stability issues, researchers have explored several strategies, including increasing the proportion of hydrophobic blocks in block copolymers, utilizing electrostatic interactions between hydrophobic cores and oppositely charged drugs, cross-linking hydrophobic cores, and conjugating targeting molecules to the ends of the PM chains. Despite these efforts, optimizing stability and drug delivery remains challenging.

Furthermore, fewer polymeric micellar formulations have been successfully marketed, with most still in the clinical research phase. This slow progress is attributed to the incomplete understanding of the interactions between the micelle structure and the human physiological environment, the limitations of single animal tumor models for preclinical research, and the challenges of micelle performance in complex physiological settings. To overcome these challenges, future research should focus on the activity of micelle structures in vivo, developing comprehensive animal tumor models, and creating in vitro systems to accurately assess the efficacy and toxicity of the formulations. This approach will accelerate the introduction of polymeric micellar formulations into the market.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study does not contain any studies with human or animal subjects performed by any of the authors.

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